Research protocol Title: The feasibility of an artificial intelligence conversational agent to improve varenicline adherence: A study protocol

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Abstract:

Background: Interventions to increase medication adherence may help improve treatment and healthcare system efficiencies and cost-effectiveness. Digital health solutions are such intervention that can help improve medication adherence by providing reminders, answering questions and tracking medication intake. "ChatV" is an evidence-based, patient- and health care provider-informed healthbot to improve adherence to varenicline, a smoking cessation medication.

Objective: To conduct a feasibility study to examine if the ChatV healthbot is used as intended, as well as to determine the appropriateness of proceeding with a randomized controlled trial.

Methods: We will conduct a mixed-methods feasibility study where 40 participants will be prescribed varenicline and interact with the healthbot programmed to provide medication reminders, answering questions about varenicline and smoking cessation, and tracking medication intake and number of cigarettes. Follow-up survey data will be collected at 1, 4, 8, and 12 weeks and a semi-structured interview will be conducted at 12 weeks to understand participants' experiences using the healthbot. A health equity lens will be adopted during participant recruitment and data analysis to understand and address the differences in uptake and utilization of this digital health solution among diverse socio-demographic groups. The Taxonomy of Implementation Outcomes will be used to assess the feasibility, i.e., acceptability, appropriateness, fidelity, adoption and usability. In addition, medication adherence and smoking

cessation will be measured to assess preliminary treatment effect. Interview data will be analysed using framework analysis method.

Results: The study has been approved by the Centre for Addiction and Mental Health's Research Ethics Board (#50/2022). Participant enrollment for the study began in May 2024.

Conclusion: By employing predetermined progression criteria, the results of this preliminary study will inform the determination of whether to advance towards a larger randomised controlled trial to test the effectiveness of the healthbot. Additionally, this study will explore the acceptability, appropriateness, fidelity, adoption, and usability of the healthbot. These insights will be instrumental in refining the intervention/healthbot.

Trial registration information:

Registry name: Clinicaltrials.gov

Registration URL: https://classic.clinicaltrials.gov/ct2/show/NCT05997901

Registration number: NCT05997901

Key words: Medication Adherence, Smoking Cessation, Varenicline, Healthbot, Evaluation

Introduction

Medication adherence presents a significant and pressing challenge across global healthcare systems [1]. This problem spans across various medical conditions, from chronic illnesses like hypertension, diabetes, and cardiovascular disease, to acute infections [2]. Non-adherence to medication regimens can lead to a cascade of problems, including decreased treatment effectiveness, a higher risk of disease progression or complications, medication resistance, increased healthcare costs, and a reduced overall quality of life for patients [3]. It also places an additional burden on healthcare providers who must constantly navigate the complexities of patient adherence to optimize treatment outcomes. Addressing medication adherence is not only a matter of improving individual health, but also a vital step toward more efficient healthcare systems and improving population health.

One notable area where medication adherence could have a significant effect on public health is with smoking cessation medications. Tobacco smoking is not only extremely addictive [4], it damages almost every organ in the body [5] and is a leading cause of health inequalities [6]. Despite decades of efforts to reduce the smoking prevalence in Canada [7], over four million (15%) Canadians smoked in 2020 [8]. Tobacco use remains the leading cause of preventable death in Canada [9]. and following smoking cessation, the risk for developing tobacco-related diseases gradually decreases over time [10].

Varenicline, a partial agonist of the alpha4 beta2 nicotinic receptor, is one of the most effective smoking cessation medications associated with a doubling of long term quitting with 12 weeks of continuous treatment [11]; however, adherence is a major barrier to achieving and maintaining abstinence [12-14]. Among those who take varenicline for smoking cessation, over one third stop to taking the medication by the second week of treatment, and these patients are significantly less likely to quit smoking [15-18]. In addition, several studies that have examined the correlation

between socio-demographics and adherence to varenicline have found male sex [15, 19], older age [15, 19-21], white race [21, 22], and higher education to be associated with better adherence [21]. Conversely, one study found greater age was associated with poorer adherence [21].

One of the most effective strategies to improve adherence to medication is tailored behavioral interventions [23]. Research has also shown that the use of technological solutions is crucial to providing personalized, cost-effective, and evidence-based interventions [24]. One such digital health solution is web based programs integrating conversational agents or "healthbots" that can be helpful in improving adherence to medication [25]. Healthbots have greater functionality compared with applications providing simple text message reminders since they can track medication intake, provide information about side effects, and answer medication-related questions [26, 27].

The "ChatV" healthbot is an example of such a digital health solution that we developed to improve adherence to the smoking cessation medication varenicline [28]. We utilized a theory-based patient-centred approach through the Discover Design Build and Test framework [29] to design the healthbot by conducting a rapid review to explore the barriers and facilitators to varenicline adherence, interviewing 20 patients and 19 healthcare providers to understand similar barriers and facilitators as well as features to be included in a healthbot that may improve varenicline adherence. The data from these sources was analyzed using the COM-B (Capability, Opportunity, Motivation- Behaviour Change) [30] model of behaviour change and its associated framework (Theoretical Domain Framework) [31] and taxonomy (behaviour change techniques taxonomy) [32] to identify the features to be included in the healthbot. We used the Wizard of Oz methodology [33] to build a library of responses that were programmed in the healthbot to answer users' questions. We are currently beta testing the minimal viable product that has the

following features: 1) scheduling and receiving reminders for varenicline dosing; 2) setting a smoking quit date; 3) answering questions related to varenicline (e.g., guidance for missed doses) and smoking cessation (e.g., strategies to reduce cravings); 4) providing information and strategies to manage side effects [12, 15, 18]); 5) tracking medication use and smoking; and 6) encouraging participants to increase their motivation to maintain medication intake and continue their quit attempts. Throughout the development of the healthbot, a health equity lens was adopted to address any disparities in varenicline use and healthbot features between different demographic characteristics.

In this protocol, we detail our plans to examine the uptake, usability, acceptability, and appropriateness of ChatV (i.e. feasibility) [34] and to determine whether progression to a fully powered randomized controlled trial (RCT) is warranted.

Methods

Design

We will conduct a non-randomized single arm feasibility study.

Participant recruitment.

We will recruit 40 participants. In order to ensure diversity with respect to age, gender, race, and socio-economic status, we will purposefully recruit participants through a variety of methods, including: the Centre for Addiction Mental Health's (CAMH) research boards where recruitment flyers are posted for patients to explore research opportunities; through healthcare providers at CAMH programs (e.g., Smoking Treatment for Ontario Patients (STOP) Program, Aboriginal services, Rainbow services) and partnering organizations (Rainbow Health Ontario); the STOP Program's list of people who are seeking treatment for smoking and who have consented to be contacted for future research studies; and social media and community boards. Research staff

members will conduct a pre-screening for those people who are interested, and if eligible, participants will be enrolled in the study.

Eligibility.

Individuals seeking treatment for their tobacco use who smoke 10 or more cigarettes a day, are willing to set a quit date in the next 30 days, are willing to take varenicline for 12 weeks, are aged ≥ 18 years, speak/read English, have a smartphone with data plan, report being committed to answering questions during follow-up, and live in Ontario.

Exclusion criteria.

Have contraindications to varenicline use, are pregnant, planning to become pregnant, or breastfeeding, or participated in the co-design phase.

Ethics.

The CAMH Research Ethics Board (REB # 050/2022) has provided approval to conduct the study and all participants will provide written informed consent before participation.

Procedures.

The research team will inform potential participants about the study and evaluate if they meet the inclusion criteria. If they qualify, participants will receive a consent form and arrange a phone-based discussion to obtain consent. After obtaining consent, participants (n=40) will complete an online questionnaire, covering: socio-demographic characteristics, nicotine dependence [35], and an adapted scale to measure varenicline adherence self-efficacy [36-38]. After completing the questionnaire, participants will have a virtual or in-person visit with a healthcare provider for eligibility confirmation and to obtain a prescription for varenicline for the first four weeks (one tablet [0.5 mg] daily for the first three days, one tablet [0.5 mg] twice daily for the next four days, and one tablet [1 mg] twice daily for three weeks). In addition, research staff will show

participants how to use the healthbot on their phones. Medication will be provided in-person or, in the case of virtual contacts, mailed to the participants. A follow-up visit will be scheduled at two weeks where healthcare providers will assess the participant's tolerance of varenicline and provide a prescription for the remaining eight weeks (one tablet (1 mg) twice daily or a different dose depending on the tolerance of each participant). Any unanticipated problems (i.e., adverse events that are unexpected in terms of severity, nature or frequency; are related, or possibly related to participation in the research; and that suggest that the research places other research participants at greater risk of harm) will be documented as applicable and reported to the Research Ethics Board, and adverse drug reactions will be reported to the Market Authorization Holder (APOTEX) as applicable.

Participants will be required to complete surveys at 1, 4, 8, and 12 weeks. When participants join the study they will be able to opt to respond to these questions using either the healthbot or an online platform. Those who do not complete the online or healthbot follow-up within the designated timeframe will receive a phone call from our research staff. Additionally, after 12weeks of joining the study, participants will be invited to participate in a 1-hour semi-structured phone interview. Participants will receive honorarium in the form $30 gift card after completion of the 4 week follow up survey, and $40 gift card after completion of the 12 week interview.

Measures.

The Taxonomy of Implementation Outcomes of Proctor et al. [39] guides our selection of implementation outcomes (Table 1) as follows:

Acceptability **"**is the extent to which an innovation is agreeable, palatable, or satisfactory to a stakeholder" [39]. In order to measure acceptability we will utilize the Acceptability of

Intervention Measure (AIM) in the follow up surveys, as well as in the semi-structured phone interviews.

Appropriateness is the "perceived fit or compatibility of an innovation with a practice setting or context" [39]. In this study, appropriateness will be assessed on an individual basis, including factors such as alignment with users' attitudes, needs, and background, as measured in the 12-week survey., with the Intervention Appropriateness Measure (IAM), a validated 4-item intervention appropriateness scale [40], and explored in depth in the semi-structured interviews.

Fidelity is "the extent to which an intervention is used as intended" [39].For this study, in the semi structured interviews we will investigate the functions of the healthbot that participants used, the purposes for which they employed it (such as answering questions or seeking support), the frequency of usage, and the quality, specifically whether the healthbot provided accurate information.

Adoption is "the intention, decision, or initiation of use for an evidence-based practice, characterizing it at the level of the provider or organization" [39]. Since the concept of adoption is closely related to the actual usage of systems, researchers investigating behavioral intervention technologies, such as the healthbot, have extended this level of analysis to include consumer behavior. [41]. In this study, we will measure the adoption of the healthbot by analyzing analytics data throughout the 12 weeks that the participant is scheduled to take the varenicline. This data will allow us to evaluate the timing (day/time) of user interactions with the healthbot, the specific features utilized, and the duration of engagement. Thus, we will have objective data of actual adoption of the healthbot by each participant. Additionally, during the semi-structured interviews, we will probe for participants' subjective perceptions of their use of the healthbot

Usability will be assessed using the System Usability Scale (SUS) [42]. The SUS is a 10-item measure assessing usability and user satisfaction with technology.

The AIM, IAM and SUS all have items that are rated on a 5-point Likert scale (1=completely/strongly disagree to 5=completely/strongly agree).

Medication Adherence and Smoking Status Participants will be asked about their smoking status [43] and adherence to varenicline, using timeline follow-back (TLFB) [44], in the surveys collected at 1, 4, 8, and 12 weeks. Participants will report the number of pills taken since the previous assessment. Participants who log their varenicline use in the healthbot will be able to refer to these data when filling out the TLFB. We chose the TLFB method for assessing adherence because the 12-week TLFB measure demonstrates a moderate correlation with saliva varenicline levels and is widely regarded as the most practical measure of varenicline adherence [16]. In order to assess the feasibility and accuracy of measuring adherence using TLFB, participants will also be asked to send pictures of their varenicline blister packs at 1, 4, 8 and 12 weeks. This additional measure will also help explore which method to assess adherence should be used for any future research studies (e.g., RCT). Smoking abstinence will be defined by a negative response to the dichotomous 7-day point prevalence question, "Have you had a cigarette, even a puff, in the last seven days?"

Table 1. Summary of measures

Measures	**Survey timeline**					**Interview**	**Analytics**
	Baseline	Week 1	Week 4	Week 8	Week 12	Week 12	Week 1-12
Demographics	X						
Adoption						X	X

Acceptability		AIM	AIM	AIM	AIM	X	
Appropriateness		IAM	IAM	IAM	IAM	X	
Fidelity						X	
Usability		SUS	SUS	SUS	SUS	X	
Medication Adherence		TLFB	TLFB	TLFB	TLFB	X	
Smoking Status		X	X	X	X	X	

Analysis of survey data.

We will calculate descriptive statistics, including means, medians, ranges, and standard deviations, for the demographic data as well as for the AIM, IAM, and analytics data captured by the healthbot internal logs. All scores will be analyzed using the appropriate guidelines provided by Weiner[40] (acceptability and appropriateness) and the U.S. Department of Health and Human Services [45] (usability). Consistent with previous studies, adherence will be defined as taking ≥ 80% of prescribed varenicline [46-49]. We will not treat adherence as a continuous variable because it is likely to be strongly bimodal, and is not necessarily linearly associated with the cessation outcome. We will calculate the percentage of participants that were adherent at week 12 and who reported not having smoked in the last seven days. These results will serve as progression criteria to determine whether a full scale RCT is warranted. Although the sample size will be insufficient for meaningful regression analysis, especially given potentially non-linear effects of age, we will also test for differences across age and gender groups using t-tests and chi-squared tests. Power for these comparisons will be low; therefore, this analysis will be an exploratory evaluation of large adherence or outcome differences that may be important to future study design, and interpretation will focus on observed differences and confidence intervals.

Analysis of semi-structured interviews.

We will use framework analysis [50] to analyze the data. Specifically, we will use the Proctor et al.'s implementation outcomes [39], with an intersectional lens, as the a priori framework. Framework analysis is method used to draw descriptive and explanatory conclusions from qualitative data and includes six steps: 1) verbatim transcription of interviews; 2) familiarization of interviews; 3) coding/labelling the data; 4) developing a framework by grouping and categorizing codes; 5) indexing transcripts using the developed framework; and 6) reducing and charting data into a matrix. Interview findings will help us contextualize the findings from the surveys and information collected from the use of the healthbot. For example, we will understand why the healthbot was or was not used (adoption): if it was used as intended (fidelity), what about the healthbot participants' found agreeable and what they did not (acceptability); what features, if any, aligned with participants' attitudes, needs, and background (appropriate); and how other features would need to change in order to align with their needs. In addition, we will be able to understand how social identity (e.g., age, gender) and power structures (e.g., ageism, sexism) played a role in these results. This will provide us with important information to improve the healthbot through an equity lens.

Triangulation of findings.

Once the survey data and interviews are analyzed, we will triangulate the results by listing all the findings on the same page to identify instances where findings from each method align (convergence), provide additional insights on the same topic (complementarity), or seem to conflict with one another (discrepancy or dissonance) [51, 52]. Triangulating the data will allow us to contextualize the quantitative findings and explore "inter-method discrepancy" that might lead to a better understanding of how the healthbot works and the modifications needed.

Exploring the feasibility of the approaches on recruitment, retention and data collection

This study, using the 'Stop, Amend, Go' progression criteria for pilot studies [52], will help determine if proceeding with a RCT is a logical next step and whether additional adjustments are necessary. We will only conduct a full scale RCT if none of the criteria outlined in Table 2 meet the 'Stop' criterion (unless we see that there are contextual issues that can be modified to overcome the identified problems). If one or more of the concepts in Table 2 meets the 'Amend' criteria, the trial will proceed to an RCT only if the issue(s) can be addressed. If all concepts in Table 2 satisfy the 'Go' criterion, we will proceed with planning an RCT.

Table 2. Criteria to decide if RCT is warranted

Criteria	**Stop**	**Amend**	**Go**
Patient recruitment	If <30 patients are recruited within 12 months	If 30-40 patients are recruited within 12 months	If 40 patients are recruited within 12 months
Patient Retention	If <25% patients answer the 12 week survey	If 25.1-79.9% patients answer the 12 week survey	If ≥ 80% patients answer the 12 week survey
Missing Data – Medication Adherence or Smoking Status	If > 60% of adherence data and/or smoking status are missing	If 21–59% of adherence and/or smoking status data are missing	If ≤ 20% of adherence and/or smoking status data are missing

Acceptability, Appropriateness	If mean score for the AIM and/or IAM ≤ 8	If mean score for the AIM and/or IAM 9-12	If mean score for the AIM and/or IAM ≥ 13
Usability	If mean SUS score ≤ 40	If mean SUS score 41-67	If mean SUS score ≥ 68
Adoption	If mean use ≤ 20 times	If mean use 21-79 times	If mean use ≥ 80 times

Results

Participant enrollment for the study began in May 2024.

Discussion

Despite the proven effectiveness of varenicline in aiding smoking cessation [53], a significant number of individuals attempting to quit continue to smoke because they struggle with adhering to their varenicline regimen [12-14]. While there are proven strategies to help people adhere to their medications, they have been hard to implement. Digital technology for medication adherence has started to emerge [54, 55]; whether these tools can be feasibly implemented and adopted, especially within diverse and disadvantaged populations, remains largely unknown.

In this protocol, we outline the methodology to assess the uptake, usability, acceptability, and appropriateness of ChatV and assist in determining whether it is appropriate to advance to an RCT to gauge the effectiveness of the intervention. This study will address many limitations of previous mHealth trials [56, 57] including using an intervention that clearly outlines the behaviour-change theory used, and intervention content. In addition, this study provides well outlined a priori criteria for progressing to an RCT. This will enhance its replicability.

Furthermore, this study will provide insights into potential mechanisms underlying the intervention's impact, shedding light on the effectiveness, or ineffectiveness, of its various components and offering possible explanations.

In summary, the results of this feasibility study will provide much needed data and insight into the potential implementation of ChatV to augment adherence with smoking cessation medications. In addition, this project has the potential to increase our understanding of how digital tools can improve adherence to other medications in a cost-effective manner.

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Data Availability

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

Authors' contribution

NM conceived the study with the support of JR, PS, SV, LZ, MR.

NM (lead), KM, ME, SH, RT, PS, have shaped the intervention (healthbot).

NM (lead), KM, ME and were involved in gaining ethical approval.

NM and KM wrote the first draft of the manuscript.

All authors reviewed and edited the manuscript and approved the final version of the manuscript.

Conflict of interests

The authors declare that they have no conflicting interests with respect to this manuscript; however some authors have general disclosures to report. NM reports receipt of funding from Canadian Institutes of Health Research, Canadian Cancer Society, and from the Discovery Fund of CAMH. PS reports receipt of funding from Canadian Institutes of Health Research, Canadian Cancer Society, Pfizer Inc., Pfizer Canada, and Ontario Lung Association. PS also reports that through an open-tender process, Johnson & Johnson, Novartis, and Pfizer Inc. are vendors of

record for having provided smoking cessation pharmacotherapy for research studies at free or discounted rates. PS holds the Vice-Chair, Research and Giblon Professor in Family Medicine Research, a University Named Professorship at the University of Toronto. OM reports receiving grant and salary support from the Centre for Addiction and Mental Health and the Department of Family and Community Medicine at the University of Toronto through the New Investigator Award.

Abbreviations

RCT: Randomized Controlled Trial

CAMH: Centre for Addiction Mental Health

STOP: Smoking Treatment for Ontario Patients

REB: Research Ethics Board

AIM: Acceptability of Intervention Measure

IAM: Intervention Appropriateness Measure

SUS: System Usability Scale

TLFB: Timeline Follow-Back

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