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Protocol

Harm Reduction Text Messages Delivered During Alcohol Drinking: Feasibility Study Protocol

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Abstract

Background: Recent research using mobile phone interventions to address public health issues such as smoking, obesity, depression, and diabetes provides a basis for trialing a similar approach toward reducing the negative consequences of risky drinking. **Objective:** This feasibility study aims to recruit drinkers between 18–34 years to a website where they will design and enter their own personal messages (repeating or one-off) to be sent to their mobile phones when they are drinking to remind them of their pre-drinking safety intentions. **Methods/Design:** Participants in the treatment group will have access to the messaging function for 3 months and will be compared to a control group who will have 3 months access to a web chat site only. Data collection will occur at baseline, 3 months, and 6 months. The primary outcome is a change in unintended negative consequences from drinking at 3 months. Secondary outcomes include the acceptability of the intervention to this population, recruitment rate, participant retention, reduction in alcohol consumption, and the self-motivation discourse in participant messages. **Discussion:** Existing alcohol interventions in New Zealand attempt to reduce alcohol consumption in the population, but with little effect. This study aims to target unintended negative consequences resulting from drinking by empowering the drinkers themselves to deliver safety messages during the drinking session. If proven effective, this strategy could provide a cost-effective means of reducing the public health burden associated with risky drinking. **Trial Registration:** Australia and New Zealand Clinical Trials Register (ANZCTR): ACTRN12611000242921

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KEYWORDS

harm reduction; alcohol; eHealth; mobile phone; brief intervention; smartphone

Introduction

New Zealand statistics about the unintended negative consequences of drinking show that young drinkers do not heed public health messages sufficiently [1]. There are numerous immediate problems caused by risky drinking, including acts of violence, driving under the influence, unintended sex, hangover, cognitive impairment, physical and verbal assault, physical accidents, relationship problems, loss of productivity,

compromised mental health, and increased burden on medical and legal services [2,3]. For example, a study of the New Zealand drinking population in 2009 found that the risk of alcohol-associated accident and injury was almost 50% for those younger than 24 years compared to a 20% risk among drinkers of all ages [4].

Risky drinking can be defined generally as drinking to drunkenness [5], or quantified as more than 6 standard drinks for men (4 for women) in one drinking session [2]. In the

2007–2008 New Zealand Health Survey, 25% of respondents were identified as weekly risky drinkers. Most weekly risky drinkers were between 18–24 years (33.8% of males and 18.8% of females) followed by those between 25–34 years (16.3% of males and 12.6% of females). Young women in the 16–17 year age group were more likely to be weekly risky drinkers (16.4%) compared to young men in this same age group (9.0%) [2]. In New Zealand, the two demographic groups that engage in weekly risky drinking most frequently are between 18–24 years and 25–34 years.

Brief interventions, such as an assessment of drinking behavior and discussion about the consequences and how to change, have traditionally been left to health professionals in the public sector [6–8] or in the university campus environment [9–12]. Web-based alcohol interventions are now gaining popularity by providing information and strategies on reducing consumption and keeping safe [13–15]. Although medical and web interventions have shown some measure of success [11,16–20], particularly in the university population [12,21,22], the continuing alcohol problem among those between 18–34 years is an indication that alternate approaches are needed.

Computer- and mobile phone-based technologies have been utilized effectively in a number of health interventions, such as smoking, diabetes, obesity, and depression prevention [23–27]. The rationale behind mobile phone interventions for smoking is to send messages or relevant video to smokers' phones when they are most likely to be tempted to smoke as a reminder of cessation intentions [24]. Similarly, a text message received while drinking could serve as a reminder of safety intentions and counter the distraction of drinking "buddies" and the drinking environment [28]. Engaging the participants in planning their own messages could add to the intervention effect due to the positive correlation between health behavior change and personally defined goals and plans [29–31]. The receipt of a planned, self-designed message sent at appropriate pre-scheduled drinking times could potentially resonate with a message recipient (whose judgment is clouded by alcohol) and result in safer behavior [32]. An additional rationale behind the drinker designing their own message (versus messages designed by a third party) is one of ontology. Researchers traditionally use focus group discussions with representatives of the target population to construct the messages used in health interventions. However, the brain of the drinker, dulled by the sedative effect of alcohol, requires a message that fully resonates within their memory [28]. It is our view that such a message can only be written by the drinkers themselves.

We have designed a feasibility study to look at whether drinkers between 18–34 years are able to fulfill their intentions of drinking safely and/or consuming less alcohol if they receive self-generated reminders of those intentions via mobile phone text messages when drinking.

The study aims to address several gaps in the alcohol brief-intervention literature, namely (1) delivery of a brief intervention by non-health professionals; (2) use of text messages as a prompt to moderate drinking and implement intentions to keep safe while drinking; (3) use of an intervention during alcohol consumption; (4) use of an intervention designed

and controlled by the participants themselves; (5) how text message-prompted smoking cessation translates to the field of alcohol consumption; and (6) an insight into the self-motivation talk of drinkers.

The planned intervention puts the power and opportunity for change into the hands of those who are most at risk from the consequences of risky drinking. The intervention delivery mechanism, the mobile phone, is one that the younger drinking population is extremely comfortable using and it has been shown that they use it to transmit health information [33]. In New Zealand, 90%–94% of young people between 18–34 years own a mobile phone [34]. Changing health behaviors requires motivation, volition, and a sense of personal efficacy [30,35–37]. The process of planning the messages to be sent to their mobile phones may increase the participants' sense of self-efficacy. Their likelihood of succeeding in their intentions could also be increased by their proactive planning of the message and scheduling of the delivery [35]. The delivery of the message during the act of drinking should cut across the physical effects of alcohol and the social environment, thereby, increasing the probability of the participant taking action on their intentions [28,38,39]. In addition, participants can respond to their own changing needs by changing the messages and message delivery times at any time. This responsiveness has been extended by a smartphone application, available for the iPhone and the Windows Phone 7, which will enable messages to be created or edited without direct access to the website. The act of planning the text delivery times and messages aims to empower the participant and add to the salience and recognition of the messages when received on their phone.

Before a full, randomized controlled trial of this intervention can be undertaken, a feasibility study needs to be run. To this end, the website and smartphone apps have been developed and tested to ensure that the website information, question format, and data collection align with the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) protocol [40].

Methods

Objectives

The long-term objective of the feasibility study is to trial concepts needed to inform a randomized controlled trial (RCT) which will assess whether a mobile phone harm reduction strategy can reduce the number of unintended consequences resulting from a drinking session.

The primary objectives of this study are the acceptability of the intervention, a change in amount of alcohol consumed and/or a change in alcohol-related consequences, the self-talk of this population in relation to alcohol and safe drinking, and the recruitment rates and loss to follow-up over time. Such data will inform sample size calculations and the design of a subsequent RCT.

Study Design

This is a parallel group randomized controlled trial.

Study Population

The study population will be recruited within the Auckland Council region using media advertising, including radio and newspapers. Corporate businesses, bars, and clubs will be contacted for permission to display recruitment posters on their premises. Tertiary campuses in the study region will also be targeted through student radio, flyers, and posters, and student email lists from the campuses (where they can be sourced). Participants will be invited to sign up on the study website where they can access further information about the study. They will be asked 4 key questions to determine whether they fulfill the inclusion criteria. Those not eligible for the study will be thanked for their time, and they can sign up to receive a copy of the study results and/or notification of any subsequent trials.

Participants will not be paid for their participation, but will be entered into a monthly draw for mobile phone top-up vouchers.

Inclusion Criteria

Participants will be between 18–34 years, have experienced at least one unintended consequence from drinking in the previous 3 months as measured by the selected Screening Test: Young Adult Alcohol Problem Severity Test (YAAPST), have access to the Internet, and own a mobile phone on any plan. Non-drinkers will not be excluded from participation as they may experience unintended consequences due to their association with drinkers. Non-drinkers may socialize with drinking friends and be the “responsible” person in the group. As such, they may want to use the text message service to remind themselves of this responsibility. We did not want to exclude non-drinkers from the study as non-drinkers can be caught up in unintended negative consequences when out with drinking friends. The Alcohol Use Disorders Identification Test alcohol consumption questions (AUDIT-C) scores will identify these non-drinkers and we will control for them in the statistical analysis.

There will be no limit to the number of participants. Recruitment will remain open for 8–10 months.

Exclusion Criteria

Adults will be excluded if they have not experienced unintended consequences from drinking, they are outside the target age

range, or they do not have their own mobile phone or access to the Internet.

Blinding and Randomization Allocation

Participants will be allocated 2:1 to the control and intervention groups, respectively, to ensure adequate numbers for study comparison. There is evidence of a high level of attrition in the control group in Internet-based interventions. Therefore, we chose the 2:1 allocation to reduce the risk of control group dropout. The researchers will be blinded to treatment allocation. Participants fulfilling the inclusion criteria will be asked to consent to the study and answer demographic, drinking, and consequences questions before gaining on-going access to the website. Participants will be randomized to each of the two groups by computerized central randomization using stratified blocks (block size = 6). Two stratification factors will be used: gender (male/female) and age (≤ 24 years and > 24 years) to ensure balance in these key prognostic factors between the intervention and control groups. Once randomized, intervention participants will receive an appropriate email with instructions and reminders for setting up and accessing their messages.

Study Intervention

Intervention Group

The study website will enable participants to create the messages they wish to have sent to their mobile phones, at the times they schedule. These messages might relate to their strategies to reduce alcohol consumption or to keep safe during and after drinking. By default, the messages will be repeated weekly based on the initial day of the week and time specified by the participant. Participants will be able to create once-only messages by entering a specific date. All messages will continue to be sent, as per the participant schedule, until they are deactivated by the participant. Participants can change their messages and schedules at any time. They will also have access to the website community pages (outlined below).

Participants who own an iPhone or Windows Phone 7 will also be able to download an application to their phone to enable them to control the messages from their mobile phone. The intervention group will have access to the intervention for six months. [Figure 1](#) illustrates the study design.

Figure 1. Study intervention and control groups.



Control group

Participants in this group will have access to a simple website for 3 months, where they can post messages about any topic of

interest to them and participate in community discussions. The community pages will also have links to useful websites providing information on drinking safely and participants will receive a text message as these links are updated. This group

will understand that they are in the control group and, after 3 months, they will receive an email or text message inviting them to access the intervention.

There will not be a limit placed on the number of messages created by the participants or on the frequency with which these messages can be sent to their mobile phones. A log of messages sent and a log of message content/schedule changes will be recorded from the website and will inform statistics on intervention usage.

Baseline Assessments

The following data will be collected via the study website from all participants at baseline and saved directly into the Microsoft SQL Server database 2008 Enterprise R2.

Demographic Information

Information about gender, ethnicity, employment status, age of first drink and first drunkenness, and readiness to change drinking habits [41] will be collected.

Drinking History

Items 1–3 of the AUDIT-C will be used to assess alcohol intake [42]. This measure has been well validated in university students between 18–21 years [43–46], both male [47,48] and female [49]. Due to its brevity, the AUDIT-C has good utility as a computerized version [50] and when incorporated into general health risk questionnaires [51]. One limitation of the AUDIT-C is that Item 2, which provides the scale for number of alcoholic drinks consumed on a typical day, uses consumption ranges. To identify small changes in drinking habits [48] a question on typical daily consumption of each of wine/champagne, beer, spirits, alcopops/ready-to-drink beverages (RTD), and “other” alcoholic beverages will be included [52–55].

Other Dependencies

Question 2 of the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) will be asked to gauge other dependencies within this population. Previous research has shown a relationship between dependencies and difficulty in reducing drinking/negative consequences [56–58]. The ASSIST correlates well with the AUDIT ($r = .82$) when assessing alcohol as the substance of abuse [56].

Consequences Measure

The YAAPST was developed for use with American university students between 18–21 years [59], and is a sensitive measure for mild alcohol-related consequences, such as hangover, feeling sick, being late for work/school, etc [60]. The YAAPST also includes items on unintended sex and driving while drunk [61–68]. The measure can be scored as a lifetime occurrence of consequences, past year frequency, or past year severity [69]. There is good reliability for recall over a 12-month period [70]. Therefore, we expect similar reliability over a shorter period of time. This study will compare consequences at baseline, 3 months, and 6 months. To make the 3- and 6-month comparisons and avoid crossover of data, we will limit each recall period to 3 months.

One of the aspects that we will look at is whether the assessment items can be reduced and still collect the data we need. The

intervention sign-on process tracks the point at which potential participants drop out before sign-up and we will be reviewing this for dropout particularly at the assessment points.

Primary Outcomes

Primary outcomes will be collected at 3 and 6 months and include:

1. Whether the intervention engaged the interest of the participants sufficiently to make them proactive users of the mobile phone messages.
2. The acceptability of the intervention as measured by recruitment and dropout rates.
3. Safety, assessed from participant feedback and by measuring reported website misuse such as spamming others. Participant time from sign-up to last message sent until 6 months will be measured to provide an indication of the longevity of the program.

In addition, a change in unwanted consequences reported by participants in the intervention group between baseline and 6 months will provide an indication of the longevity of the intervention.

The quantitative outcomes of interest include a change in unwanted consequences and drinking. The initial question battery of AUDIT-C, YAAPST, and ASSIST will be repeated at 3 and 6 months. In addition, an open question asking the participant if they thought they had changed their drinking behavior in the previous 3 months, and if so, what changes they had made will be asked also.

The messages created by the participants will be analyzed to gain an understanding of the self-talk of this drinking population.

Sample Size

This is a feasibility study and the results will be used to inform the required sample size for a well-powered randomized controlled trial. Every effort will be made to recruit as many participants as possible during the 6-week recruitment period.

Withdrawal Criteria

There are no withdrawal criteria for this study. Participants wishing to drop out of the study can do so by returning to the website to turn off their messages. The termination of messages will be the proxy measure of dropout rate.

Data Management

The lead researcher will design, validate, and verify the security of the databases used in this study. The SQL 2008 R2 databases will be managed by Starsoft Ltd, the writers of the software. All questionnaire data will be assigned range checks and will return instructions to the user as data items are entered. All data will be entered directly by the participants, who will enter their personal log-in and password to access their messages on the website [40].

Data Analysis

This trial has been designed in collaboration with a senior statistician at the National Institute of Health Innovation, University of Auckland, who will continue to advise and assist

with analyses of the trial data. The data from the Microsoft SQL database will be exported to an Excel spreadsheet and then imported into a statistical analysis package for integrity checks prior to analysis.

The qualitative data obtained from the messages created by the participants will be reviewed by, and discussed with, a senior academic qualitative researcher at the University of Auckland who has contributed to the theoretical underpinnings of the research design. The theory underlying this design is post-positivist, seeking to infer from a non-falsified hypothesis what is probably true or what will probably be useful. Analysis of qualitative data, namely the participant messages and feedback, will use a general inductive approach to gain an understanding of self-talk around alcohol and safety. As this is a feasibility study, participants will be asked to provide feedback on the usefulness of the intervention and on suggestions for improvement. The messages and comments will be assessed by thematic analysis using NVivo 9 from QSR International.

Treatment Effects

The relationship between frequency of text message use and behavior change (ie, change in reported drinking and/or change in safety behaviors) will be investigated. For each group, paired *t* tests will be used to assess the treatment effect between baseline and 3 months. Change from baseline to 3 months in drinking and consequences scores will be analyzed using linear regression and the model will include group and the baseline values. To assess the effect of factors such as age, gender, and ethnicity, adjusted linear regression analysis will be conducted. And if there are sufficient participants, subgroup analysis will be conducted.

Data collected at 6 months will be analyzed according to the preceding 3-month protocol. If there are sufficient data, repeated measures analysis will be run to compare the two groups across the full 6-month follow-up. Scatter plots will be generated to show the change in scores over time. Change in consequences score will be plotted at each follow-up assessment against message intensity (volume of messages sent) and correlation between these two variables will be calculated. Alcohol/consequences data will be plotted against frequency/intensity of messaging to give an indication of the messaging relationship on outcomes.

Procedure to Account for Missing Data

Analysis will be on an intention-to-treat (ITT) basis. Those lost to follow-up will be included in the data analysis and are defined

as those not using the messaging function or those who fail to complete the outcomes measures at 3 months and 6 months. Missing data will be replaced by the last observation carried forward (LOCF) with no change assumed since the last message sent. If feasible, sensitivity analyses will be performed excluding participants with missing outcome data to assess the robustness of the study findings.

Ethics

Ethics permission for this study has been received from the Central Regional Ethics Committee (ethics number CEN/11/03/010). As part of this ethical obligation, the researcher has committed to sharing research results and other issues of interest to Māori (indigenous New Zealanders) arising from this research in appropriate seminars. Maintenance of confidentiality and compliance with New Zealand's privacy legislation will be obtained at the point of participant sign-up on the study website. Participation in the study is voluntary and participants will be free to withdraw at any time. Participants will be anonymous, signing into the website with a code name. Their password will be encrypted and held in the database in an encrypted format. Data will be entered, stored, and backed-up in a secure commercial database: Microsoft SQL 2008 R2 fully encrypts all data. A secure socket layer (SSL) certificate will protect data as it is entered into the website. Participants will be acknowledged in all study-related publications and presentations.

Discussion

Alternate methods of prompting young drinkers to keep safe while drinking must be explored. These methods should resonate with the population they target. The relevance of the message and of message delivery is an important aspect of intervention success. The high ownership and uptake of mobile technology by young people in many countries [34] makes this medium an ideal vehicle for an intervention that aims to provide safety reminders at relevant times during drinking.

Success of this feasibility study will lead to a full RCT, preparatory to a publicly available website. In addition, an understanding of the self-talk of the study population may provide insight into other avenues that may be pursued to encourage safety while drinking. If the main RCT is successful, the intervention would provide a low-cost method of providing continuous support to risky drinkers.

Authors' Contributions

Ms. Renner conceived of and designed the study with significant input from Dr. Walker and Professor McCormick. Ms. Parag approved the statistical design. Professor Beutow contributed to and reviewed the philosophical rationale behind this approach. Ms. Renner designed the website and smartphone apps and oversaw the development. All authors collaborated on the writing of this paper.

Conflicts of Interest

Ms. Renner is director of a computer software company (Starsoft Ltd) which has developed the website and smartphone apps pro bono for this project. Professor McCormick is an advisor to the Australasian Brewers Association. He critically appraises

literature for the association. The Brewers Association has never provided Professor McCormick with any research funding. Dr. Walker and Ms. Parag do not have competing or conflicting interests.

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Abbreviations

ASSIST: Alcohol, Smoking and Substance Involvement Screening Test
AUDIT-C: Alcohol Use Disorders Identification Test alcohol consumption questions
CHERRIES: Checklist for Reporting Results of Internet E-Surveys
ITT: intention-to-treat
LOCF: last observation carried forward
RCT: randomized controlled trial
RTD: ready-to-drink
SSL: secure socket layer
YAAPST: Young Adult Alcohol Problem Severity Test

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Protocol

A Feasibility and Efficacy Randomized Controlled Trial of an Online Preventative Program for Childhood Obesity: Protocol for the EMPOWER Intervention

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Abstract

Background: The home and family environment is a highly influential psychosocial antecedent of pediatric obesity. Implementation of conventional family- and home-based childhood obesity interventions is challenging for parents, often requiring them to attend multiple educational sessions. Attrition rates for traditional interventions are frequently high due to competing demands for parents' time. Under such constraints, an Internet-based intervention has the potential to modify determinants of childhood obesity while making judicious use of parents' time. Theory-based interventions offer many advantages over atheoretical interventions, including reduced intervention dosage, increased likelihood of behavioral change, and efficient resource allocation. Social cognitive theory (SCT) is a robust theoretical framework for addressing childhood obesity. SCT is a behavior change model rooted in reciprocal determinism, a causal paradigm that states that human functioning is the product of a dynamic interplay of behavioral, personal, and environmental factors. **Objectives:** To evaluate the efficacy of the Enabling Mothers to Prevent Childhood Obesity Through Web-Based Education and Reciprocal Determinism (EMPOWER) program, an Internet-based, theory-driven intervention for preventing childhood overweight and obesity. The project goal is supported by two specific aims: (1) modification of four obesogenic protective factors related to childhood obesity (minutes engaged in physical activity, servings of fruits and vegetables consumed, servings of sugar-sweetened and sugar-free beverages consumed, and minutes engaged in screen time), and (2) reification of five maternal-mediated constructs of SCT (environment, expectations, emotional coping, self-control, and self-efficacy). **Methods:** We will recruit mothers with children ages 4 to 6 years from childcare centers and randomly assign them to either the theory-based (experimental) or knowledge-based (control) arm of the trial. Data for the intervention will be collected at three intervals: baseline (week 0), posttest (week 4), and follow-up (8 weeks). At each phase of data collection, we will collect from both groups (1) measures of the four obesogenic protective factors, and (2) summated SCT construct scores. Constructs will be measured by a psychometrically valid and reliable SCT-based instrument. Behaviors will be evaluated by a behavior log. We will use a repeated-measures one-between-, one-within-participants design to evaluate intervention results. Constructs will be modified through Web-based learning modules, online interactive worksheets, and mother-child home-based activities. Process evaluation will assess program fidelity.

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KEYWORDS

Pediatrics; child; social cognitive theory; family; overweight; obesity; program; intervention

Introduction

Since 1980 the prevalence of childhood obesity has tripled among school-age children and adolescents in the United States [1]. Etiologically, pediatric obesity is strongly influenced by the environment [2]. Researchers have attempted to modify antecedents of childhood obesity in a variety of environmental contexts, including communities, schools, and after-school programs [3]. From an ecological perspective, the home and family environment is perhaps the most influential psychosocial milieu of pediatric obesity. Parents play an integral role in shaping the eating and exercise behaviors of developing children [4]. Furthermore, children consume an estimated two-thirds of their dietary intake within the home environment [5]. As a result, there has been an increased call for interventions that target young children within the context of the home and family environment [6,7].

However, unlike alternative intervention formats that focus on children as the salient agents of change, researchers implementing family- and home-based interventions have discovered that targeting parents exclusively produces more significant outcomes [8-16]. Within the family and home context, there has been a greater focus on targeting mothers as the primary change agents. It has been well established that overweight and obesity disproportionally affect low-income and minority children. Subsequently, there has been a natural proclivity to integrate family- and home-based obesity programming with maternal-based, government-funded nutrition programs such as the Special Supplemental Nutrition Program for Women, Infants, and Children [17]. Additionally, there is evidence that maternal behaviors including gestational weight gain and smoking contribute to higher risk of pediatric obesity [18]. Breastfeeding has also been cited as a protective factor against childhood obesity [19].

While there is little dispute that parents are powerful change agents in the lives of young children, focusing solely on parents presents several challenges. These barriers must be addressed if family- and home-based interventions are to be accepted as an effective preventative treatment for childhood overweight and obesity. The Enabling Mothers to Prevent Childhood Obesity Through Web-Based Education and Reciprocal Determinism (EMPOWER) program will address four salient barriers confronting the advancement of family- and home-based childhood overweight and obesity interventions: (1) efficacy of theory-based family- and home-based interventions, (2) deficit in theoretical construct measurement, (3) low program participation and high attrition rates, and (4) absence of intervention implementation process evaluation.

Efficacy of Theory-Based Interventions

We systematically reviewed randomized control trial family- and home-based interventions targeting children ages 2 to 7 years and found that only 3 of the 9 interventions applied a theoretical framework [20]. It is generally recognized that theory-based interventions are more efficacious than atheoretical interventions [21]. The economic advantages of theory-based interventions are primarily attributed to design and measurement efficiencies. Measurement tools for theory-based interventions

are developed through psychometric modeling. Validated theoretical models can provide detailed insight into the dynamics that underlie behavior change. By reifying the specific theoretical constructs that predict a given behavior, interventionists can design programs that are more likely to result in behavior modification. To evaluate the efficacy of theory-based family- and home-based interventions, our project will compare the social cognitive theory (SCT)-based EMPOWER intervention (experimental) with an equivalent atheoretical, knowledge-based intervention (control).

Deficit in Theoretical Construct Measurement

Although theory-based interventions can produce significant outcome measures, it is critical that interventionists operationalize the theories they employ. Concurrently, researchers must measure changes in the reified constructs from before to after the intervention using psychometrically valid instruments. In doing so, they can evaluate theoretical constructs and advance more effective intervention designs. Without adequate measurement, it becomes difficult to determine which mediating variables were attributed to the positive health outcomes of the intervention. Among the family- and home-based theory-based interventions, we were unable to confirm any that operationalized or measured the constructs of the theoretical frameworks the researchers applied. The current investigation will overcome this deficit by operationalizing and measuring five constructs of SCT.

Low Program Participation and High Attrition Rates

An additional barrier to family- and home-based interventions is the time commitment required of parents to participate in face-to-face educational sessions. Researchers employing family- and home-based interventions have commented that programs emphasizing these modalities have resulted in lower recruitment and retention rates [22]. To maximize participation and retention, our study will employ Web-based learning as the primary catalyst of behavior modification. Online learning offers flexibility and convenience to parents. It also promotes self-paced learning and skill mastery. An Internet-based, theory-driven family- and home-based intervention offers the potential to improve outcome measures, minimize overhead costs, foster program replication, and enable wide-scale intervention dissemination.

Absence of Process Evaluation of Intervention Implementation

Process evaluation is applied in interventions to evaluate program fidelity, dose, reach, stakeholder satisfaction, and exposure of the intervention modalities. Only two of the family- and home-based interventions we reviewed incorporated process evaluation [10,13]. Among these cases, we were unable to verify any that incorporated intervention implementation process evaluation. Implementation process evaluation is a specific type of process evaluation that examines fidelity of program delivery. Assessment of implementation allows the researchers to ensure the program was delivered to the participants in the prescribed fashion. Failure to evaluate program fidelity can make it difficult to confirm whether nonsignificant program outcomes were due to ineffective intervention components or inadequate

transference of intervention deliverables. Our protocol will employ several layers of intervention implementation process evaluation to properly assess outcome measures.

Specific Aims

Specific Aim 1

The American Medical Association, in collaboration with 15 health care organizations, developed a series of recommendations for the prevention and treatment of child and adolescent obesity [23]. The key lifestyle behaviors identified by the committee will serve as the basis for the behavioral outcome measures of this study. The four obesogenic protective factors measured in the intervention will be the child's (1) engagement in 60 minutes of moderate to vigorously intense physical activity each day, (2) consumption of 3 or more cups of fruits and vegetables each day, (3) replacement of sugar-sweetened beverages with sugar-free beverages, and (4) limitation of screen time (television/computer time) to no more than 2 hours per day.

Therefore, the first specific aim of this study is to compare the effects of the EMPOWER intervention (experimental) with an equivalent knowledge-based intervention (control) on the four identified obesogenic protective factors from baseline (week 0) to postintervention (week 4) and 1-month follow-up (week 8) in children ages 4 to 6 years as measured through a valid and reliable behavior log.

Specific Aim 2

SCT is a robust theoretical framework for eliciting behavior change [24]. SCT is based on the premise of reciprocal determinism, a causal model that posits that human functioning is the result of environmental, personal, and behavioral factors. SCT is rooted in human potential and emphasizes modeling, symbolizing, forethought, self-regulatory, and self-efficacy capabilities. The key constructs of SCT will serve as the theoretical outcome measures for the study. The five SCT constructs that will be operationalized for the EMPOWER program will be (1) environment, which comprises the external stimuli to which an individual is exposed, (2) expectations, which are the anticipations that an individual has about a specific outcome and the values the individual places on those outcomes, (3) emotional coping, which is an individual's ability to control emotional and psychological states associated with acquisition of a new behavior, (4) self-control, which results from explicit and specific goal setting for accomplishing a behavior, and (5) self-efficacy, which results from confidence in personal capability to perform a behavior.

The second specific aim of this study is to compare the effects of the EMPOWER intervention (experimental) with a knowledge-based intervention (control) on the five SCT maternal-mediated constructs from baseline (week 0) to postintervention (week 4) and 1-month follow-up (week 8) in

mothers of children ages 4 to 6 years as measured by a SCT-based instrument.

Methods

Instrumentation

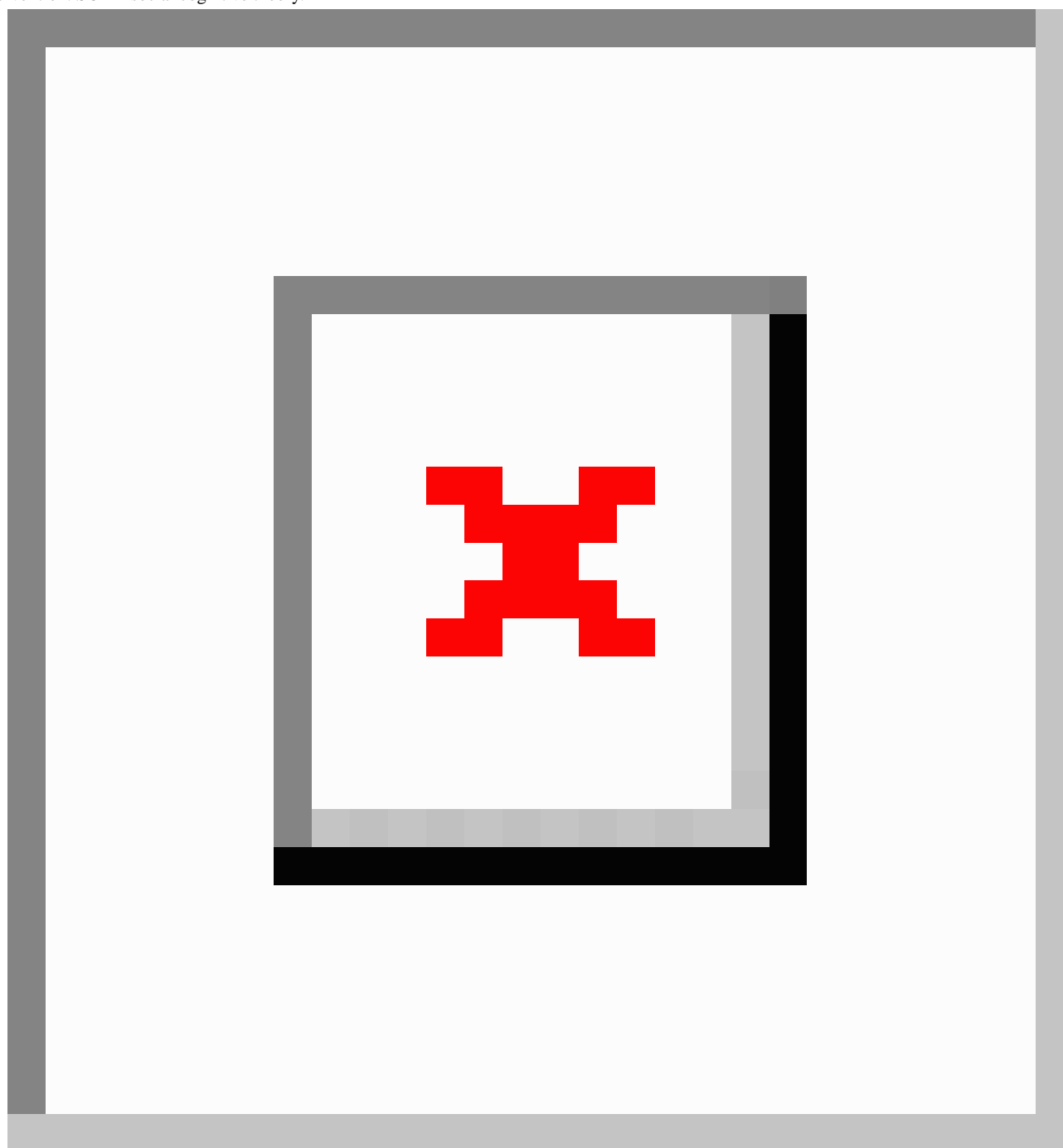
In support of specific aims 1 and 2, we are collecting data to develop an instrument capable of measuring the five listed maternal-mediated SCT constructs for predicting the four obesogenic protective factors outlined in this study. Instrumentation will encompass three stages of data collection and analysis. Stage 1 is complete and included evaluation of face and content validity of the instrument by a panel of six experts over two rounds, in addition to readability assessment by the Flesch Reading Ease Test and Flesch-Kincaid Grade Level Test [25]. The instrument was word processed in Microsoft Word Professional 2010 (Microsoft Corporation, Redmond, WA, USA) and analyzed by the software's readability statistics function. Based on the findings of the software, the instrument had a Flesch Reading Ease Test score of 72%. Scores ranging from 70% to 79% are categorized as "fairly easy" in terms of reading ease [25]. The software populated a Flesch-Kincaid Grade Level test score of 5.7, indicating the reading level of the instrument was between a fifth- and sixth-grade school reading level according to US educational standards [26].

Stage 2 will assess the test-retest reliability of the instrument by having the same group of participants ($n = 30$) complete the instrument two separate times with 4 weeks between administrations. We have set acceptable test-retest coefficient values a priori at 0.70. Stage 3 will evaluate construct and predictive validity of the instrument through structural equation modeling. Each of the four behavioral determinants of childhood obesity (endogenous variables) will be modeled separately according to the five SCT constructs (exogenous variables). Applying a participant to parameter ratio of 5:1, we will require a sample size of 165 to build each model. The final specified models will serve as the theoretical framework for designing and measuring the EMPOWER intervention.

Interventions

The most innovative component of the intervention is the novel medium of delivery (see Figure 1). Despite the highly promising potential of Web-based programs, this modality has not been adequately tested and reported in the childhood obesity intervention literature. The proposed brief intervention will span 2 months. The four obesogenic protective factors will be targeted through weekly online modules for a total of four modules. The Internet-based program will be hosted on the University of Cincinnati's Blackboard Version 9 (Blackboard Inc, Washington, DC, USA) platform. Each week participants will be sent email messages to promote program involvement and participation.

Figure 1. Logic model for the Enabling Mothers to Prevent Childhood Obesity Through Web-Based Education and Reciprocal Determinism (EMPOWER) intervention. SCT = social cognitive theory.



Theory-Based Intervention (Experimental)

Each of the four modules for the experimental group will incorporate affective, cognitive, and experiential pedagogical approaches to promote maternal-mediated behavior change in children based on the five selected SCT constructs. Module curricula will include 15-minute audiovisual sessions developed and produced by the research team. Interactive online worksheets and newsletters will complement each module. The interactive worksheets will be designed to reinforce the concepts conveyed in the audiovisual sessions. Self-efficacy for the four obesogenic protective factors will be built through home-based activities completed by participating mothers and their children.

Knowledge-Based Intervention (Control)

The complementary and equivalent knowledge-based program will also target the four obesogenic protective factors; however, the control program will not focus on modification of SCT constructs. Instead, the program will center on delivery of general health knowledge regarding the four obesogenic protective factors as opposed to theory-based behavior modification. Newsletters and audiovisual sessions will complement each module, but we will not include interactive components designed to increase self-efficacy in the mothers.

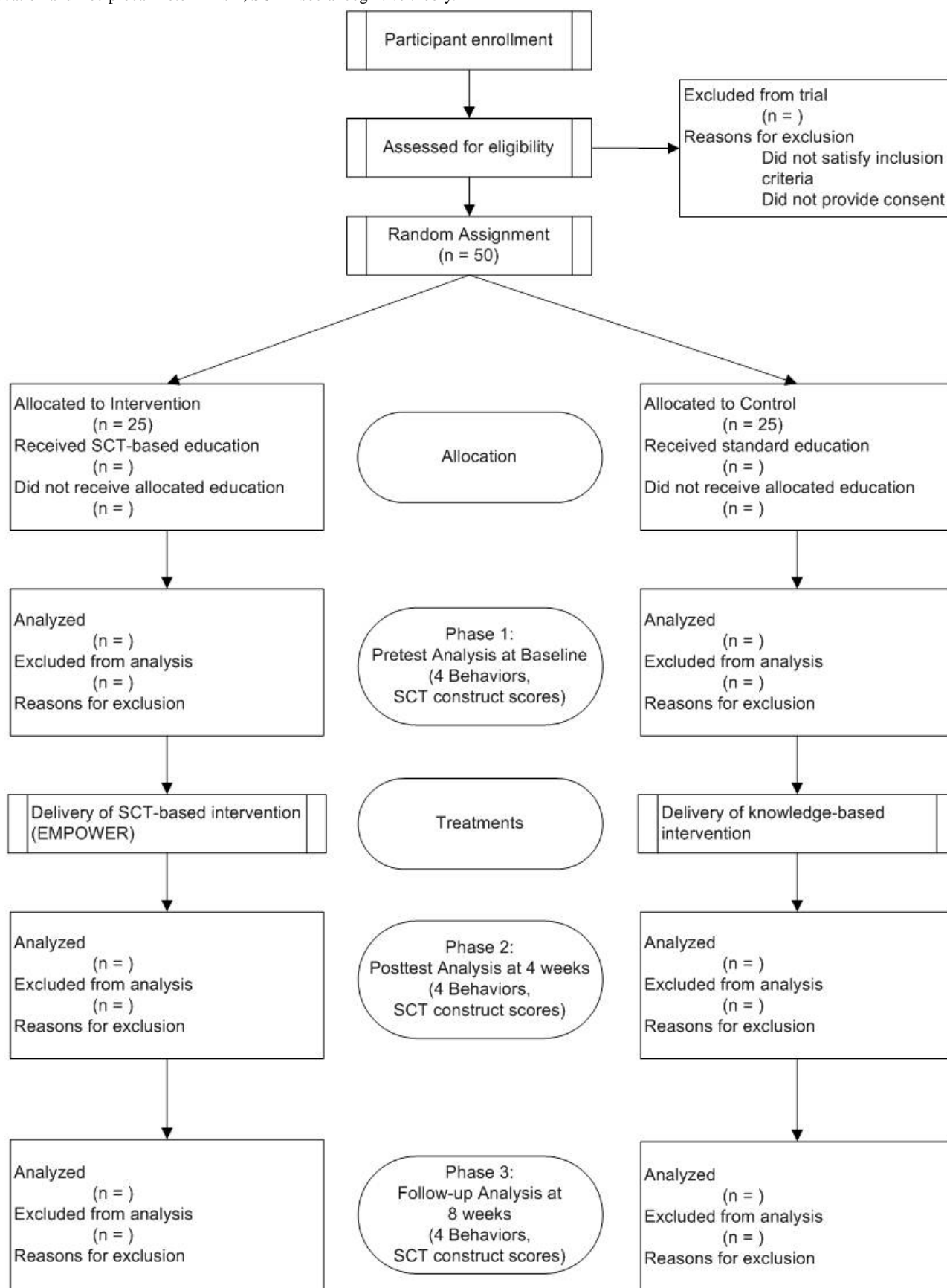
Intervention Design and Sampling

Design

The proposed 8-week program will use a group randomized experimental design to test the efficacy of the protocol. Statistically, we will use a repeated-measures one-between-, one-within-participants design. The protocol will be delivered to two cohorts randomly assigned to receive either the theory-based (experimental) or knowledge-based (control) protocol (see [Figure 2](#)). The primary independent variable in

the proposed study is the intervention. This is a fixed, categorical variable with two levels: EMPOWER intervention and knowledge-based intervention. The second independent variable in the study is time (within-participants effect). This is also a fixed, categorical variable with three levels: (1) baseline, (2) postintervention (at 4 weeks), and (3) 1-month follow-up (8 weeks after baseline). The outcome measures for comparison between the experimental and control groups are the four obesogenic protective factors and the five SCT constructs.

Figure 2. Flow of participants through the randomized control trial. EMPOWER = Enabling Mothers to Prevent Childhood Obesity Through Web-Based Education and Reciprocal Determinism, SCT = social cognitive theory.



Sample Size for Efficacy Trial

Based on previous studies, significance criteria for this investigation were set at an alpha of .05, a power at 80%, and an effect size at 0.20 [12,14,27]. We established the number of groups at 2 and the number of measurements at 3. Correlation between repeated measures was set at .05 and nonsphericity correction at 1. Inputting these criteria into G*Power resulted in a sample size of 42 [28]. To account for potential attrition, we inflated the sample size by 20%, resulting in a total sample size of 50 with 25 participants allocated to each group.

Participant Enrollment

We selected mothers as the primary agents of change in this intervention [29-33]. Children ages 4 to 6 have been targeted for this study because this age range has been demonstrated to be a strong predictor of future health [30,34]. Eligibility to participate in the intervention will be limited to the following inclusion criteria: (1) mothers with (2) high-speed Internet access, (3) working email, and (4) at least one child in the age range of 4 to 6 years. Exclusion criteria will be (1) non-English-speaking mothers, (2) pregnant mothers, and mothers with (3) a child outside the age range of 4 to 6 years, (4) a child inside the age range of 4 to 6 years with a physical disability that would interfere with participating in daily moderate to vigorously intense physical activity, (5) a child with a medical condition associated with weight gain, (6) a child prescribed medication associated with weight gain, or (7) a child enrolled in an additional weight management program. We will seek and obtain university institutional review board approval before implementing the intervention. Eligible mothers will be required to provide consent prior to enrollment. Children will be required to provide oral assent prior to enrollment.

Participant Recruitment

The intervention will target the general population in Cincinnati, Ohio, USA. We will recruit 50 families from 10 to 15 local childcare centers (preschools, daycares, and kindergartens) to participate in the investigation [15]. Childcare center recruitment will entail calling local childcare center managers and requesting their support for the initiative. Presentations will be made to the childcare center managers describing the benefits of the program. During the presentations, we will emphasize the childcare centers' role as a community stakeholder to garner support. Participant recruitment activities will include delivering flyers and 15-minute presentations to potential recipients at the childcare centers.

Random Assignment

Eligible, consenting participants will be randomly assigned to either the theory-based (experimental) or knowledge-based (control) arm of the trial. The participant assignment protocol will be based on block randomization (block size will remain confidential to maintain allocation blindness). Allocation of block assignment will be determined using random number generator computer software. Participants will not know to which cohort they have been assigned to improve external validity. However, as we will recruit participants within the same childcare facilities, it is possible there will be spillover effects between the intervention and control groups. For

example, mothers in the intervention group may share what they are learning with mothers in the control group. To buffer this effect, we will ask participants not discuss intervention-based activities with others in the facility. Maintenance of confidentiality will be evaluated through process evaluation at the beginning and end of the intervention.

Process Evaluation

Process evaluation will occur concurrently with each module to assess program fidelity and dose. Process evaluation is akin to quality control, in which standardized methods are employed to ensure programming is delivered systematically to all participants. In the absence of process evaluation, researchers increase the risk of committing a type III error. From a quality control perspective, a type III error occurs when weak or null results occur due to inconsistent or inadequate intervention delivery. To reduce the risk of committing a type III error, the proposed intervention will incorporate several layers of implementation process evaluation:

- Log-in codes and tracking data will be used to assess whether the website and subsequent module materials were accessed.
- Date and duration of activity will be logged to assess whether audiovisuals were viewed and adequate time was spent to complete each activity.
- Online, interactive worksheets and module quizzes will have forced-response validation to gauge transference of information.
- Reminder emails will be sent to assess promotion.
- At the completion of the intervention, respondents will be requested to complete an open-ended questionnaire regarding acceptability and perceived usefulness of the program. Additionally, data regarding maintenance of confidentiality will be collected.
- Participants who drop out of the program will be contacted and asked why they discontinued the intervention. To help control for attrition the sample size has been inflated by 20% above what was required by the study power analysis.

Data Analysis

We will collect data for the intervention over three phases: phase 1 at baseline (week 0), phase 2 at posttest (week 4), and phase 3 at follow-up (week 8). At each phase of data collection, we will collect from both groups (1) measures of the four obesogenic protective factors, and (2) summated scores for the SCT constructs. SAS version 9.3 (SAS Institute, Cary, NC, USA) will be used to conduct statistical analyses of the intervention. Each of the outcome measures will be tested using PROC MIXED to analyze the data collected in the repeated-measures statistical design. The model will account for gender (male, female) as a potential covariate.

The null hypothesis for the time effect is that the means of the outcome measures at each of the three levels will be equal. If we find statistically significant differences, we will plot least square means and apply the Scheffé post hoc test. Normality of the distribution of outcome measures, homogeneity of variances, and the Mauchly test of sphericity will be used to test the assumptions of repeated-measures analysis of variance.

Variables that are not normally distributed or that display variance heterogeneity will be transformed to obtain distributions that are closer to normality and variance homogeneity. The Huynh and Feldt adjustment to any *F*-distribution degrees of freedom will be applied if the covariances between the repeated measures being analyzed do not follow a spherical distribution.

Discussion

The proposed project will advance the fields of public health, health promotion, and health education through the following means.

Optimization of Multicomponent Programs

While many interventionists employ theories of human behavior in designing their programs, few measure and evaluate the changes in the theoretical constructs they apply. The current proposal will employ construct operationalization and intervention delivery process evaluation to identify which constructs of the SCT have the largest impact on obesogenic protective factors in the target population. Optimization of SCT constructs will assist health practitioners in shaping public health policy, facilitating resource allocation for future interventions, and fostering educational advancements.

Intervention Delivery

Implementation of traditional family- and home-based interventions in the target population is challenging for parents, often requiring them to attend numerous educational sessions. Even with incentives, attrition rates for traditional interventions are often high due to competing demands for parents' time. Given the current economic climate, time constraints are likely to intensify for parents, making traditional intervention delivery more problematic. Under such constraints, an Internet-based

intervention has the potential to modify antecedents of childhood obesity while making judicious use of parents' time. An efficacious online, theory-driven, family- and home-based intervention will offer health practitioners a novel vehicle for addressing childhood overweight and obesity in the target population.

Limitations of the Proposed Protocol

The proposed protocol is not without limitations. Analysis of the study's specific aims is limited by the self-reporting accuracy, integrity, and honesty of the participants. Participants will be requested to provide information on the four obesogenic protective factors and constructs of SCT. Inaccuracy in memory or misinterpretation of instrument items may skew the final analysis. Even with accurate self-reporting, the proposed timeline may not be sufficient to detect statistically significant differences in behaviors from before to after the intervention. Additionally, the four obesogenic protective behaviors will be based on 24-hour recall, which may not be representative of a typical day.

Participation in this study will be voluntary and will require both the parent's and child's assent. Childhood obesity is a sensitive topic, and some parents may not wish to have their child participate, believing that involvement in such an intervention speaks ill of their parenting skills. Children may not wish to participate for various reasons such as embarrassment or a lack of interest. In the current proposal, we target mothers as the primary agent of change. This is in tandem with the majority of family- and home-based interventions; however, researchers are increasingly calling for more involvement of fathers and grandparents [35]. Limiting the intervention only to mothers increases efficiency for a pilot study but invariably is not inclusive of the entire familial environment.

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Conflicts of Interest

None declared.

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Abbreviations

EMPOWER: Enabling Mothers to Prevent Childhood Obesity Through Web-Based Education and Reciprocal Determinism

SCT: social cognitive theory

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Protocol

Internet-Based Intervention to Promote Mental Fitness in Mildly Depressed Adults: Design of a Randomized Controlled Trial

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Abstract

Background: Investing in mental well-being is considered a supplement to current mental health service delivery in which the treatment and prevention of mental disorders are core components. It may be possible for people to enhance their well-being by boosting their “mental fitness.”

Objective: Psyfit, an online, multi-component, fully automated self-help intervention, was developed with the aim of improving well-being and reducing depressive symptoms. The efficacy and cost-effectiveness of this intervention will be examined in a randomized controlled trial.

Methods: In this two-armed randomized controlled trial, a total of 290 participants will be assigned to use Psyfit (experimental condition) or to a 6-month waiting list (control condition). Adults with mild to moderate depressive symptoms interested in improving their mental fitness will be recruited from the general population through advertisements on the Internet and in newspapers. Online measurements by self-assessment will be made prior to randomization (pre-test), 2 months after baseline (post-test), and 6 months after baseline (follow-up).

Results: The primary outcome is well-being. Secondary outcomes are depressive symptoms, general health, vitality, and economic costs. Analysis will be conducted in accordance with the intention-to-treat principle.

Conclusions: This study will examine the efficacy and cost-effectiveness of an online intervention that aims to promote well-being in people with elevated levels of depressive symptoms. If shown to be effective, the intervention could prove to be an affordable and widely accessible intervention to improve well-being in the general population.

Trial Registration: The study is registered with the Netherlands Trial Register, part of the Dutch Cochrane Centre (NTR2126).

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KEYWORDS

Mental health; public health; preventive medicine; depression, well-being; happiness

Introduction

Depression, anxiety disorders, and alcohol dependency are highly prevalent mental disorders [1,2] and among the 10 disorders with the greatest disease burden [3]. These disorders are associated with reduced quality of life [4] and high economic costs due to productivity losses and high levels of health service uptake [5]. In addition, many more people suffer from poor well-being [6], subclinical depression [7], and stress at work [8] putting them at greater risk of developing a mental disorder later on. In the current dynamic and innovative knowledge- and service-driven economy, more people are faced with mentally demanding jobs. This places unique demands on people's emotional, social, and cognitive capacities [9,10]. Countries are challenged by the adverse consequences stemming from these demanding circumstances, such as burnout, absenteeism, and subsequent economic costs. Therefore, it is important to reach people at an early stage when the development of a full-blown mental disorder might still be prevented. So far, preventive interventions developed for this reason focus mainly on the prevention of mental health problems and disorders, and less on the improvement of well-being [11].

The World Health Organization (WHO) defines mental health as "a state of well-being in which the individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively, and is able to make a contribution to his or her community." This definition of mental health represents a paradigm shift from focusing on the narrow medical constructs of illness and disease only, to embracing well-being as well [12].

The WHO definition also underscores the notion that mental health is not merely the absence of mental illness. Well-being and mental illness, although correlated, are independent concepts and not just opposites on a single continuum. People presenting with low levels of well-being have similarly poor psychosocial outcomes as people suffering from mental illness [13]. Likewise, people with mental disorders are capable of experiencing well-being, to some degree [14]. In general, people with high levels of well-being are physically healthier, live longer, are more productive at work, and use less health care [15,16]. Longitudinal and experimental evidence suggests that positive affect and well-being may generate these desirable outcomes [17]. The available evidence suggests that the enhancement of well-being might be a valuable public health strategy in mental health promotion.

With this positive approach to mental health in mind, we developed an Internet-based self-help intervention ("Psyfit") aimed at the promotion of well-being. Below, we elaborate on the public health rationale for this type of intervention, including the definition of well-being, the relevance of the Internet as an implementation vehicle, and the use of positive psychology interventions as a starting point.

Definition of Well-being

There are three different types, or concepts, of well-being. The first is subjective well-being, which is a cognitive and/or affective appraisal of one's own life as a whole and seeking a

balance between positive and negative emotions [18]. The second is the concept of psychological well-being. This concept builds on the work of Carol Ryff who was dissatisfied with the emphasis on subjective well-being and focused more on the optimal functioning of the individual [19]. In Ryff's view, psychological well-being contains six elements: self-acceptance, autonomy, environmental mastery, personal growth, purpose in life, and personal relations with others. According to this view, the attainment of personal happiness is not the goal in life, but rather self-actualization and meaning. The third concept arose from the work of Corey Keyes who called for a broader and less self-centered orientation towards well-being and for the expansion of subjective and psychological well-being to include social well-being; in other words, a complete state model of mental health [6]. Social well-being refers to the extent to which a person feels at home in society, trusts other people, and makes sense out of the world. The WHO's definition is clearly rooted in this perspective.

Using the Internet: eHealth

The promotion of well-being requires the delivery of effective and accessible interventions aimed at sustainable behavioral change. The Internet might offer the opportunity to reach this goal. Using persuasive technology techniques, programs designed to change attitudes and behaviors can be made for computers, game systems, and mobile devices [20] so that they are highly engaging and enjoyable at the same time. Internet interventions are defined as highly structured; self- or semi self-guided; founded on evidence-based, face-to-face interventions; tailored to provide follow-up and feedback; personalized to the user; interactive; and enhanced by animation, audio, or video technology (if possible) [21].

eMental Health interventions can vary from plain information, tailored advice, single exercises, and interactive self-help programs to structured online therapies with or without guidance from a therapist. The major advantages of eMental Health are that Internet interventions can be offered on a broad scale, they are able to engage hard-to-reach people, and they can reduce therapists' time (ie, reduce costs) [22].

In the field of Internet interventions, the efficacy of interventions aimed at the reduction of depressive symptoms or anxiety has been demonstrated meta-analytically [23]. The majority of these programs are based on cognitive behavioral therapy [24] and problem-solving therapy [25,26].

Positive Psychology Interventions

The positive psychology movement has developed many interventions that focus on flourishing and positive functioning. These include counting one's blessings [27-29], practicing kindness [30,31], setting personal goals [32-34], expressing gratitude [28,29], and using personal strengths [28]. A comprehensive meta-analysis of 51 positive psychology interventions has demonstrated moderate effect sizes for enhancing well-being and reducing depressive symptoms [35].

However, experimental research on well-being interventions offered over the Internet is still scarce and the results are mixed. A randomized controlled trial with 2 separate interventions (working with your strengths and problem solving) and a

placebo control group showed mixed results [36]. Well-being was improved, but there was not a significant impact on mental illness. In another trial [28], the Internet was used for the recruitment of participants and the collection of data. The single exercises (using signature strengths in a new way and recapitulating three good things) enhanced well-being and reduced depressive symptoms for up to 6 months. Also, “writing and reading a gratitude letter” was effective, but only in the short term. However, a more critical look at the interventions reveals that these exercises were not truly Internet-based interventions as described in the previously cited definition by Ritterband [21] because the interventions were neither interactive nor personalized. Another two randomized controlled trials examined the effects of multi-component interventions [37, 38]. In a workplace setting, an intervention called “Resilience Online” did not demonstrate any significant effects [37]. In another study using an online version of positive psychotherapy, depressive symptoms were significantly reduced, but there was no improvement in subjective well-being [38].

The Current Study

The aim of this study is to evaluate the efficacy and cost-effectiveness of Psyfit, an online well-being program [39]. The study will add to the existing literature by testing a multi-component and flexible Internet-based intervention to promote well-being. To date, the research in this area is limited to either single interventions focusing on one well-being exercise at a time [28, 36] or to multiple protocol-based interventions [37,38]. In these studies, participants in the intervention groups are allocated to an inflexible intervention, although most people would prefer to choose what they need and feel up to doing [30,40,41]. For this reason, Psyfit offers a choice of different interventions that participants can tailor themselves.

The primary objective of this study is to evaluate the effectiveness of the Psyfit intervention in comparison to a waiting list control group. We hypothesize that the intervention group will demonstrate a significant increase in well-being and a reduction in depressive symptoms at post-test and follow-up compared to the control group. Secondary study objectives are to conduct an economic evaluation and to examine if particular subgroups benefit differently (ie, more or less) than others from the intervention.

Methods

Study Design

This study is designed as a randomized trial with two parallel groups. In the experimental condition, participants will receive 2 months free access to Psyfit. In the control condition, participants will be put on a waiting list for 6 months before they are offered access to Psyfit. The study is designed to compare the efficacy and cost-effectiveness of Psyfit relative to the waiting list control condition. A secondary objective is to examine whether certain groups (eg, based on depressive symptoms, gender, and education level) benefit differently from the intervention. Participants in both conditions will have unrestricted access to professional help, if needed. The study protocol, interventions, participant information, and informed consent procedure have been approved by the Dutch Medical

Ethics Committee for Mental Health Care (METIGG), under registration number 9218.

Inclusion and Exclusion Criteria

The participant group is defined as everyone willing to improve their “mental fitness.”

Participants will be included if they: (1) are 21 years or older; (2) present with very mild to moderate depressive symptoms with a score between 10-24 on the Center for Epidemiological Studies Depression Scale (CES-D); (3) have moderate or low levels of well-being as measured with the Mental Health Continuum-Short Form (MHC-SF); (4) have access to a computer and the Internet; and (5) have sufficient knowledge of the Dutch language. The CES-D [42] and MHC-SF [43,44] inclusion and exclusion scores are based on established cut-off points.

People with serious depressive symptoms (CES-D score ≥ 25) or active suicidal thoughts or plans (determined from the Web Screening Questionnaire [45]) will be excluded from this study. Those who fail to meet these selection criteria will be notified by email and will be advised to contact their general practitioner if their depressive symptoms exceed the threshold limit. In cases of suicidal ideation, people will be urgently referred to the national online suicide-prevention platform for help.

Recruitment

Participants will be recruited through banners on Internet websites related to mental health and well-being. In addition, advertisements will be placed in newspapers and monthly magazines on health-related topics.

The recruitment message for the study is formulated positively (ie, not with a focus on symptoms and problems): “Would you like to increase your mental fitness? Would you like to feel better? Improve your mental fitness and participate in our study of an online self-help program, Psyfit.” The analogy is made with physical fitness: “There are certain lifestyle behaviors you could adopt that can make you feel mentally fit.” Preliminary focus group research has shown that people with minor mental health problems, those experiencing stress, or those who just “don’t feel good” are attracted by the “mental fitness” message [46].

The advertisements will include the website address where people can register for Psyfit (www.psyfit.nl). This website contains complete information about the study and a demonstration video of the intervention. Those interested in participating can leave their name and email address. The email and Internet Protocol (IP) addresses will be checked for multiple registrations. Following this, prospective participants will receive an email with additional information about the study and a link to the online informed consent form and online questionnaire.

Randomization

The online randomization procedure will be carried out at the individual level. After returning the informed consent form and completing the baseline questionnaire, people who meet the inclusion criteria will be randomly allocated to the experimental

group (Psyfit) or to the waiting list and they will be notified by email. Randomization will be stratified by gender, education, and severity of symptoms based on CES-D scores (scores between 10-15 and 16-24). A computer program will allocate participants using a generated randomization list. Block randomization in blocks of two will be performed to ensure equal distribution of participants across conditions.

Intervention Group: Psyfit

Psyfit is offered as an online and fully automated self-help intervention without active support from a therapist (see [Figure 1](#) for a screenshot of the intervention). Participants tailor their own intervention program to their personal needs and measure their progress by several self-tests. In addition, they can discuss their experiences in an online community accessed via Psyfit.

The content of the well-being program, Psyfit, is based on an extensive literature review [10]. Elements in the intervention originate from positive psychology [28,35], mindfulness [47], cognitive behavioral therapy [48], and problem-solving therapy [49].

Psyfit consists of six modules, each containing a 4-week program:

1. Mission and goals (living from a deeply felt mission and personal values);
2. Positive feelings (positive thinking and working on your positive affect);

3. Positive relations (connection with other people and your environment);
4. Living in the moment (consciously living and enjoying);
5. Thinking and feeling (change negative thinking patterns, optimistic thinking); and
6. Master your life (managing personal energy, stress, and problems).

In theory, each module is likely to have impact on well-being. During the study, the Psyfit website is accessible only to the participants in the experimental group. An email will be sent to each participant assigned to Psyfit with a personal username and password. From the moment the participant logs on, a 2-month free access to the intervention is activated. If a participant doesn't log on, a reminder email with the log-on codes will be sent after one week and, if necessary, after two weeks and again after three weeks. Participants are allowed to use the program at any time they want during the trial period. Participants are advised to choose and finish at least one module during the intervention period. During each 4-week module, participants receive background information on the specific subject, view short films, and receive a weekly assignment that they are expected to complete during that week. On average, this takes 20 to 30 minutes each day.

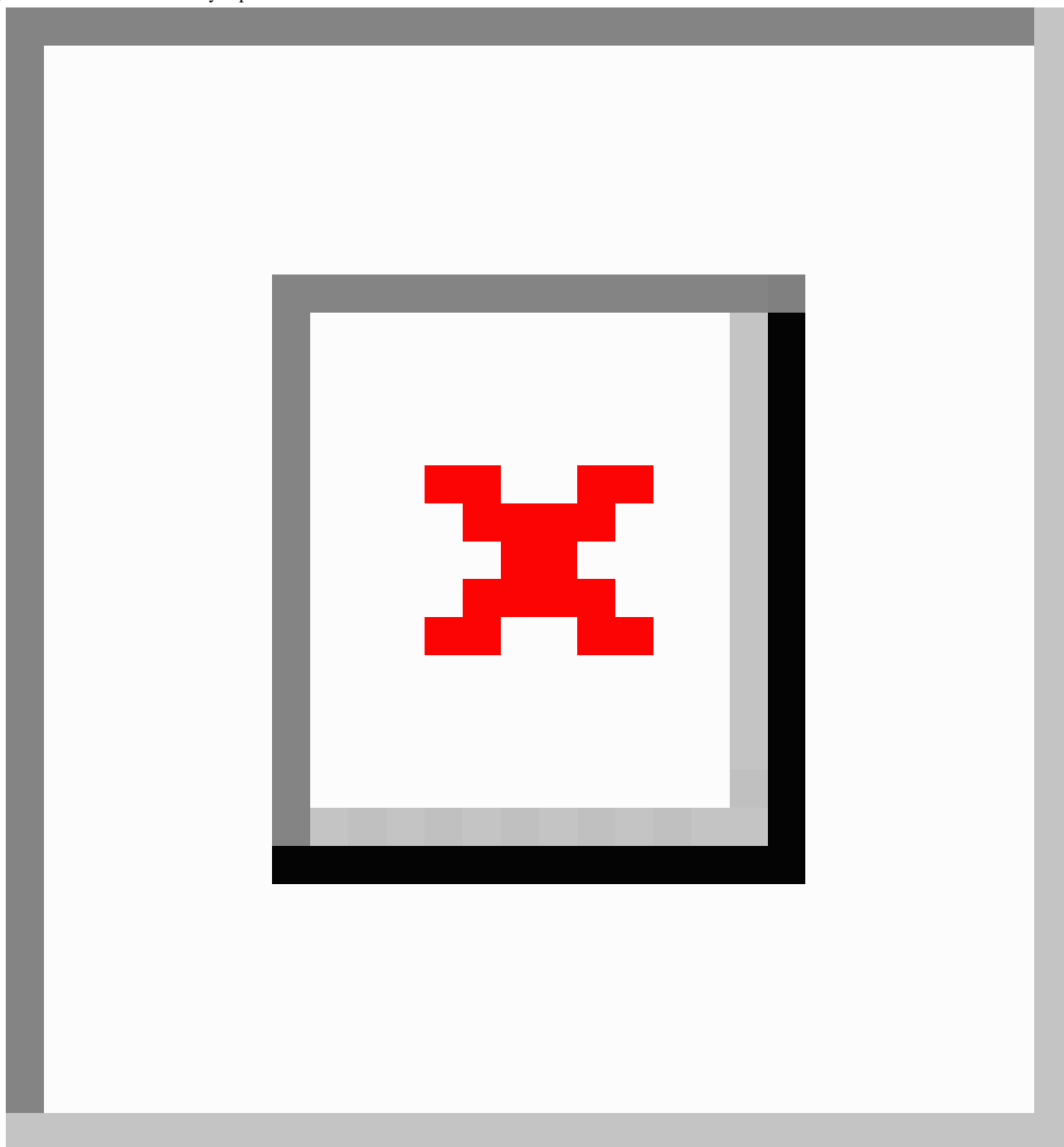
Participants are free to use all other functionalities offered in Psyfit and can always choose to start a new module. For an overview of functionalities, see [Textbox 1](#).

Textbox 1. Functionalities in Psyfit

- General self-test to assess individual well-being level beforehand and after 2 months.
- A personal plan in which the participant can reflect on his or her goals, motives, and pitfalls.
- A "mood meter" for monitoring changes in the mood of the participant. The outcomes are presented in a graph.
- Automatic email service twice a week with reminders, tips, and advice.
- Online community for sharing experiences and peer-to-peer support.
- Contact form: participants can ask questions and receive feedback from a psychologist via email. If required, the participant is referred to professional care. Technical assistance is also provided.
- "My Psyfit": the participant can download and print out a personal PDF blueprint of the intervention with all the modules, exercises, and progress measurements completed.
- Videos: each module starts with a video showing a Dutch expert explaining the relevance of this particular module.
- Module self-tests: each module starts and ends with a short self-test to see if the particular skill has improved.

The participant can work through the intervention independently (self-help) but can fill in a contact form with a question if necessary. Psyfit could be likened to a toolbox from which people can "pick and mix" whatever they like and need. The

web statistics module will systematically track and trace the actions of each participant, such as the number of log-on times, the time spent on the website, and the modules chosen. This enables adherence to the intervention to be examined.

Figure 1. Screenshot of the Psyfit portal.

Control Group

Participants in the control condition are placed on a waiting list for 6 months. After a 6-month follow-up assessment, they will receive their personal user name and password for Psyfit.

Assessments

The primary outcome measure is well-being. Secondary outcome measures include depressive symptoms, general health and vitality, and economic costs (as measured by health care use, days of absence, inefficient job performance, and work productivity). For an overview of outcomes and instruments, see [Table 1](#).

Measurements will be taken at baseline (pre-test), directly after the intervention (post-test, 2 months after baseline), and 6 months later (follow-up). All measurements are self-report measures and will be administered via email with a link to the questionnaire on the Internet.

High dropout rates are a characteristic feature of online trials and can be as high as 50% [50]. Therefore, email reminders and rewards (eg, raffle of six iPods and vouchers) for filling in the questionnaires will be used. It is expected that this will lead to a lower attrition rate.

Table 1. Questionnaires and assessment times.

Questionnaire ^a	Measurement	T0	T1	T2
		Pre-test	Post-test ^b	Follow-up ^c
MHC-SF	Well-being/positive mental health	X	X	X
WHO-5	Well-being	X	X	X
CES-D	Symptoms of depression	X	X	X
MOS SF-36 subscales	Vitality and general health	X	X	X
TIC-P and PRODISQ	Health service uptake and production losses	X	X	X
CSQ-8	Client satisfaction		X	
Demographics	Age, gender, education, marital status, job status	X		

^a all questionnaires are discussed within Instruments section

^b 2 months after T0

^c 6 months after T0

Instruments

Well-Being and Positive Mental Health

Well-being will be assessed with two questionnaires measuring different concepts. The Mental Health Continuum-Short Form (MHC-SF) [51] is a 14-item self-report questionnaire that categorizes measures of well-being as “languishing,” “moderate,” or “flourishing.” Participants rate the items on a 6-point scale from 0 (never) to 5 (every day). The MHC-SF measures subjective well-being as well as psychological and social well-being. These aspects are all addressed in Psyfit; therefore, this questionnaire was chosen. The MHC-SF has shown good internal consistency ($> .80$) and discriminant validity [44,52].

The WHO-Five Well-being Index (WHO-5) contains 5 positively formulated items on mental health [53]. Participants are asked to rate the items using a 6-point scale ranging from 0 (never) to 5 (all of the time). The WHO-5 has been validated in different populations [53] and is useful as a screening instrument for depression [54]. It was chosen as a measurement instrument because of its brevity and the concurrent validity with depression.

Depressive Symptoms

Depressive symptoms will be measured by the Dutch version of the Center for Epidemiological Studies Depression Scale, the CES-D [55]. The CES-D is a 20-item self-rating scale with item scores ranging from 0 to 3 (higher scores indicating more depression), and a total score from 0 to 60. The CES-D has acceptable reliability and validity with a cut-off score of 16 for mild depressive symptoms [42] and a cut-off score of 25 for severe depressive symptoms [56]. When applied via the Internet, the CES-D appears to be a reliable and valid instrument [45].

Vitality and General Health

Two quality of life related constructs, “vitality” and “general physical health” will be measured with two scales from the Medical Outcomes Study Short Form-36 (MOS SF-36) [57]. The vitality subscale contains 4 items which are rated on a

4-point scale ranging from 1 (all the time) to 6 (never). The “perception of general health” subscale consists of 5 items which are rated on a 5-point Likert scale (1 = “exactly right” to 5 = “exactly wrong”). The MOS SF-36 has demonstrated good reliability and validity [58].

Economic Costs

The economic evaluation will be conducted from a societal perspective. It includes utilization costs of any type of health care and medicines (direct medical costs), costs incurred by the participants for travel and parking (direct non-medical costs), and costs due to production losses (indirect non-medical costs) [59,60]. All costs will be expressed in Euro (€) on an annual per capita basis for the reference year 2010. Data on direct medical and non-medical costs are obtained by using the Dutch Cost Questionnaire for Psychiatry (TIC-P) [59]. Six items from the Productivity and Disease Questionnaire (PRODISQ) will be used to measure indirect non-medical costs [61] stemming from productivity losses due to days of absence and presenteeism/inefficient job performance.

Other Variables

Participant satisfaction with the intervention will be measured with an adapted Dutch version of the Client Satisfaction Questionnaire-short form (CSQ-8) [62,63]. The internal consistency of this scale in the Dutch population is very high (Cronbach alpha = .93). The 8-item self-report questionnaire has a scale ranging from 1 to 4 and a total score range from 8 to 32.

Furthermore, participants will be asked about important life events and whether they are currently receiving treatment from a mental health specialist.

Sample Size

Depressive symptoms and well-being are used as a starting point for the power calculation. We aim to be able to show differences between Psyfit and the waiting list control condition with a standardized effect size (Cohen's d) of 0.33 or larger. A standardized effect of 0.33 can be considered as the lower limit of a moderate clinical effect [64] and is based on a meta-analysis

of well-being intervention research [35] and a recent randomized controlled trial [36]. To demonstrate this effect, and assuming an alpha of 0.05 and a statistical power (1-Beta) of 80%, we need 145 participants in each condition; therefore, we need 290 participants in total for the trial.

Analysis

Results will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement regarding eHealth [65,66]. We will adhere to the intention-to-treat (ITT) principle, which means all participants who have been randomized will be included in the analyses. Missing data at T1 and T2 will be imputed using the expectation-maximization (EM) method, as implemented in Statistical Package for the Social Sciences (SPSS) Missing Value Analysis. The program imputes missing values by maximum likelihood estimation using the observed data in an iterative process [67]. In online trials dropout is to be expected, and sometimes a large amount of missing data has to be estimated. Although ITT analysis is the approach of choice according to the CONSORT statement, there may also be pitfalls, such as when the missing-at-random assumption is not plausible and the results of the analysis are subsequently biased [68]. Therefore, a completers-only analysis and a per-protocol analysis will be conducted in addition (sensitivity analysis). Reasons for dropout in the study will be checked at random by telephone follow-up (dropout analysis).

To examine differences between the two conditions, we will use multiple regression analyses with the clinical outcomes on continuous measures (MHC-SF, WHO-5, CES-D, and the vitality and general health scales from MOS SF-36) as dependent variables and an intervention-control group dummy as predictor variable. We will compute standardized effect sizes (Cohen's *d*). Cohen's *d* is computed by subtracting the mean post-test intervention score from the mean post-test control group score and dividing the difference by the pooled standard deviation [69].

Moderator analyses will be conducted to examine which groups benefit more (or less) from the intervention by regressing the outcomes on independent variables such as gender, education, mild/moderate depressive symptoms, the treatment dummy, and the interaction with the treatment dummy and the selected independent variables.

The economic evaluation will be conducted from a societal perspective, thus including the intervention costs (ie, Psyfit), the costs of health care uptake (TIC-P), the participants' out-of-pocket costs for obtaining health care (TIC-P), and the economic costs due to productivity losses in paid work (PRODISQ). The incremental cost-effectiveness ratio (ICER) will be calculated. Uncertainty in the ICER will be captured using a bootstrap approach, producing a scatter of simulated ICERs over the ICER-plane and by drawing an ICER acceptability curve of the likelihood that Psyfit is more cost-effective for a range of willingness-to-pay (WTP) ceilings.

All analyses will be conducted using two-sided tests and alphas of .05. For this purpose, the most recent version of the SPSS software will be used.

Discussion

This online trial will examine whether an Internet-based self-help intervention for the enhancement of well-being is effective in terms of clinical outcomes and economic costs. A second objective is to examine whether certain groups benefit more or less from the intervention. The enhancement of well-being on a large scale may contribute to public mental health by resulting in better health, fewer mental disorders, and enhanced quality of life on a population level [11,70].

This study has several *a priori* limitations. First, dropout may occur in either of the two groups. To examine any selectiveness, we will conduct dropout analysis and a telephone survey for examining reasons for dropout. Moreover, we will conduct intention-to-treat analyses in which missing values are replaced by their most likely estimates. Second, we will only use self-report questionnaires, not formal diagnostic instruments, to establish diagnoses. Therefore, we will not know whether participants meet the criteria for a Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) diagnosis so results about prevention of mental disorders will not be available. We opted for self-rating because the intervention should be easily accessible and highly applicable because of its public nature. We don't want to scare people off by intensive diagnostic procedures. A third limitation of this study concerns the use of questionnaires that are not (yet) validated for online purposes. Psychometric properties of online assessments may differ from their paper-and-pencil counterparts [71]. On the other hand, the CES-D [45] and the MHC-SF [52], which are used in this study, have been proven to be reliable and valid instruments even if used on the Internet. Finally, the open recruitment strategy may attract certain groups, for example, more higher-educated people or more spiritually engaged and higher-motivated people. Therefore, care must be taken in generalizing the results.

Our study also has several strengths. It is likely to add to the existing literature because it is—at least to our knowledge—the first evaluation of an online flexible and multiple-component intervention aimed at the improvement of well-being to include people with mild depressive symptoms. As such, we will be able to draw conclusions about the potential impact of such an intervention on mental health. Although the recruitment procedure could be a weakness as previously mentioned, at the same time it creates the opportunity to strengthen external validity (real world implementation potential) by analyzing which target groups are attracted by the “open access” and positively formulated recruitment strategy.

Online interactive programs may attract large numbers of people, therefore, even small or moderate effect sizes can have an impact on population health. If proven to be effective, Psyfit may be an affordable instrument that can be distributed on a large scale to enhance population well-being.

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Conflicts of Interest

Linda Bolier and Merel Haverman are the developers of Psyfit.nl.

Authors' Contributions

LB is the principal investigator and wrote the manuscript. MH is responsible for recruitment of participants and data collection. All authors contributed to the design of the study. EB, BB, JK, and FS are advisors in the project. HR obtained funding for the study. All authors provided comments and approved the final manuscript.

Multimedia Appendix 1

CONSORT-EHEALTH checklist (V1.6) [72].

[PDF File (Adobe PDF File), 556KB - [resprot_v1ile2_app1.pdf](#)]

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Abbreviations

CES-D: Center for Epidemiological Studies Depression Scale

CONSORT: Consolidated Standards for Reporting Trials

CSQ-8: Client Satisfaction Questionnaire

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition

EM: expectation-maximization

ICER: incremental cost-effectiveness ratio

IP: Internet Protocol

ITT: intention-to-treat

METIGG: Medical Ethics Committee for Mental Health Care

MHC-SF: Mental Health Continuum-Short Form

MOS SF-36: Medical Outcomes Study Short Form (36 items)

PRODISQ: Productivity and Disease Questionnaire

SPSS: Statistical Package for the Social Sciences

TIC-P: Trimbos Institute and Institute of Medical Technology questionnaire for Costs associated with Psychiatric illness

WHO: World Health Organization

WHO-5: WHO-Five Well-being Index

WTP: willingness-to-pay

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Protocol

Wikis and Collaborative Writing Applications in Health Care: A Scoping Review Protocol

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Abstract

The rapid rise in the use of collaborative writing applications (eg, wikis, Google Documents, and Google Knol) has created the need for a systematic synthesis of the evidence of their impact as knowledge translation (KT) tools in the health care sector and for an inventory of the factors that affect their use. While researchers have conducted systematic reviews on a range of software-based information and communication technologies as well as other social media (eg, virtual communities of practice, virtual peer-to-peer communities, and electronic support groups), none have reviewed collaborative writing applications in the medical sector. The overarching goal of this project is to explore the depth and breadth of evidence for the use of collaborative writing applications in health care. Thus, the purposes of this scoping review will be to (1) map the literature on collaborative writing applications; (2) compare the applications' features; (3) describe the evidence of each application's positive and negative effects as a KT intervention in health care; (4) inventory and describe the barriers and facilitators that affect the applications' use; and (5) produce an action plan and a research agenda. A six-stage framework for scoping reviews will be used: (1) identifying the research question; (2) identifying relevant studies within the selected databases (using the EPPI-Reviewer software to classify the studies); (3) selecting studies (an iterative process in which two reviewers search the literature, refine the search strategy, and

review articles for inclusion); (4) charting the data (using EPPI-Reviewer's data-charting form); (5) collating, summarizing, and reporting the results (performing a descriptive, numerical, and interpretive synthesis); and (6) consulting knowledge users during three planned meetings. Since this scoping review concerns the use of collaborative writing applications as KT interventions in health care, we will use the Knowledge to Action (KTA) framework to describe and compare the various studies and collaborative writing projects we find. In addition to guiding the use of collaborative writing applications in health care, this scoping review will advance the science of KT by testing tools that could be used to evaluate other social media. We also expect to identify areas that require further systematic reviews and primary research and to produce a highly relevant research agenda that explores and leverages the potential of collaborative writing software. To date, this is the first study to use the KTA framework to study the role collaborative writing applications in KT, and the first to involve three national and international institutional knowledge users as part of the research process.

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Introduction

Collaborative Writing Applications and their Potential Impact on Global Knowledge Translation

In both developed and developing countries, vast numbers of health care decision makers—providers, patients, managers, and policy makers—are failing to use research evidence to inform their decisions [1]. According to behavior change theories [2-4], self-efficacy is one of the most important cognitive determinants of behavior. By involving knowledge users in the dissemination of knowledge [5], social media—highly accessible, interactive vehicles of communication—have the potential to increase users' self-efficacy [5-7] and empower users to apply knowledge in practice. Acknowledging this potential and recognizing that social media capitalizes on the free and open access to information, scientists, opinion leaders, and patient advocates have called for more research to determine whether social media can equip decision-making constituencies to improve the delivery of health care [8,9], decrease its cost [5,10], and improve access to knowledge within developing countries [8,11,12].

Collaborative writing applications [13,14] are a category of social media that has enjoyed a surge in popularity in recent years including within the health care sector [5,7,8,13]. Although no two applications are identical, all consist of software that allows users to create online content that anyone can edit or supplement [15]. Thus, Internet users have turned to wikis [16,17] to produce a Wikipedia entry on the Global Plan to Stop Tuberculosis [8]; to Google Knol [18] to exchange research on influenza at the Public Library of Science [19]; and to Google Docs [14,20] to review the literature on emergency medicine [21,22].

While new collaborative writing applications are continually surfacing, wikis are perhaps the most popular. Wikipedia's medical articles are viewed about 150 million times per month and exist in 271 languages [8]. New wikis have appeared in all fields of health care [13,21,23-30], and studies of developed countries found that 70% of junior physicians use Wikipedia in any given week, that 50% to 70% of practicing physicians use it as a source of information in providing care [8,31], and that 35% of pharmacists refer to it for drug information [32]. Patients also use wikis to share their experiences [33] and to find information [8]. The Canadian Agency for Drugs and Technologies in Health (CADTH) is exploring the use of wikis

to update knowledge syntheses [34,35] and the United States' National Institutes of Health (NIH) is training its scientists in editing them [36]. In addition, academic institutions like Harvard [37] and Stanford [13] are using wikis to train health care professionals [13,16,38-43]. Wikis have come to exemplify social media's tremendous promise to enable health care professionals, patients, and policy makers to implement evidence-based practice at remarkably low cost [21,22,44-46]. In doing so, they could improve the health of millions of people around the world [8,12].

Knowledge Users' Needs

Even as decision makers increase their use of wikis and other collaborative writing applications, questions remain about their safety [47,48], their reliability [49-53], their lack of traditional authorship [54,55], and the legal implications for decision making [56,57]. Researchers also question clinicians' intention to use the applications in their practice [21] and to contribute knowledge collaboratively [8,22]. For these reasons, the International Medical Informatics Association (IMIA), the Association of Faculties of Medicine of Canada (AFMC), and the Federation of Patients and Consumer Organization in the Netherlands (NPCF) have partnered with our research team to conduct a scoping review to determine the extent of published evidence on these questions.

The Canadian Institutes of Health Research (CIHR) define a knowledge user as "an individual who is likely to be able to use the knowledge generated through research to make informed decisions about health policies, programs, and/or practices [58]." A knowledge user includes, but is not limited to, a practitioner, policy maker, educator, decision maker, health care administrator, community leader, or an individual in a health charity, patient group, private sector organization, or media outlet. In knowledge syntheses like this scoping review, CIHR requires that designated knowledge users be actively involved in all aspects. In line with this definition, the designated knowledge users in this project are IMIA, AFMC, and NPFC. These three organizations represent three different groups of stakeholders interested in the findings of this scoping review. They have been involved from the beginning of this project and will play an essential role in the dissemination and implementation of its results.

The world body for health and biomedical informatics is the IMIA [59]. As an "association of associations," the IMIA acts as a bridge between its constituent nationally based informatics associations and its academic and industry members from around

the world, and further to all interested organizations and individuals. The IMIA has a seat at the World Health Organization's (WHO) World Health Assembly, which aims to (1) promote informatics in health care and biomedical research; (2) advance international cooperation; (3) stimulate research, development, and education in this domain; and (4) disseminate and exchange information in this domain.

Representing Canada's 17 faculties of medicine, AFMC is the voice of academic medicine in Canada [60]. The member faculties of AFMC graduate over 2300 physicians each year; have 10,148 undergraduate medical students in training and 12,453 postgraduate trainees; and employ 21,687 full- and part-time faculty members. Thus, AFMC is a leading advocate on issues relating to health education, health research, and clinical care. Recently, AFMC has embarked on a series of projects aimed at meeting changing societal needs with innovative educational programs based on e-learning and social media. For example, in 2008, AFMC initiated the Canadian Healthcare Education Commons [61], whose mission is to provide an online environment—including wikis among other tools—to share educational material, designs, and practices in whatever form across the health care continuum and between professions in Canada.

In the Netherlands, the NPCF brings together hundreds of patient and consumer organizations to speak as one voice in areas of common interest, such as patients' rights and access to care [62]. In the NPCF's vision, eHealth is an essential enabler for real empowerment of patients and self-management of their health. Patient participation is very important for improving health care as the views and experiences of patients and consumers can be heard in order to shift towards a participatory health care model.

As designated knowledge users for this CIHR-funded research project, these three institutions (IMIA, AFMC, and NPCF) have helped define the need for this scoping review. In particular, these institutions want to explore the features that explain wikis and collaborative writing applications' rising popularity [6,16] and clarify the differences between wikis and other applications, like Google Knol [8,18,19,63,64] and Google Docs [20,22]. Specifically, these institutions need to know how various applications can enhance the delivery of health care (eg, by empowering patients in decision making [65,66]), improve health care communication and education [13,20,38,67,68], and benefit health in developing countries [8]. These institutions intend to use this evidence to formulate policies for the applications' safe and effective use.

Gaps in the Knowledge Addressed by this Proposal

We have seen that the rapid rise in the use of collaborative writing applications in health care has created a need for a systematic synthesis of the evidence concerning their potential impacts and an inventory of the barriers and facilitators that affect their use. A scoping review is the ideal methodology to employ for a number of reasons. According to the CIHR, a scoping review is explorative and used when the relevant literature is considered to be broad and diverse as is the expanding literature about collaborative writing applications [69]. Moreover, the study of these applications is an emerging

field that is being examined with diverse methods [20,38,50], with different theoretical frameworks [21], and in different contexts [35,70]. While researchers have conducted systematic reviews on information and communication technologies [71,72] and other social media (virtual communities of practice [73], virtual peer-to-peer communities, and electronic support groups [74]), none have reviewed collaborative writing applications. Therefore, in synergy and partnership with three national and international institutional knowledge users, we propose a scoping review that will map the literature on the use of wikis and other collaborative writing applications in health care in order to synthesize the applications' positive and negative impacts and inventory the barriers and facilitators that affect how they influence the delivery of health care.

Purposes for Conducting this Scoping Review

The overarching goal of this project is to explore the depth and breadth of evidence about the effective, safe, and ethical use of collaborative writing applications in health care systems around the world.

Specifically, the purposes of conducting this scoping review are to:

1. Map the literature on collaborative writing applications (including wikis, Google Knol, and Google Docs) in health care;
2. Compare the applications' features by investigating how they are used in collaborative writing projects;
3. Describe the evidence of each application's positive and negative effects as a knowledge translation (KT) intervention in health care;
4. Inventory and describe the barriers and facilitators that affect the applications' use; and
5. Produce an action plan and a research agenda delimitating three areas: where sufficient evidence exists to make clear and judicious policy recommendations about the use of collaborative writing applications in health care, where further knowledge synthesis is needed, and where more primary research remains to be done.

Conceptual Frameworks

Since this scoping review concerns the use of collaborative writing applications as KT interventions in health care, we will use the Knowledge to Action (KTA) framework [75,76] to describe and compare the various studies and collaborative writing projects we find. We intend to use the framework as a roadmap for determining where studies of collaborative writing applications and real projects that use those applications fit along the KT continuum. The role of collaborative writing applications in KT has not yet been determined: it is possible that applications play a different role at different phases in the KTA process. For example, a wiki used to update a systematic review [34,35] would not play the same role as a wiki used to promote global public health [8], a Google Knol used to exchange knowledge about influenza [19], or Google Docs used to teach scientific writing [20]. Finding and categorizing studies and collaborative writing projects will identify gaps in the

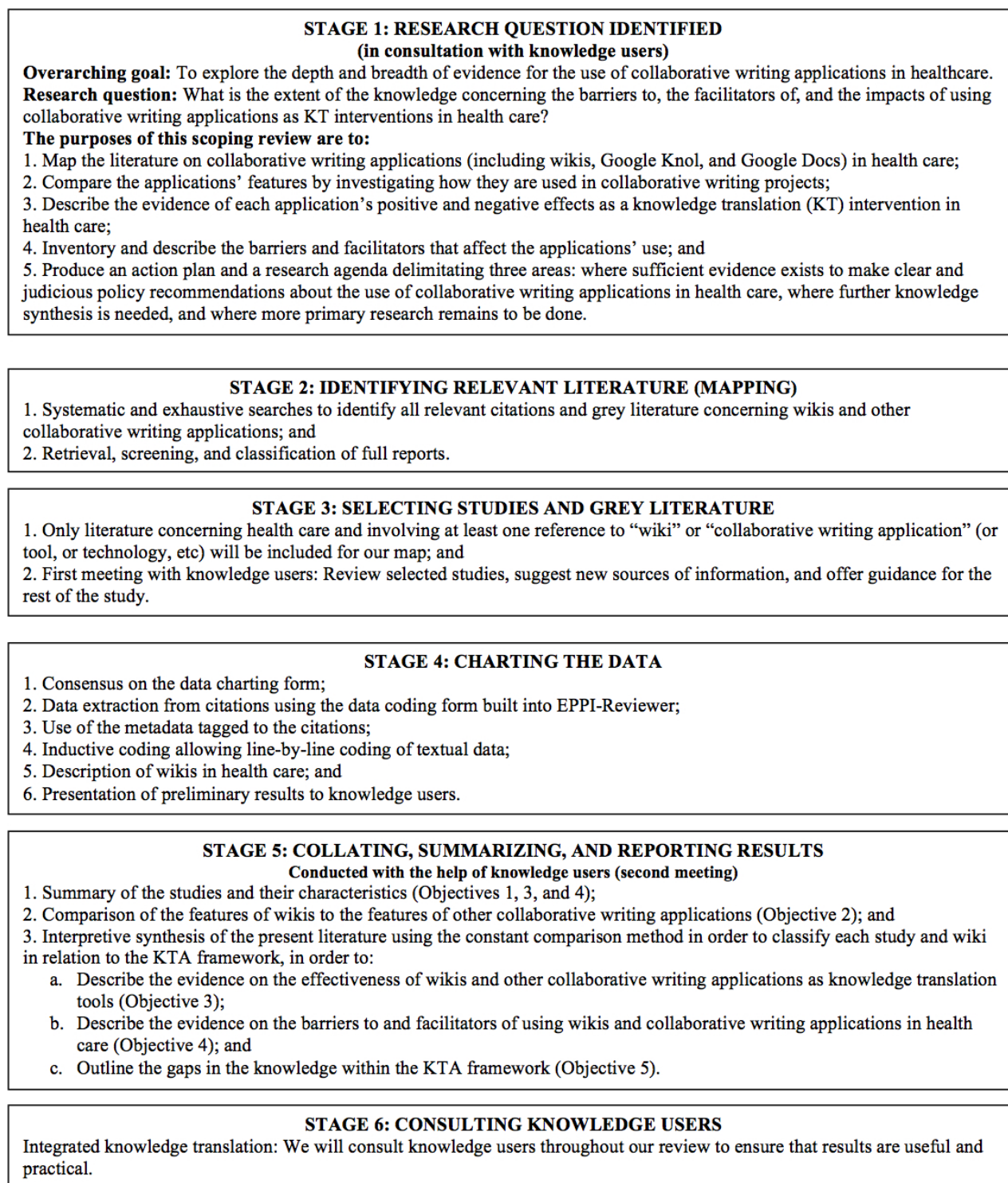
knowledge about the applications' use as KT interventions. These gaps will then inform our production of a research agenda.

Finally, we will describe how the studies use different behavioral and organizational models of change [79,80] to study collaborative writing applications. We will also use the taxonomy from a systematic review on the factors affecting the adoption of information and communication technology to inventory and describe the barriers and facilitators identified in this scoping review [72].

Methods

To accomplish the purposes of this scoping review, we will employ the scoping review methodology described by Arksey and O'Malley [79] and further developed by Levac et al [80]. This methodology has six stages: (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 knowledge users (Figure 1).

Figure 1. Stages of the scoping review.



Stage 1: Identifying the Research Question

The research question was developed by consulting the knowledge users to determine their needs and questions about using collaborative writing applications for KT. Their questions can be summarized as follows: “What is the extent of the knowledge concerning the barriers to, the facilitators of, and the impacts of using collaborative writing applications as KT interventions in health care?” As was previously stated, and in response to this question, the overarching goal of this project is to explore the depth and breadth of evidence about the effective, safe, and ethical use of collaborative writing applications in health care systems around the world. The purposes of our scoping review will be used to attain this goal, and therefore orient our search for publications and the grey literature. The participants targeted by this scoping review are any person involved in a KT intervention in health care (eg, patients, health care professionals, policy makers, students, educators, providers, managers, and researchers). For the purposes of our study and having referred to the writing on the subject [14-16], we have defined “collaborative writing applications” as a category of social media that enables the joint and simultaneous editing of a webpage or an online document by many end users [15]. Thus, the term covers wikis, Google Knol, and Google Docs, but does not exclude new applications for use in a future update. In terms of outcomes, our scoping review will apply no restrictions since it is important that we describe all relevant outcomes used in the literature.

Stage 2: Identifying Studies and the Grey Literature

We will begin by comprehensively mapping publications and the grey literature to identify all sources of information within the broad remit of our overall question. To facilitate this stage, we will use software developed by the Evidence for Policy and Practice Information and Co-ordinating Centre (EPPI-Centre) [81]. Using EPPI-Reviewer 4.0 [81-85], we will create a database of publications and grey literature on collaborative writing applications in health care. EPPI-Reviewer is a multi-user web-based application for managing and analyzing data for use in research synthesis. The search methods that will be used for identifying studies and the grey literature are described below.

Electronic Searches

We will search publications identified in the following bibliographic databases: the Cochrane Effective Practice and Organisation of Care (EPOC) Review Group Specialised Register; the Cochrane Library (including Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database, and NHS Economic Evaluation Database); EMBASE; PubMed; CINAHL; PsycINFO; Education Resources Information Center (ERIC); and ProQuest Dissertations and Theses. Our team’s information specialist (KA) developed a search strategy, which was peer-reviewed by an information specialist from the Medical Library of the Radboud University Nijmegen Medical Centre in The Netherlands. The search strategy is broad enough to generate an extensive map of the literature on wikis and other collaborative writing applications. We will impose no

restrictions on language or date. Our preliminary search strategy (Multimedia Appendix 1), which used the terms “wiki,” “wikis,” “Web 2.0,” “social media,” “Google Knol,” “Google Docs,” and “collaborative writing applications,” identified 7174 citations before removal of duplicates.

Other Sources

We will conduct additional searches by (1) scanning the reference lists of included studies; (2) reviewing the two most recent editions of the proceedings and abstracts of relevant conferences, symposia, and colloquia; (3) searching web-based registries of clinical trials; (4) contacting experts to request details of any known studies (eg, the authors of WikiProject Medicine [8]); and (5) searching the following repositories of grey literature: the New York Academy of Medicine Library’s Grey Literature Report, OpenSIGLE, the Health Technology Assessment international (HTAi) Vortal, and CADTH’s online search engine.

We will also search for grey literature on the Internet using the search engines Google, Bing, Yahoo, Mednar, and Scopus. Google, Bing, and Yahoo are the most widely used search engines [85]; Mednar and Scopus focus on scientific content. We will use the advanced search option, select no preferred language, and turn off the option for regional differences. Based on previous research [85,86], we expect a large number of results. For this reason, when searching with Google, Yahoo, Bing, and Scopus, we will use a more specific search string query, such as “wiki in health care,” “Google Knol in health care,” “Google Docs in health care,” and “collaborative writing applications in health care.” We will study the first 100 results in Google, Bing, and Yahoo, which all display results by relevance using a link analysis system or algorithms [85]. We will then analyze the top 100 results for each search engine to identify all collaborative writing projects inventoried. We will complete our comprehensive search of the Internet by consulting existing lists of wikis in health care [23,87]. The founding authors of each identified collaborative writing project will be contacted and asked for all published or unpublished descriptions of the features of the application they used (eg, wiki, Google Knol, or Google Docs), studies of the impacts of the application, and studies of the barriers to, and facilitators of, the use of the application.

To ensure we include all relevant studies, we will invite all interested Internet users and researchers to share papers that could potentially fall within the scope of this review. A public online Mendeley library has been created to allow anyone to make contributions to the current collection of citations. To add citations to this online library, interested individuals are invited to access the library [88]. Furthermore, if interested individuals prefer to use a wiki to share their citations, they are invited to do so by using the HLWIKI [89]. A Google Docs spreadsheet [90] will also allow potential collaborators to add citations for consideration for this scoping review. We will use these different social media resources to verify if any new citations will be identified by comparing the lists of citations created in these three resources to the lists we will be creating within EPPI-Reviewer. Any individual’s contribution to these three resources will be recognized and appropriately credited.

EPPI-Reviewer

All sources of information (publications and grey literature) will be imported into EPPI-Reviewer using the Research Information Systems (RIS) tagging format. For webpages, we will use Mendeley [91], a free online reference manager built to facilitate the tagging and describing of web-based sources of information. We will then import these tagged webpages in RIS format into EPPI-Reviewer for further analysis. All duplicates will be removed within EPPI-Reviewer.

Stage 3: Selecting Studies and the Grey Literature

This stage will consist of an iterative process in which we search the literature, refine our search strategy, and review articles for inclusion. Two reviewers will independently screen all titles, abstracts, and grey literature in EPPI-Reviewer and retain only material concerning the field of health care and involving collaborative writing applications such as wikis, Google Knol, and Google Docs. The team's reviewers will meet at the beginning, during the middle, and at the end of the review process to discuss their selection of literature and to refine the search strategy, if needed. Two reviewers will then independently review full articles and grey literature for inclusion. If they disagree, a third reviewer will arbitrate. EPPI-Reviewer will facilitate consensus by allowing multiple users to classify studies independently before comparing their results. EPPI-Reviewer will also produce summary discrepancy reports. Its interface will facilitate final decisions.

Stage 4: Charting the Data

We have already developed a preliminary data-charting form and determined which information to extract. This form will be built into EPPI-Reviewer to facilitate our coding of data. Two authors will use the form to extract data from the first 10 studies and/or grey literature independently before meeting to determine whether their approach to data extraction is consistent with the research question and the purpose of the review. Thus, for the first 10 sources of information, charting will be an iterative process in which researchers continually update the data-charting form. Once the reviewers reach consensus on the form, they will send it to all team members for final comments and suggestions, after which the reviewers will use it to extract data for each publication. The reviewers will compare their extraction results within EPPI-Reviewer. If they disagree, a third reviewer will determine the final version of the data extracted.

Using EPPI-Reviewer's inductive coding function, which allows textual data to be coded line-by-line, and using the metadata already tagged to each citation in RIS format, two reviewers will qualitatively describe the sources of information with regard to the following variables: authorship, year of publication, country, status of publication (ie, published or grey literature), journal, Medical Subject Headings (MeSH) terms used, participants (patients, health care professionals, policy makers, educators, or students), study setting, study design (eg, experimental, non-experimental, or qualitative), collaborative writing application used in the intervention group, goal of the intervention (conducting reviews, developing guidelines, promoting evidence-based practice, promoting evidence-informed policy making, promoting shared decision

making, or teaching health care), description of the comparison, description of the outcomes, description of the positive and negative impacts, description of barriers and facilitators, use of a behavioral or organizational theory of change to describe barriers and facilitators. For every collaborative writing project that involved the use of a collaborative writing application, we will code the following variables: website address, audience, contributors, editors, supporting organization, editorial policy, recognition of authorship, presence of publicity, number of pages, language, type of content, application used (eg, wiki software), references to published descriptions, references to studies assessing the project's impact, and references to studies on barriers and facilitators. Using EPPI-Reviewer, we will compare the reviewers' coding to ensure that our results are trustworthy. Any discrepancy will be resolved by discussion. If consensus is not possible, a third reviewer will decide.

Stage 5: Collating, Summarizing, and Reporting Results

Collating and Summarizing

As described in the framework by Arksey and O'Malley [79], our analysis (referred to as "collating and summarizing") will involve a descriptive numerical summary and an interpretive synthesis.

First, we will summarize the studies and their characteristics as described in the charting stage (Purposes 1, 3, and 4). This description will constitute our map of the literature on collaborative writing applications in health care. We will report the frequency of studies according to variables defined in Stage 4, such as the study design, the type of intervention that took place, the outcomes that were measured (health care process outcomes or health outcomes), the positive and negative impacts, the barriers and facilitators, and the explicit use (or non-use) of a theoretical framework.

Our description of impacts (Purpose 3) will remain qualitative and will serve to identify the potential for future systematic reviews. Examples of impacts are an increase in professionalism by medical students (a positive impact) [38] and the dissemination of inaccurate information on HIV/AIDS medication (a negative impact) [50]. We will begin our description by developing a coding scheme using qualitative content analysis, a method whereby researchers interpret textual data subjectively by systematically classifying and coding data and identifying patterns [92]. Using a random sample of 10% of all data, two reviewers will identify the positive and negative impacts mentioned by the studies and mark recurrent impacts with codes [92]. They will begin by reading the data repeatedly to immerse themselves and obtain a broad perspective [93]. Then, with EPPI-Reviewer's full text mining capacity, they will read the content word-by-word, highlighting words that appear to capture impacts and assigning them codes, which they will then organize into categories. They will also develop a tree diagram to organize the categories into a hierarchical structure [94]. Next, we will develop definitions for each code and category. These codes and categories will constitute our coding scheme and will guide reviewers' content analysis of the rest

of the data. The two reviewers will discuss units of text that could not be coded and will create new codes as necessary.

Our description of barriers and facilitators (Purpose 4) will be based on a validated taxonomy developed by Gagnon et al [72]. The reviewers will read each publication independently and identify the unit of text (a sentence or paragraph representing an idea) relevant to each main outcome of interest (barriers and facilitators). Using EPPI-Reviewer, they will then code each unit of text according to the code list. If necessary, the reviewers will create new codes for units of text that cannot otherwise be coded, thus refining and expanding the list. The reviewers will resolve any coding discrepancies through discussion. During the coding process, codes will be aggregated into themes, which will be nested under a main theme.

The same constant comparison method [92] will be used to compare the features of the collaborative writing applications by analyzing their use in different collaborative writing projects (Purpose 2). Again, a coding scheme will be developed from a random sample of 10% of the data, following the process used for coding impacts. In this case, the categories will correspond to meaningful clusters that reflect the relationships between the applications' features. We will code the data using this scheme, as per the process described previously. We will also construct a table that compares the collaborative writing applications used for each project and identifies the presence or absence of features using the developed coding scheme. The resulting synthesis will allow knowledge users—IMIA, AFMC, and NPCF in particular—to make recommendations for the use of the applications that more accurately reflect the applications' strengths and weaknesses.

Also using the constant comparison method, we will perform directed content analysis [92] to classify each project that used a collaborative writing application in relation to the KTA framework. The KTA framework will serve as a map on which collaborative projects will be plotted according to each project's explicit or implicit goal as interpreted by the reviewers' analysis of the project's features and characteristics. Thus, each project will occupy a space within the KTA framework that reflects the phase of the KTA framework that the project is likely to influence. The KTA framework will describe the phases and detail the relationships between them, helping to determine the initial coding scheme. Projects that cannot be coded will be identified and analyzed later to determine whether they represent a new process within the KTA framework or a subcategory of an existing process. This directed approach to content analysis will allow us to validate the KTA framework for the study of future collaborative writing projects. It will also allow the KTA framework to be extended if new processes or subprocesses are identified.

The conceptual framework generated by our directed content analysis will allow us to classify applications according to the phase of the KTA process that they influence. It will do likewise for applications' positive and negative impacts (Purpose 3) and the barriers to, and facilitators of, using the applications as KT tools in health care (Purpose 4). In addition, the analysis will guide: (1) our formulation of clear, evidence-based policies where sufficient evidence exists about the use of wikis and other

collaborative writing applications as KT interventions; (2) our analysis of gaps in the knowledge; and (3) our identification of areas where more primary research is needed and areas where there is enough data to conduct systematic reviews (Purpose 5).

Reporting Results

To present the results of our qualitative analyses, we will employ descriptive tables, frequency tables, and diagrams. A table will describe the characteristics of each study included in our review. Additional tables will classify the studies according to their principal characteristics: participants, study setting, study design, study intervention, aim of the collaborative writing applications, and outcomes studied. A summary table will group those studies that assessed the impacts of the use of a collaborative writing application, showing the phase of the KTA process that the application influenced and describing the studies' results. Another summary table will present all the studies that assessed barriers and facilitators, the theory used by each, the KTA process influenced, and—using a validated taxonomy—a description of the barriers and facilitators found. These tables will be useful for knowledge users interested in the impacts of using collaborative writing applications in health care and on the barriers and facilitators that affect their use. To compare applications, a Venn diagram will be constructed that situates each application in relation to the others. This will help knowledge users understand how each application can be used. Finally, a diagram that situates the different collaborative writing applications within the KTA framework will help knowledge users understand the applications' role in KT. This conceptual map will be very useful in designing systematic reviews and primary studies in the future.

Stage 6: Consulting Knowledge Users

Our scoping review will involve the knowledge users throughout the review's duration in order to generate usable and practical results. This integrated KT model is important to giving the review perspective, meaning, applicability, and a clear purpose. By laying out their needs for the products of this review, knowledge users have already shaped our research purposes. We will continue to involve knowledge users by conducting two teleconferences during the course of the review. In the first teleconference (after Stage 3), we will share the preliminary findings of the review to validate our findings and guide the review's completion. This meeting will be an opportunity for IMIA, AFMC, and NPCF to identify additional sources of information that we should consider. The second, and final, meeting will be held near the end of Stage 5, when we will use the preliminary findings from Stage 5 (presented in tables and diagrams) as a foundation for the formulation of an action plan and a research agenda (Purpose 5). Our knowledge users will have the opportunity to build on the evidence presented and offer more meaning, content expertise, and perspective to the preliminary findings. These meetings will guide our writing of the final report and the two-page policy briefs that knowledge users find accessible and useful.

Discussion

This review will generate results that will be highly pertinent to the knowledge users who will collaborate on the project, as

well as to the broader community they represent. In general, it will draw upon the evidence to refine the community's understanding of the use of collaborative writing applications as KT instruments. First, it will identify the features that differentiate collaborative writing applications; second, it will discuss the positive and negative impacts of different collaborative writing applications and the barriers and facilitators that affect their use. Using the KTA framework, we will group the applications by KTA phase. This will allow us to produce a strategic action plan that is grounded in knowledge users' feedback and makes recommendations about the use of collaborative writing applications as KT interventions where justified by the evidence. Also, it will allow us to develop a research agenda that can identify areas that need more systematic review or primary research. Ultimately, we expect our findings to benefit knowledge users in health care organizations around the world, especially in developing countries where clinicians are most likely to value applications that share free, reliable, health information. The review will also help build a strong partnership between knowledge users and scientists, which will be useful for further research. Furthermore, knowledge users and researchers around the world are invited to pursue this endeavor in collaboration with us by contributing to the synthesis of new knowledge on wikis and collaborative writing

applications in health care. This novel use of crowdsourcing to identify citations and to update the database of citations created with this study will add to the results of ongoing studies concerning the potential use of crowdsourcing to supplement the process of knowledge synthesis and scoping reviews [95,96]. In addition to contributing to the guidance on the use of collaborative writing applications, this scoping review will advance the science of KT by testing and improving tools that could be used to evaluate other social media. In particular, this review will be the first to use the KTA framework to study the role of collaborative writing applications in KT. Using this framework will help us determine a research agenda that will be instrumental in future explorations of applications such as wikis, Google Knol, and Google Docs.

Conclusions

For all the promise and power of collaborative writing applications for KT, the applications are also fraught with important barriers and the potential of adverse effects. This argues for rapid guidelines for the implementation and development of these new social media. To date, this is the first study that will use the KTA framework to examine the role collaborative writing applications can play in KT. It is also the first to involve three national and international institutional knowledge users—IMIA, AFMC, and NPCF—in the process.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Definitive search term strategy in different databases and number (n) of citations found for each database (October 2011).

[[PDF File \(Adobe PDF File\), 34KB](#) - [resprot_v1i1e1_app1.pdf](#)]

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Abbreviations

AFMC: Association of Faculties of Medicine of Canada
CADTH: Canadian Agency for Drugs and Technologies in Health
CIHR: Canadian Institutes of Health Research
EPOC: Effective Practice and Organisation of Care
ERIC: Education Resources Information Center
IMIA: International Medical Informatics Association
KT: knowledge translation
KTA: Knowledge to Action
MeSH: Medical Subject Headings
NIH: National Institutes of Health
RIS: Research Information Systems
WHO: World Health Organization

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Proposal

HIV Drug-Resistant Patient Information Management, Analysis, and Interpretation

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Abstract

Introduction: The science of information systems, management, and interpretation plays an important part in the continuity of care of patients. This is becoming more evident in the treatment of human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS), the leading cause of death in sub-Saharan Africa. The high replication rates, selective pressure, and initial infection by resistant strains of HIV infer that drug resistance will inevitably become an important health care concern. This paper describes proposed research with the aim of developing a physician-administered, artificial intelligence-based decision support system tool to facilitate the management of patients on antiretroviral therapy.

Methods: This tool will consist of (1) an artificial intelligence computer program that will determine HIV drug resistance information from genomic analysis; (2) a machine-learning algorithm that can predict future CD₄ count information given a genomic sequence; and (3) the integration of these tools into an electronic medical record for storage and management.

Conclusion: The aim of the project is to create an electronic tool that assists clinicians in managing and interpreting patient information in order to determine the optimal therapy for drug-resistant HIV patients.

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KEYWORDS

Medical Informatics; Bioinformatics; HIV drug resistance; Machine Learning

Introduction

The current trend in patient health care is personalized medicine where treatment is individualized, rather than a response to set physical presentations. Thus, access to and interpretation of personal patient information is vital in order to provide a sustainable and useful medical service. The science of information systems, management, and interpretation plays an important role in the continuity of care of patients. This is becoming more evident in the treatment of human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS). This paper describes proposed research where the aim is to develop a physician-administered artificial intelligence-based decision support system tool that will facilitate the management of patients on antiretroviral therapy.

The enveloped human immunodeficiency virus infects and destroys the human immune system over a long period of time [1]. The two known strains of HIV are HIV-1 and HIV-2. The rate of replication and infection of the HIV-2 is substantially slower than that of the HIV-1 and accounts for 95% of all HIV infections [2]. HIV-1 is subdivided into four groups representing four separate introductions of simian immunodeficiency virus into humans:

1. Group M is the major HIV-1 group with respect to prevalence (the number of people infected) and incidence (the number of new infections) of the virus;
2. Group O is the outlier group and is mostly restricted to west-central Africa;

3. Group N was discovered in 1998 in Cameroon and is extremely rare; and

4. Group P is a strain closely resembling the gorilla simian immunodeficiency virus.

Currently, Group M is subdivided into nine subtypes or clades—A, B, C, D, F, G, H, J, and K—based on variations in genetic sequence characteristics [3]. However, it is possible for

viruses from different subtypes to form mosaic genomes called circulation recombinant forms (CRF). In sub-Saharan Africa, HIV/AIDS is the leading cause of death [4] and it is one of the fastest growing epidemics in South Africa [5-8], where currently there are 5.7million confirmed cases of HIV/AIDS [9]. Demographic information on confirmed HIV-infected patients in South Africa is presented in Table 1.

Table 1. Estimated HIV prevalence rates in South Africa [9].

	Women	Men	Total population		
Age range	20–64	20–64	15–46	20–64	All ages
% with HIV	18.1	17.7	18.8	17.9	11.1

HIV infection can be effectively managed with antiretroviral (ARV) drugs, usually in the form of highly active antiretroviral therapy (HAART), which is comprised of a regimen of three drugs from at least two of the following five drug classes [10-13]: reverse transcriptase inhibitors (RTI), nucleoside reverse transcriptase inhibitors (NRTI), protease inhibitors (PI), integrase inhibitors (II), and fusion inhibitors (FI).

Factors that influence treatment of HIV/AIDS with ARVs include poor treatment regimen prescribed by the physician; the World Health Organization (WHO) stage of the disease, which is related to the progression of the disease; levels of plasma drug concentration achieved; how strictly the patient adheres to the regimen; drug resistance [14]; and toxic effects of the drug. Drug resistance is the most critical aspect of treatment. Three common reasons leading to the development of HIV antiretroviral drug resistance are high replication rates, selective pressure, and initial infection by resistant strains of HIV. Thus, it is inevitable that drug resistance will become a reality in most patients' treatment.

Preventative measures must be taken in order to develop infrastructure that will aid in the management of drug-resistant HIV patients. It is essential to develop techniques that will extract valuable information from little patient data. There must be a means developed to manage, analyze, and interpret patient data.

The aim of this study is to develop a physician-administrated information system that facilitates the clinical management of HIV-positive patients on antiretroviral therapy. This system should be Web-based, patient centric, ascribe to the principles of personal medicine, promote complete health management, and incorporate continuity of care. Creation of this tool will involve:

- Development of an artificial intelligence computer algorithm that analyzes HIV drug resistance data and provides singular interpretable information for a physician indicating which ARVs a patient will be resistant to;
- Investigation of the application of a computer algorithm to predict current and future CD₄ lymphocyte cell count information given a genomic sequence and other data;
- Integration of the above tools with an electronic medical record system such that it facilitates the storage, acquisition, and management of patient information; and

- Development of a Web-based electronic tool that assists clinicians in determining the optimal therapy for drug-resistant HIV patients.

Background

Medical Informatics

The appropriate application of computer science and associated technology has extended medical care beyond traditional diagnosis and patient management, resulting in extensive cost efficiencies and improved public health outcomes [15]. Areas of medical informatics application include patient records, practice management, clinical measurements, patient education, prescription writing, Web/database resources, clinical records, data collection, clinical decision support, and clinical measurements. Recently, there has been an intentional move towards investigating the synergy between medical informatics and bioinformatics [9]. Bioinformatics is the application of computer science techniques to study how information is represented and transmitted in biological systems starting at the molecular level [16].

The application of genomes in medicine has altered many aspects of medicine. Genome analysis that enhances clinical practice has been successfully applied to asthma [17], cancer [18-20], diabetes [21], and cardiovascular disease [22].

HIV Drug Resistance Prediction Algorithms

Testing for HIV drug resistance may consist of wet or dry chemistry laboratory tests, or by employing electronic computerized algorithms [23]. The use of computer algorithms falls under the field of medical informatics. Computer based interpretation algorithms using genomes can also be used to predict HIV drug resistance.

These interpretation algorithms can be generally divided into one of two groups:

- Those based on known domain knowledge (ie, they are based on the fact that certain combinations of known genome mutations cause unequivocal resistance), and
- Those not based on predefined domain knowledge. These algorithms include machine learning and statistical methods.

Interpretation Algorithms Based on Domain Knowledge

Domain knowledge interpretation algorithms are based on scientific and published interactions between certain mutations

and/or combination of mutations with resistance. This means that all computational decisions concerning resistance are based on known mutation-resistance rules found in published scientific literature. REGA, Agence Nationale de Recherches sur le SIDA (ANRS), and Stanford's HIVdb algorithm [24] are three examples of well-known domain knowledge interpretation algorithms. These algorithms are widely used in the field and are regarded as gold standards.

REGA and ANRS classify ARV resistance according to three levels: susceptible, intermediate, and resistant. "Susceptible" indicates that a particular ARV drug will be effective against HIV; "intermediate" indicates that the ARV drug is partially effective; and if the ARV is not effective at all, it is classified as "resistant." HIVdb classifies HIV drug resistance according to five levels: susceptible, potential low-level resistance,

low-level resistance, intermediate resistance, and high-level resistance. These algorithms employ Boolean-based rules, some with penalties, and predict resistance by determining which mutations are present and/or absent.

Two other domain-based algorithms are the Drug Resistance SEquence ANalyzer (DR_SEQAN) and RetroGram. DR_SEQAN was coded by the Universidad Autónoma de Madrid for a Windows environment using Visual Basic. DR_SEQAN classifies three levels of resistance: high-level resistance, increased susceptibility, and no resistance. RetroGram was developed by *InferMed Ltd* (London, UK) and is built using Arezzo and PROforma. RetroGram generates a suitability ranking for ARV drugs using expert rules. Table 2 describes the accuracy of predicting drug resistance of some algorithms based on domain knowledge.

Table 2. Accuracy of predicting ARV drug resistance by the domain-based algorithms, Drug Resistance SEquence ANalyzer (DR_SEQAN), RetroGram, REGA, and HIVdb [28].

Drug	Accuracy of algorithm (%)			
	DR_SEQAN	RetroGram	REGA	HIVdb
Indinavir	70.8	70.0	84.0	78.0
Nelfinavir	66.1	70.5	77.7	73.7
Lopinavir	85.7	88.1	81.0	69.0
Lamivudine	83.1	79.7	78.0	78.0
Zidovudine	79.2	64.6	72.9	68.8
Stavudine	60.0	38.8	67.1	37.6
Didanosine	93.3	20.2	27.9	27.8
Nevirapine	87.9	65.2	72.7	90.9

Interpretation Algorithms Not Based on Known Domain Knowledge

Many different pattern recognition and machine-learning algorithms have been applied to find a predictable correlation between genotypic and phenotypic data (called "virtual phenotyping") [25]. Machine learning may be used to develop a model that predicts virological response. Machine learning is an artificial intelligence computer science technique that tries to find a mathematical model that maps between inputs and outputs of a domain problem.

Virtual phenotyping is growing in popularity. Kuritzkes supports virtual phenotyping as a tool for interpreting viral genotypes [26]. The following are some of the algorithms that have been used:

- Least absolute shrinkage and selection operator (LASSO)
- Ridge regression
- Neural networks, such as multilayer perceptron (MLP) and radial basis neural networks (RBNN)
- Principle component analysis
- Support vector machines (SVM)
- Linear regression models

- Hidden Markov models
- Decision trees
- Multiple correspondence analysis
- Associative classifiers
- k-nearest neighbor algorithm (kNN)

Results produced by these interpretation algorithms are shown in Tables 3–5. These interpretation algorithms have achieved various levels of success, but there are shortcomings in some of the current versions [27]:

- Resistance is interpreted separately for each drug even though therapy consists of combination therapy;
- There is a general lack of data, especially for non-B HIV-1 subtypes;
- Rule-based interpretation is based on the algorithm creator's knowledge;
- Interpretation algorithms are not always updated even though HIV drug resistance is a rapidly evolving field; and
- Other factors that contribute to treatment failure are not taken into account, such as treatment history, resistance history, viral load history, CD₄ count history, or plasma drug concentrations.

Table 3. Accuracy of predicting ARV drug resistance using the interpretation algorithms, support vector machines (SVM), multilayer perceptrons (MLP), and radial basis neural networks (RBNN) [29].

Drug	Accuracy of algorithm (%)				
	SVM (Energy) ^a	SVM (DEnergy) ^a	MLP (Energy) ^a	MLP (DEnergy) ^a	RBNN
Indinavir	92.6	88.6	87.0	82.5	92.5
Nelfinavir	84.9	80.1	86.6	87.1	94.1
Lopinavir	88.6	82.4	92.3	87.9	94.4

^a See Bonet et al [29] for detailed information about Energy and DEnergy

Table 4. Accuracy of predicting ARV drug resistance using k-nearest neighbor (kNN), decision tree [30], and associative classifier [31] algorithms.

Drug	Accuracy of algorithm (%)		
	kNN	Decision tree	Associative classifier
Indinavir	73.6	93.9	93.0
Nelfinavir	81.1	89.5	92.1
Lopinavir	80.8	82.5	89.6

Table 5. Accuracy of predicting ARV drug resistance (%) or correlation coefficient (*r*) reported for various other algorithms and machine-learning techniques.

Algorithm	Accuracy (%)	Correlation coefficient (<i>r</i>)
HIVdb [32]	84.3	n/a
Visible Genetics/Bayer Diagnostics Guidelines 6.0 [32]	86.3	n/a
AntiRetroScan [32]	89.4	n/a
Committee of neural networks [33]	78.0	n/a
Geno2Pheno [34]	n/a	.6

These shortcomings have led to the creation of many different interpretation algorithms, which produce different resistance measures even if applied to the same resistance profile. These differences are because the studies each used different datasets,

subtypes, analysis on drug-naïve and drug-experienced patients, and so forth. Conclusions of some studies that reported on the discrepancy of the interpretation algorithms are shown in Table 6.

Table 6. Summary of discrepancies reported using various interpretation algorithms.

Study	Comments
Ravela et al [23]	Studied 4 interpretation algorithms (ANRS-3-02, TRUGENE VGI-6, REGA 5.5, and HIVdb-8-02) and concluded that there was a discrepancy in interpretations in 33% of all resistance profiles tested. The most discordant were NRTIs.
Snoeck et al [35]	Confirmed that there are discordances between the algorithms tested. Suggested it may be due to subtypes.
Vergne et al [36]	Confirmed discrepancies and attributed it to the application of the interpretation algorithms to drug-naïve or drug-experienced patients.
De Luca et al (2003) [37]	Concluded that discrepancies in the interpretation algorithms may influence the use of resistance testing over virological outcomes.
De Luca et al (2004) [38]	Studied the application of 13 interpretation algorithms of drug-naïve patients and concluded that there are discordances.
Vercauteren and Vandamme [27]	Determined that there is a high level of discordance between the interpretation of NRTI resistance. Also suggests that there should be a "standardization of unique interpretative rules."
Poonpiriya et al [39]	Indicated that there are discrepancies in the 7 interpretation algorithms they studied.

Collation and interpretation of the contradictory outputs of these algorithms is difficult for physicians treating complex drug-resistant HIV cases, as information is only valuable when it is presented in a clearly interpretable way.

Predicting CD4 Count

HIV can be successfully managed with ARV drugs, but information relating to the progression of HIV is vital. HIV infection may be monitored using laboratory [40,41] and clinical

marker information [42,43]. Information about a patient's CD₄ lymphocyte cell counts are the most widely used data for HIV progression and is recognized as a standard measure of immunodeficiency in HIV-positive patients [44,45]. Thus, the proper use and analysis of information regarding CD₄ cell counts is vital in CD₄-guided treatment of HIV [46].

Although the use of CD₄ count is part of the standard of care in developing countries, the measurement of CD₄ count requires many complex and expensive flow cytometric procedures, which burden the minimal resources available [45]. The ability to predict current CD₄ cell count will aid in easing the burden on these resources. A physician may use an electronic tool to economically determine an approximate CD₄ cell count. If the predicted count is low or indicates that a change in treatment is required, then the physician might order the more expensive laboratory procedure to determine the exact CD₄ cell count. The ability to obtain information about future CD₄ count changes will have many benefits to physicians. For example, it will facilitate definite treatment actions, such as changing the regimen in order to prevent opportunistic infection (eg, pneumocystis pneumonia) and delay the onset of AIDS.

Neural network machine-learning algorithms have been used to predict viral load [7,47]. Altmann et al [48] created a machine-learning algorithm that predicts success or failure of therapy, based on viral load, with 80% success. This was later changed by predicting the probability of treatment success based on a degree of predicted HIV drug resistance [49]. However,

there is not a chemical test or computer model developed yet to forecast changes to the CD₄ count.

Decision Support System Tool for Managing Therapy

Although models have been created to choose treatment regimens, very few are available in the public domain and/or are easily accessed through a graphical human (user) interface. Currently, there are Web portals that allow one to determine some aspects of HIV drug resistance treatment. These information portals allow one to determine the current HIV resistance profile, graph trends in viral and CD₄ counts with basic alerts, or store basic patient information. BioAfrica (www.bioafrica.net) is an African-based bioinformatics resource [50]. BioAfrica contains bioinformatics resources that can perform sequence alignments, epitope analysis, tools for proteomics, subtyping and virus genotyping, an RNA virus database, and an HIV drug resistance database and tools. The HIV drug resistance database and tools section is based on the REGA collaborative mode and the Calibrated Population Resistance Tool (CPT). REGA is a drug resistance database developed by the REGA Institute, MyBioData Biomedical IT Solutions, and the Katholieke Universiteit Leuven. It contains interpretation algorithms and stores some clinical data related to HIV treatment. CPT was developed at Stanford University and determines the prevalence of HIV drug resistance in a population.

Some of the other international Web portals for managing HIV treatment information are listed in Table 7.

Table 7. Descriptions of Web portals for managing HIV treatment information.

Web portal	Description
Stanford University HIV Drug Resistance Database [51]	This portal determines the interpretation results of the REGA Institute rules, Agence Nationale de Recherches sur le SIDA (ANRS) rules and the Stanford HIVdb rules. It also allows the use of specific user-defined rules using the Algorithm Specification Interface (ASI) and also allows one the opportunity to create a graphical record of a patient's ARV history, viral loads, CD ₄ counts, and sequence data.
HIVResistanceWeb [52]	This information portal allows information sharing on ARV resistance and clinical virology. It has a store and forward email-based system that allows one to interact with experts.
Los Alamos HIV database [53]	This information portal contains data on genomes, epitopes, drug resistance mutations, and vaccine trials. It is funded by the Division of AIDS of the National Institute of Allergy and Infectious Diseases (NIAID).

These individual information portals are limited by the following:

- The tools they employ in determining HIV drug resistance information. Each information portal uses its own interpretation algorithm and, if collaboration does exist, it consists of simply reporting the outputs of the various algorithms. This causes confusion as some of these interpretation algorithms are disparate, even when the same mutations are analyzed.
- They do not have any means of a real-time expert consultation.
- They are not integrated into a full electronic medical record, which will add the advantage of continuity of care and facilitate tele-HIV-management.

- No individual portal has a variety of tools that can be used to manage HIV therapy.

Methods

Part 1: Developing a Single Interpretation Algorithm

The goal of Part 1 is to develop an HIV drug resistance interpretation algorithm capable of providing a single interpretation to genomic analysis.

This part of the study is divided into three main objectives: (1) determining the extent of the disparate information provided by some gold standard interpretation algorithms using the latest version of the interpretation algorithms; (2) developing a novel algorithm to collate the HIV drug resistance interpretation information of these gold standard algorithms into a single easily

understandable output; and (3) analyzing the collated algorithm in terms of specificity, sensitivity, and accuracy.

1. Determining the extent of the disparate nature of some gold standard interpretation algorithms using the latest version of these algorithms.

Over time with each new version, interpretation algorithms have improved in predicting ARV drug resistance. Previous comparisons between interpretation algorithms have had some shortcomings:

- Each interpretation algorithm has different measures or levels of resistance;
- Non-contemporary versions of interpretation algorithms were used in the interpretation;
- The interpretation algorithms were applied to different data sets; and
- Few interpretations make use of complex statistical analysis to determine if the differences are in fact significant or not.

The latest versions of different interpretation algorithms will be applied to a single data set extracted from a publicly available anonymized database, the Stanford HIV drug resistance database [51]. The measures of resistance for each interpretation algorithm will be determined, grouped, and analyzed.

2. Developing a novel algorithm to collate the HIV drug resistance interpretation of these gold standard interpretation algorithms into a single output.

The gold standard algorithms may be collated by:

- Weighted output. Different levels of complexity may be applied to determine a single interpretation from multiple interpretations. A simple majority-voting scheme may be applied, where a count of the interpretations of each algorithm is kept. The single interpretation is obtained by determining the resistance outcome with the highest weighting.
- Machine learning on gold standard outputs. Different machine-learning techniques may be applied to the data in order to obtain a single interpretation. Machine-learning techniques work by determining a mapping between a given set of input and desired outcomes and then, using this learnt mapping function, it predicts the output, given a set of inputs. Each interpretation produced for a single resistance profile by the different interpretation algorithms can be the input to a machine-learning algorithm. The output will be the actual HIV-ARV resistance measure determined by fold resistance values. The algorithm will then learn a mapping between the interpretation results obtained using various interpretation algorithms and the actual HIV-ARV resistance measure. One such algorithm that may be employed is a support vector machine.
- Creating a simulated boosted dataset both by modeling the strengths and weaknesses of the gold standards.

3. Analyzing the collated algorithm in terms of specificity, sensitivity, and accuracy.

The specificity, sensitivity, and accuracy associated with predicting ARV drug resistance will be calculated for each algorithm and then compared using statistical analysis.

Contribution

The literature does not indicate the current state of disparity between gold standard interpretation algorithms. Combining the interpretation algorithms to form one single interpretation is novel.

Part 2: Predicting CD4 Count From Genome Data

This part of the study may be divided into three parts:

1. Investigating the possibility of creating a machine-learning algorithm that predicts the current CD₄ count of a patient using genome sequences, viral loads, and time;
2. Investigating the possibility of creating a machine-learning algorithm that forecasts the medium term change in CD₄ count of a patient using current genome sequence;
3. It is acknowledged that genome sequencing is more expensive and resource intensive than CD₄ cell count measurement. However, the cost of genome sequencing is offset by the numerous bioinformatics applications that may be applied to the genome sequence to predict and analyze other physiological measurements and diseases. This study, however, will also investigate the possibility of creating a machine-learning algorithm that forecasts the medium term change in CD₄ count of a patient using standard of care data.

Methods

Datasets will be obtained from the Stanford HIV drug resistance database (<http://hivdb.stanford.edu/>), which is publicly available and contains data from clinical trials. Subtype B consensus protease (PR) genome sequences, CD₄ count, viral load, and the number of weeks from the baseline measure of CD₄ count for each patient sample will be determined by joining individual datasets using the sample identifier (the unique number that identifies a sample) and date. Data of patient's genome sequences and associated viral load and CD₄ count data at different time points will be extracted.

The changes in CD₄ count will be grouped into categories and a classification model will be built based on the changes. Different groups of inputs will be created and each will feed into the machine-learning algorithm separately, forming three models. Some of these input groups will be:

- Input1: consisting only of genome sequence;
- Input2: consisting of genome sequence and current viral load; and
- Input3: consisting of genome sequence, current viral load, and number of weeks from the current CD₄ count to baseline CD₄ count.

Contribution

Currently, there is not a chemical test or computer model developed to forecast future changes to the CD₄ count.

Part 3: Developing Web-based Tool for Determining Optimal Therapy

The goal of Part 3 is to develop a Web-based electronic tool that assists clinicians in determining the optimal therapy for patients indicative of HIV drug resistance.

There is evidence that suggests that resistance testing is beneficial:

- A two-factorial (genotyping and expert advice), randomized, open label, multicenter trial [54] was undertaken to determine if there is any benefit in using genotyping rather than the expert's direct knowledge when prescribing ARVs. The conclusion was that genotyping benefits the overall optimal care of HIV patients.
- The VIRalliance SAS [55] group clearly demonstrated in their study that "resistance testing prior to initiating or switching antiretroviral therapy" is essential.
- Mascolini et al [56] questioned 600 clinicians about the effect of resistance testing on their diagnosis and regimen they prescribe. They confirmed that "if the assay detected partly or multidrug-resistant virus, then the large proportions of respondents (indicated that they would) change their treatment choice."
- Hirsch et al [57] found that "resistance testing can improve virological outcome among HIV-infected individuals."
- The Can Resistance Enhance Selection of Treatment (CREST) [25] study (a 48-week follow-up randomized trial) found that genotypic drug resistance testing may be beneficial in the management of HIV infection.

Objective

The goal is to combine the tools mentioned previously, and possibly other bioinformatics tools, into one seamless application.

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Conflicts of Interest

None declared.

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Methods

Java, HyperText Markup Language (HTML), PHP: Hypertext Preprocessor (PHP), and other paradigms will be used to create a Web-based portal that will integrate the different tools. An important aspect to take into account when building the model for the HIV management system is security. Dwivedi et al [58] argued that electronic medical records will only become a reality if security takes a prominent role in design considerations and during implementation. Two of the most promising techniques for incorporating security into any information system are public key infrastructure and biometrics. Public key encryption is a nondeterministic polynomial time complex technique that ensures high-level security. Biometrics use physical or behavioral traits to identify an individual. The exact means of integration and security model to be used will only be determined after the individual tools are built.

Contribution

The creation of an electronic medical record-based virtual HIV clinical support system that aids in the determination of the best HAART combination, using a combined ARV resistance interpretation, CD₄ count prediction, and the other methods described is novel.

Conclusion

The outcome of this study is to facilitate the acquisition, storage, management, analysis, and interpretation of information by physicians. In personalized medicine, it is essential that information be interpreted and presented clearly and concisely. We expect that the proposed tool will aid in this aspect.

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Abbreviations

AIDS: acquired immune deficiency syndrome
ANRS: Agence Nationale de Recherches sur le SIDA
ARV: antiretroviral
ASI: algorithm specification interface
CPT: Calibrated Population Resistance Tool
CREST: Can Resistance Enhance Selection of Treatment
CRF: circulation recombinant forms
DR_SEQAN: Drug Resistance SEquence ANalyzer
FI: fusion inhibitors
HAART: highly active antiretroviral therapy
HIV: human immunodeficiency virus
kNN: k-nearest neighbor algorithm
LASSO: least absolute shrinkage and selection operator
MLP: multilayer perceptron
NIAID: National Institute of Allergy and Infectious Diseases
NRTI: nucleoside reverse transcriptase inhibitors
PHP: PHP: Hypertext Preprocessor.
PI: protease inhibitors
RBNN: radial basis neural networks
RTI: reverse transcriptase inhibitors
SVM: support vector machines
WHO: World Health Organization

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