Mobile technology to extend clinic-based counseling for HIV+s in Uganda (EXTEND)

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Glossary of Terms

AOR	Adjusted odds ratio
AUDIT-C	Alcohol use disorders identification test (alcohol screening tool to identify hazardous drinking)
ART	Antiretroviral therapy
CAB	Community advisory board
CITI	Collaborative Institutional Training Initiative
DBS	Dried blood spot
FGD	Focus group discussion
IDI	Individual in-depth interview
TrEAT/HWHL	Trial for Early Alcohol Treatment/Healthy Women, Healthy Living
HIV	Human immunodeficiency virus
ISS	Immune Suppression Syndrome (i.e. HIV)
IVR	Interactive voice response
Live booster	Live counselor-delivered phone-based booster call
mHealth	Mobile health
MUST	Mbarara University of Science & Technology
NIAAA	National Institute of Alcohol Abuse and Alcoholism
PEth	Phosphatidylethanol (phospholipid that can be measured in blood as a marker of prior 3 weeks' drinking)
RA	Research assistant
SMS	Short message service (text message)
SOC	Standard of care
SSA	Sub-Saharan Africa
Tech booster	Automated two-way SMS or IVR delivered booster session
Unhealthy drinking	Drinking at or above a level that increases the risk of physical or social consequences,[59] defined here as AUDIT-C positive (score ≥3 for women and ≥4 for men)
WHO	World Health Organization

1. Study Synopsis

Alcohol consumption is a critical predictor of poor HIV outcomes such as reduced antiretroviral adherence and lack of viral suppression. Reducing unhealthy alcohol use among those with HIV may improve HIV outcomes and thus is a high priority, especially in sub-Saharan Africa (SSA) where HIV prevalence and unhealthy drinking rates are high. Multi-session interventions that combine in-person visits with booster phone calls to reinforce the in-person counseling have shown good efficacy. This project aims to compare the uptake, acceptability, efficacy, and cost in reducing unhealthy alcohol use and increasing viral suppression in a randomized controlled trial with persons in HIV care in rural Uganda (n=270). The study arms are (a) in-person counseling during 2 quarterly clinic visits plus live booster phone calls every three weeks in the interim (b) in-person counseling during 2 quarterly clinic visits plus tech (choice of SMS or IVR) boosters once to twice weekly in the interim; and (c) standard of care (SOC) control (brief unstructured advice, with a wait-listed intervention). The data collection for the study will include data to determine costs related to the intervention and control groups. In summary, results from this RCT will inform the design of a larger trial of a low-cost intervention to reduce alcohol use and increase viral suppression among those with HIV in SSA.

2. Introduction

Alcohol consumption is a critical predictor of poor of HIV outcomes, especially in sub-Saharan Africa (SSA), where both are extremely common.[9] Heavy alcohol use has been associated with reduced antiretroviral adherence,[10] decreased HIV suppression,[11] and increased mortality among those with HIV.[12,13] Thus, reducing unhealthy alcohol use may improve HIV outcomes and is a high priority worldwide.[14] Screening and brief counseling for alcohol use, especially multi-session approaches, have shown evidence for reducing alcohol use in resource rich settings[5] and among persons with HIV[15-18] with few exceptions.[19,20] Multi-session interventions have been efficacious among persons in SSA,[17,21,22] while those with 1-2 sessions have demonstrated mixed results.[23-25] However, there are significant cost and human resource barriers to multiple session interventions in SSA, and it is not known whether alcohol interventions can improve HIV outcomes. Thus, the long-term goal of this research is to develop and test interventions to reduce alcohol consumption and improve HIV outcomes, that can be feasibly integrated into routine HIV care in SSA.

Multi-session interventions that combine in-person visits with booster phone calls to reinforce the in-person counseling have shown good efficacy.[16,26] Because cell phone use in Uganda is high, phone-based booster sessions conducted in-between the in-person sessions (that coincide with regularly scheduled clinic visits) may be feasible. However, phone-based booster sessions delivered by a live counselor ("live boosters") can be costly, time-consuming, limited to working hours, and dependent on good phone connections. Alternatively, automated cell phone-based booster sessions ("tech boosters"), can be conducted via interactive systems such as two-way Short Message Service (SMS, i.e. text messaging) or Interactive Voice Response (IVR) that allow for brief interactive sessions, with messages that are tailored to the participants' drinking goals and gender. Such automated tailored mobile phone-based interventions have been successful in improving several health behaviors[27-31] in diverse populations. However, the uptake, acceptability, cost, and efficacy of live and tech booster calls for interventions for reducing alcohol use and improving HIV outcomes in SSA is not known. We hypothesize that automated mobile phone-based technology can be leveraged as an efficacious way to implement multi-session alcohol interventions at a low burden and cost to both providers and patients in low resource settings.

2.1. Specific Aims

The goal of this study is to estimate the uptake and acceptability, efficacy, and cost of methods of delivery of an intervention to reduce unhealthy drinking and HIV viral failure in a randomized controlled trial (RCT) among persons in HIV care in rural Uganda (n=270). The arms will be (1) in-person counseling during 2 quarterly clinic visits plus live booster phone calls every three weeks in the interim; (2) in-person counseling during 2 quarterly clinic visits plus tech (choice of SMS or IVR) boosters once to twice weekly in the interim; and (3) standard of care (SOC) control (brief unstructured advice, with a wait-listed intervention). We will measure outcomes as follows:

a) **Outcome 1 is the efficacy** of an intervention to reduce unhealthy drinking and reduce HIV viral failure. This will be measured at nine months using self-report (number of drinking days in the past 21) and phosphatidylethanol (PEth), an alcohol biomarker, and viral suppression.

b) **Outcome 2 is the uptake and acceptability** of an intervention to reduce unhealthy drinking and reduce HIV viral failure: We will examine the completion rates of the live and tech boosters, conduct post-intervention satisfaction surveys, and conduct qualitative interviews among a subsample of study participants (n=25-30) to determine acceptability and experiences with the three study arms.

c) **Outcome 3 is the estimate of the cost of the delivery methods** of an intervention to reduce unhealthy drinking and reduce HIV viral failure: We will collect data to estimate the cost of each study arm and each mode of tech booster delivery to the patients and the clinic, including both start-up costs (e.g. initial fixed costs in tech system set-up) and maintenance costs (e.g. ongoing/recurring costs such as SMS/IVR fees, and personnel costs).

This study will be conducted in a large rural Ugandan clinic where we have 10 years of collaborative alcohol/HIV research experience. The end products of this study will be the comparisons of key outcomes to estimate effect sizes and inform the design of a future large-scale trial. The long-term aim is to implement interventions that reduce alcohol use and improve HIV outcomes feasibly and at low cost in low resource settings.

3. Background and rationale

Alcohol use has a high impact on HIV transmission and outcomes. Alcohol use has been consistently associated with reduced ART adherence,[10] with the odds of missing a dose increasing with each drink.[32,33] In a longitudinal study of 438 persons at the Immune Suppression Syndrome (ISS) HIV Clinic in Mbarara, Uganda (our proposed study site), unhealthy alcohol use (AUDIT-C score for women: ≥3, for men: ≥4) was the strongest independent predictor of <90% adherence (adjusted odd ratio [AOR] 2.56; 95% confidence interval [CI]: 1.41-4.66) and incomplete viral suppression (AOR: 2.51, 95% CI: 1.69–3.72).[11] Alcohol use has repeatedly been associated with increased sexual risk behavior and HIV transmission.[34-40] Approximately 25% of persons with HIV worldwide are unhealthy drinkers.[41-47] Thus, unhealthy alcohol use is a significant barrier to suppressing HIV, and reducing unhealthy drinking is consistent with NIH HIV priorities.

Multi-session in-person alcohol interventions are efficacious but not scalable. Counseling interventions to reduce alcohol consumption from risky levels before more severe consequences occur have shown efficacy to reduce drinking by 15-30% one-year post intervention,[5,48-55] and multi-session interventions have the strongest evidence of an effect on alcohol consumption.[5] In the few alcohol intervention trials conducted in SSA, the most consistent evidence for alcohol intervention efficacy was for interventions delivered over 4-6 in-person sessions,[17,21,22] as compared to those with one session,[23,24] or one session followed by a booster call.[25] Multi-session alcohol interventions for those with HIV conducted worldwide have been successful at reducing alcohol use,[15-18,22] with only a few exceptions.[19,20] Yet multi-session interventions with several in-person visits are unlikely to be scalable or cost-effective in SSA.[8]

Cell phones may be useful for multi-session interventions. We (co-investigators Chander and Hutton) recently tested a multi-session alcohol intervention for women with HIV in Baltimore (the Healthy Women Healthy Living [HWHL] study),[16] adapted from Project TrEAT (Trial for Early Alcohol Treatment) which included both men and women.[26] Both interventions were comprised of two brief in-person sessions, separated by a month, each followed by live phone-based booster sessions 2-3 weeks later; both were efficacious in reducing drinking.[16,26] Phone-based counseling has been successful in several behavior change interventions, including alcohol reduction,[56] smoking cessation,[57] reduction of depressive symptoms,[58] and increasing physical activity,[31] suggesting phones may provide an opportunity to increase the number of intervention sessions.

Cell phone usage has risen steadily in Africa;[60] cell phone ownership in the Mbarara ISS Clinic reached 82% at the end of 2015, with an another 14% having access to a shared phone (W. Muyindike, personal communication). Basic cell phones predominate and are inexpensive in SSA (ranging from $15-$20) with low cost pay-as-you-go plans, and it is free to receive calls and SMS. Thus, cell phones hold promise for delivering interventions to broad populations in SSA, such as persons with HIV.[61]

Automated interactive (2-way) interventions also hold promise.

SMS Health interventions that allow for a 2-way interaction, delivered via SMS (up to 160 characters, available on all cell phones) or multimedia messaging service (MMS, mostly available on smart phones) have proliferated in recent years (albeit mostly in high-income countries[62]); a review of 15 systematic reviews/meta-analyses covering 89 unique SMS/MMS trials was recently published.[28] The authors found overall positive effects on medication adherence, smoking cessation, diabetes management, weight loss, and physical health, although limitations to the findings were cited. A small number of studies have examined using SMS to reduce alcohol use.[63] These studies, conducted mostly among university students and young adults, have shown feasibility[64,65] and promising results.[2,3,66-68] SMS is available on all phones and used by most (80%) cell phone users.[60] However, the usefulness of SMS may be limited among those with low literacy. Reading literacy is 78% among adults in Uganda[60] and 71% in our study population, thus SMS may be challenging for a significant fraction of the target population.

IVR IVR is an automated mobile phone-based platform that differs from SMS in that the participant hears rather than reads a message, so IVR is advantageous for those who are not literate. IVR technology allows bi-directional communication, similar to SMS. Participants respond to questions by pressing buttons on the phone keypad. IVR has been used as a way to collect daily alcohol and substance use data,[69-71] and has shown promising results for alcohol interventions[72] and for daily alcohol self-monitoring.[15,73-76] A recent trial of an intervention to increase physical activity among older adults, found that a 2-way IVR intervention performed as well as a live phone-based counselor and significantly better than the control.[31] Thus, IVR could be a promising mode of automated delivery of phone-based booster sessions in low literacy settings.

Comparison of live versus automated booster calls. There are several strengths and limitations to consider for live versus automated interventions, including issues of network quality, message length, confidentiality, and literacy requirements (Table 2). While overall, analyses suggest that interventions with live counselors have better results than technology delivered interventions,[77-80] it is not known how these modes of delivery compare for booster session delivery. There is high enthusiasm for technology-based interventions[81] and several studies using SMS or IVR for improving ART adherence in SSA have been quite successful.[82,83] Advantages to 2-way automated messaging (SMS or IVR) include flexibility in the timing of the messages, standardization, and low cost, while disadvantages include the limited ability to personalize and, for SMS, literacy (Table 2). Live boosters allow for a more personal experience but have high counselor time and cost, may depend on phone network quality, and have low flexibility in timing for the calls. Thus we feel that there is considerable equipoise between the methods and impetus to explore both tech and live booster calls, and gather preliminary data on the uptake, acceptability, effectiveness, and cost of these methods.

Cost estimates for mobile technology interventions in SSA are scarce. Few studies have examined the costs associated with mobile phone-based interventions,[28,61] via live or tech delivery, although screening and brief interventions have been shown to be cost effective in the primary care setting in the US.[48,84,85] The preliminary cost data will guide short-term decisions on which interventions to include in a future larger trial, while long-term implementation decisions will also ultimately depend on cost.[8]

Valid measurement of unhealthy alcohol use is needed. In trials aiming to reduce certain behaviors, self-report of those behaviors can be especially problematic.[86-88] For example, a recent alcohol pharmacotherapy trial showed declines in self-reported heavy drinking days in both the treatment and the control arms, while PEth declined only in the treatment arm.[89] The authors suggested that the control arm may have experienced an effect due to knowing that the intervention was to reduce alcohol (demand characteristics), and recommended using PEth in addition to self-report in future alcohol intervention trials.[89] PEth is a phospholipid which is formed only in the presence of alcohol and thus is highly specific.[90] PEth is the most sensitive medium-term biomarker,[91] and PEth levels have been well correlated (Spearman's r= 0.6-0.8) with level of consumption in controlled studies.[92-95] We found that PEth was 95% sensitive and 73% specific for detecting prior 21 day heavy drinking, and highly correlated with the number of drinking days in persons with HIV in Uganda[95] we have subsequently used PEth to confirm suspected under-reporting in that setting.[96,97]

Table 1. Comparison of live versus automated phone-based counseling. Advantages highlighted and bolded.			
	Live phone counseling	2-way SMS	2-way IVR
Importance of reading literacy	**None**	High	**None**
Importance of technical/phone literacy	**Low**	Medium	**Low**
Air time needed to respond to messages	**No**	Yes	**No**
Dependence on phone network quality	High	**Low**	Medium
Limits to length of message	**None**	160 chars	**None**
Ability to verify persons answering	**High**	Need PIN	Need PIN
Uniformity of messages*	Low	High	High
Ability to personalize (i.e. use names)	**High**	**High**	Low
Ability to tailor messages	**High**	Medium	Medium
Two-way capability	**High**	Medium	Medium
Messages remain on phone*	No	Yes	No
Capability for participant to communicate with the counselor	**High**	Medium, delayed	Medium, delayed
Flexibility in timing of boosters	Low	**High**	**High**
Flexibility in timing of attending to the message	Low	**High**	Medium: call back option
Anticipated cost per person	High	**Low**	**Low**
*May be an advantage or a disadvantage			

3.1. Preliminary Studies

Target population characteristics. We have been conducting studies of alcohol consumption among persons with HIV in Uganda since 2006.[66,96,99-104] Self-reported current alcohol consumption among persons with HIV in Uganda ranges from 18% to 31%,[101-103] an under-estimate based on our studies of self-report compared to PEth.[96,99-101] We recently conducted longitudinal cohort studies of persons who reported any prior year alcohol consumption at HIV clinic entry (Biomarker Research of Ethanol Among Those with HIV [BREATH], R01 AA018631) and of the effect of unhealthy alcohol use on HIV disease progression prior to ART initiation (U01 AA020776), as part of the NIAAA Consortiums for HIV/AIDS Alcohol Research Translation (CHAART).[7] In total, 751 persons were enrolled, 465 reported current drinking, and 242 reported unhealthy drinking via the AUDIT-C (≥3 for women, ≥4 for men). Among these, the level of drinking was high (Table 3).

Need for intervention. The participants in the BREATH study were followed quarterly after HIV clinic entry, to determine how unhealthy alcohol consumption, (AUDIT-C positive or PEth≥50 ng/ml), changed over one year. We found that overall, there was no change in unhealthy alcohol consumption (per-month AOR for unhealthy drinking: 1.01; 95% CI: 0.94-1.07). However, there was a declining trend prior to ART (per-month AOR 0.91; 95% CI: 0.83-0.99) but increases after ART start (per-month AOR 1.11; 95% CI: 1.01-1.22). This pattern of declining and then rebounding unhealthy use after ART initiation suggests that reductions in unhealthy alcohol use are possible, but a systematic intervention is needed to sustain reductions over time. These results were supported by qualitative work in the same study, in which 59 participants participated in semi-structured interviews to examine the social, contextual, and psychological factors influencing attempts to change alcohol use over the year.[105] Reasons to decrease alcohol consumption included threats to and impact on financial security, interference with fulfillment of social obligations, and threatened social standing in the community. Reasons for continued or resumed drinking, which will be addressed in the intervention adaptation, included peer pressure to drink, social inclusion, stress relief, and overall enjoyment of consuming alcohol. Motives to

drink and to reduce drinking are similar to those found in other populations,[106] including persons with HIV,[107,108] suggesting that interventions that were successful elsewhere can be adapted to this setting.

Feasibility of tech boosters for alcohol interventions. Drs. Chander and Hutton have recently adapted the TrEAT/HWHL intervention for digital delivery (computer-based with SMS and IVR booster sessions) among sexually transmitted disease clinic patients in Baltimore (R01AA018632). Initial SMS response rates (75% of participants responded to SMS messages not requiring a response) demonstrate high engagement. Dr. Camlin et al. recently developed and tested a 2-way SMS-based intervention that increased postnatal HIV clinic visits by women and their infants in Kenya.[29] Messages were developed and piloted within a theoretical framework, via a series of FGDs and IDIs, using a strategy similar to that proposed here.

4. Study design overview

This study is a randomized controlled trial (RCT) to compare the uptake, acceptability, cost and efficacy in reducing unhealthy alcohol use and increasing viral suppression by study arm among persons in HIV care in rural Uganda (n=270). The RCT study arms are (a) in-person counseling during 2 quarterly clinic visits plus live booster calls every 3 weeks in the interim, (b) in-person counseling during 2 quarterly clinic visits plus tech (SMS *or IVR*) boosters twice weekly in the interim, and (c) standard of care control (brief unstructured advice, with a wait-listed intervention). We will obtain estimates of uptake, acceptability and cost, as well as efficacy in reducing alcohol use and decreasing viral failure for each study arm. We will utilize an alcohol biomarker, phosphatidylethanol (PEth) in addition to self-report in measuring reductions in alcohol use, and we will measure viral suppression at follow up study visits (6- and 9-month visits for PEth, and 9-month visits for HIV VL). The goal is to inform the design of a future large-scale trial and, ultimately, implementation.

The trial will be conducted during a 9-month period with the intervention occurring in the first 3 months with 6 months of follow-up. The primary outcomes will be measured 6 and 9 months post-randomization. Outcome 1 is alcohol use reduction measured by the number of drinking days (of prior 21) at 6 *and* 9 months. HIV viral suppression at 9 months is a secondary outcome. We will also measure intervention acceptability and uptake, as well as cost, by study arm.

4.1. Study setting

The EXTEND study will be conducted at the Immune Suppression Syndrome (ISS) Clinic of the Mbarara Regional Referral Hospital (MRRH) in southwestern Uganda. The adult HIV prevalence in Southwest Uganda is 8% and heavy alcohol use is common while other substance use is rare. There are over 12,000 active patients at the ISS Clinic; 25% are current drinkers. The ISS Clinic and pharmacy use electronic medical records (EMR) that will be leveraged for patient recruitment, and tracking.

5. Study Procedures

5.1. Recruitment

Participants will be recruited from the electronic medical records of persons attending the Mbarara ISS Clinic. The AUDIT-C is conducted routinely at the initial clinic visit. A clinic staff member who is also a member of the research team, e.g. the screener, record room staff, will initially approach those meeting these criteria. Persons meeting the initial eligibility criteria will be asked by the clinic staff member if they are interested in taking part in a research study. Those who agree will referred to the study RA to determine further eligibility criteria and provide informed consent.

5.2. Screening

Participants will be recruited from the ISS clinic by a clinic staff member. This person will examine clinic records to identify those who are coming in for appointments who meet study criteria. Persons meeting these pre-screening eligibility criteria will be invited to meet with a study RA. Those who agree will be screened to determine further eligibility criteria by the RA. Following the screening, the RA will seek informed consent from individuals who meet the inclusion criteria below for further study participation. The baseline visit will include collection of tracking information, a baseline survey, and blood draw. Participants randomized to the intervention arms of the study will complete session 1 of the intervention.

5.2.1. Inclusion criteria

Trial inclusion criteria include:

a) HIV-infected adult (≥18 years) attending the Mbarara ISS Clinic;
b) Prescribed ART for at least 6 months (confirmed via clinic records);
c) Consume alcohol at unhealthy levels (AUDIT-C score ≥3 for women, ≥4 for men, based on the prior 3 months);
d) Have daily cell phone access;
e) Fluent in Runyankole (the local language) or English;
f) Lives within 2-hour driving distance or 60 km of the study site (Mbarara ISS Clinic)
g) Be willing and able to agree to the study procedures.

5.2.2. Exclusion criteria

Exclusion criteria include:

a) Plans to move out of the catchment area within 6 months;
b) Participation in another research study;
c) Unable to give informed consent.

5.2.3. Informed consent process

Informed consent process for the randomized controlled trial (RCT) will be guided by a written consent document but will in fact consist mainly of an interactive conversation between the research assistant and the potential study participant. The RA will use the informed consent document (available in Runyakole, subjected to translation, back-translation, and revision for accuracy, clarity, and ease of comprehension) as a guide to discuss all content in the document with the potential participant. After each major section and any key points, the RA will pause and check for understanding—for example, by asking the participant to repeat back, in their own words, what "the right to refuse" means. The consent form is intentionally vague in order to protect the patient-subjects (i.e. it does not mention HIV or the ISS clinic), but that the consent discussion will cover more detailed and specific information about the study, including the following key points:

- subjects are selected because they are HIV+, and identified as drinkers in a previous study or in clinic records
- the study is about developing a technology-based intervention on alcohol use among HIV+ patients
- the potential consequences of an unintentional disclosure of a participant's HIV status because of the study

The informed consent process for both the screening and trial will take place in a private room at the ISS Clinic or research offices for the EXTEND study. The RAs will meet with eligible participants selected for recruitment to introduce the study and gauge potential subjects' interest. Potential participants will be told the purpose of the study and the reasons that they have been approached for participation. Key points to check with the participants enrolling in the trial include:

(1) They will be randomized to one of three arms of the study;
(2) They will be asked to provide their name and locator information to allow the investigators to locate them for future visits;
(3) They will be asked to bring in a support or helper person to help them with their drinking goals in the intervention;

(4) They will receive a reminder call prior to their study visits; and
(5) They may be asked to participate in further studies in the future.

The research assistant will explain that all information provided to study staff will be kept strictly confidential and restricted from access by anyone not involved with the study operations; that all identifying information will be kept separate from their study data (such as the transcript and voice recording from the semi-structured interview); and that all study data will be kept separately from their medical chart. Participants will be informed of the randomization process involved in an RCT and that they will not have the opportunity to choose which arm of the study they will be assigned to. Subjects will be told that they may decline to participate, may refuse to discuss any topic, and may withdraw from the study at any time. Persons unsure about participating will be encouraged to defer enrollment. When a subject agrees to participate, s/he will sign the consent form drafted. Participants will be given a copy of the consent form. If there are literacy reasons why a signature is not appropriate, individuals will be allowed to mark consent forms with an X or thumb print. The consent form includes information on how to contact the study staff to report problems or adverse events, such as violence or other harms related to disclosure that may have occurred in the study.

5.3. Enrollment and randomization

Participants will be recruited from the Mbarara ISS clinic by a clinic staff member. This person will examine clinic records to identify those who are coming in for appointments who meet these criteria: age 18 and older, on ART for at least six months (a time when alcohol consumption was found to resume),[80] reported alcohol use in the prior year at clinic entry or who reported alcohol use to research staff for other research studies being conducted at the ISS clinic. Persons meeting these pre-screening eligibility criteria will be invited to meet with a study RA. Those who agree will be screened to determine further eligibility criteria: fluency in Runyakole, living within two hours travel time from the clinic, owning or having daily access to a cell phone, and screening positive on the AUDIT-C. Although men are more likely than women to drink alcohol in Uganda,[124] two thirds of the ISS Clinic patients are women,[103] thus we expect 50% of participants to be women, as in our recent study of current drinkers at the ISS Clinic.[80] Of the 200 adult patients seen per day, 95% are on ART, and 25% report any prior year alcohol use at clinic entry. Based on our experience, we expect that 85% will accept screening, 95% will speak the appropriate language, 70% will live within two hours travel time of the clinic, 50% will test AUDIT-C positive, 85% will have cell phone access, and 80% will accept study enrollment. Thus, there will be at least 9 eligible persons per day. Due to clinic space limitations, it is very feasible to enroll 1-2 persons per day.

After eligibility is determined, we will enroll and randomize participants, to one of the three study arms, as follows:

- Arm 1: In-person counseling during 2 quarterly clinic visits plus live booster phone calls every three weeks in the interim;
- Arm 2: In-person counseling during 2 quarterly clinic visits plus tech (choice of SMS or IVR) boosters once to twice weekly in the interim;
- Arm 3: Standard of Care (SOC) control (brief unstructured advice with wait-listed intervention).

Randomization will be 1:1:1 and will be conducted by the study coordinator and the data manager (to keep the RAs blinded) using pre-printed scratch cards revealing the randomization arm, in blocks of 10 to spread out the burden of the live boosters. Those randomized to Arms 1 or 2 will be referred to the study counselor for in-person counseling and training on the booster modes. Those randomized to Arm 3 will have no contact with the study counselor.

5.4. Intervention

5.4.1. Intervention delivery in Arms 1 and 2

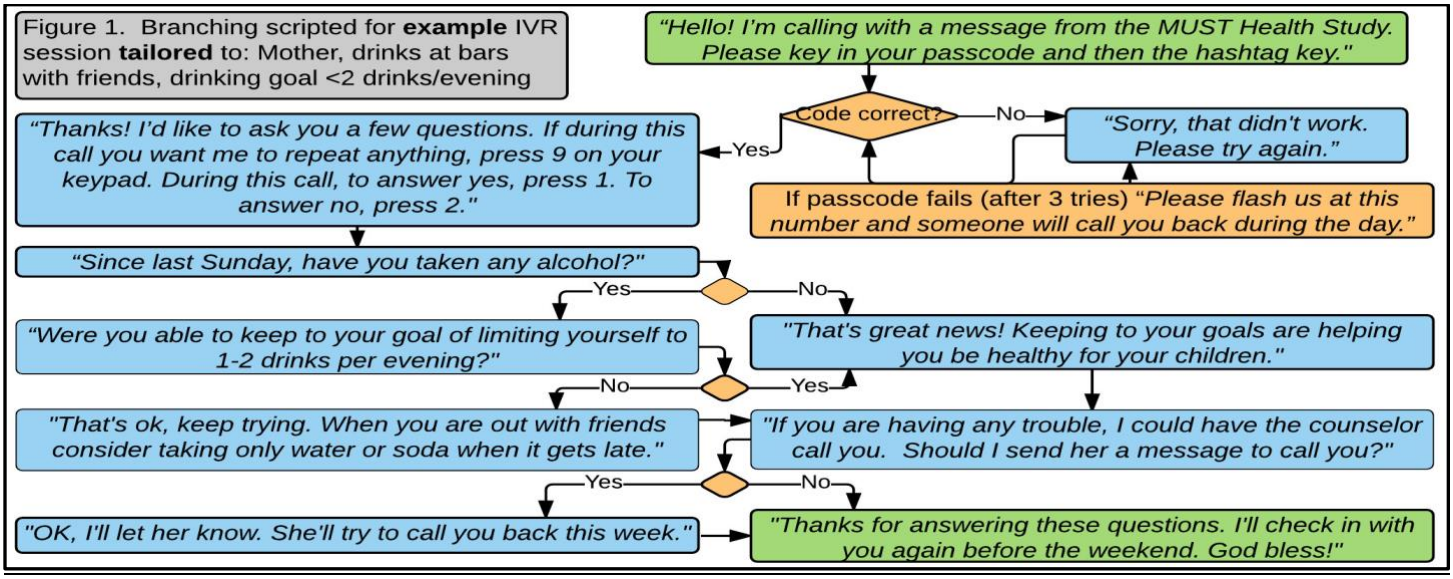
The in-person counseling using the EXTEND study workbook, the live phone call boosters, and training in the use of the tech boosters will be delivered by a counselor trained in HIV/AIDS counseling (Uganda Ministry of Health) after the baseline survey and blood draw. The EXTEND study workbook, which was adapted to the Ugandan local context from the TrEAT/HWHL intervention by the EXTEND study team, will serve as a scripted guide for the in-person counseling session. The counselor will be trained by Dr. Woolf-King in techniques to conduct the alcohol counseling

sessions; training will include mock counseling sessions. While this is not an MI intervention, Dr. Woolf-King's experience and training in Motivational Interviewing will be useful in the motivation component of the intervention. The in-person sessions will be audio-recorded and 15% will be reviewed by the Ugandan project coordinator for fidelity, using a check-list of intervention components as in previous alcohol intervention trials.[23,125]

Participation of support person/helper: Part of the study intervention involves asking study participants whether they can identify a support person or helper, to help support them with their drinking goals. Participants in the intervention arms (Arms 1 and 2) will be asked to identify a support person or helper who is a friend or relative who can support them with their drinking goals. If there is someone they can call on to be a helper, we will ask them to bring them in to participate in their second in-person counseling session. The person identified will be given some information by the counselor to guide them in supporting the participant.

For those in the live phone call booster arm, the counselor will schedule the first live booster call and make a test call to the participant's phone. During the intervention period, the counselor will try to reach the participant 3 times for each booster session, at different times of day or evening, and will try to reach up to 3 of the participants' contacts as needed. The counselor will use the script for the call (see appendix), complete a check-list of the script components, and record all attempted and completed calls in a database designed for this purpose.

For those in the technology booster arm, the counselor will obtain information for the tailoring variables during the in-person session, and will enter them into the technology program interface. The counselor will engage in demonstrations of the SMS and IVR boosters and a discussion of the pros and cons of each, to help participants decide which they prefer, based on their level of literacy, need for confidentiality, and other considerations. After the choice is made, the counselor will provide further training on using SMS or IVR, entering a PIN# to obtain the messages, and responding to the questions. As was effective in increasing engagement in previous tech interventions,[126] the counselor will send a test SMS or IVR message to Arm 2 participants and watch them enter the PIN# and access and respond to the message, assisting and sending another message as needed. The counselor will also show those choosing SMS how to delete the SMS from their phones after the session. The data manager will monitor SMS/IVR session completion; if there is a 3-week interval with no tech booster session interaction, the data manager will alert the counselor who will call the participant and his/her contacts to verify if the cell phone number is still correct. Participants in both booster arms will receive reminders before they are due for their 2nd in-person counseling session, which will be scheduled to coincide with their next clinic visit.



5.4.2. Intervention delivery in Arm 3

Participants randomized to Arm 3 (SOC) will have no contact with the study counselor for the duration of the trail (9 months). However, at their 9-month study visit, and at the end of their study participation as randomized, they will be offered the intervention and given a choice of the delivery method for the booster sessions. Although the study counselor will deliver the intervention at this time point, we will not collect intervention data associated with this group.

Table 2. RCT study visit and intervention schedule

Month 0	Study enrollment, baseline questionnaire, DBS collection, and randomization		
	Arm 1: In-person counseling plus live booster (*n=90*)	**Arm 2: In-person counseling plus tech booster (*n=90*)**	**Arm 3: SOC control (*n=90*)**
	In-person counseling session	In-person counseling + tech training	Standard care
Months 1-3	**Live booster** *(every 3 weeks over 12 weeks)*	**Tech booster** *(1X to 2x/week over 12 weeks)*	---
Month 3	In-person counseling session	In-person counseling session	Standard care
Month 3-4	One third of a subset (n=8-12 per arm): qualitative semi-structured post-intervention interview		
Month 5	Phone call reminder to attend 6-month study visit		
Month 6	Follow-up survey, DBS collection Two thirds of a subset (n=8-12 per arm): qualitative semi-structured post-intervention interview		
Month 8	Phone call reminder to attend 9-month study visit		
Month 9	Follow-up survey, DBS collection		
	Follow-up survey, DBS collection	Follow-up survey, DBS collection	Alcohol intervention offered

5.5. Study visits

Baseline survey and randomization: All participants will undergo collection of contact information, a 30-minute baseline survey, and collection of blood spots for PEth and HIV viral load testing. After these activities, randomization will be conducted by the study coordinator (to keep the RAs blinded) using previously prepared sealed envelopes, in blocks of 9 to spread out the burden of the live boosters. Those randomized to Arms 1 or 2 will be referred to the study counselor for in-person counseling and training on the booster modes. Those randomized to Arm 3 will have no contact with the study counselor.

Six-month follow-up visit. Six months after baseline, we will conduct DBS collection and a quantitative survey, measuring alcohol consumption, and domain characteristics (Table 3).

Nine-month follow-up visit. Nine months after baseline, we will conduct DBS collection and a quantitative survey, measuring alcohol consumption, intervention usability and satisfaction, social desirability, and domain characteristics (Table 3). After data and specimen collection, those in the control arm will be offered the intervention, and will be allowed to choose their preferred method of booster delivery. We will also conduct **IDIs** with 8-12 participants per study arm. These participants will be selected using the a priori categories, with roughly equal numbers of those receiving boosters by SMS and by IVR within Arm 2. The aim of the IDIs will be to explore acceptability and experiences with all three study arms, including the two modes of tech delivery. These interviews will be coded and analyzed using the methods described below (statistical analysis plan).

Individual in-depth interviews at 3-6 months: Following participation in the intervention phase of the trial, a select number of participants (8-12 per study arm) will be invited to participate in a follow-up one-on-one, semi-structured qualitative interview with a research assistant. One third of these participants will participate in the qualitative interview

within 0-1 month post intervention, i.e., between month-3 and month-4 from their baseline study visit. The remaining two thirds of the participants selected to participate in the post-intervention qualitative interviews will participate at 3 months post intervention, i.e., at month-6, which is 6 months from their baseline study visit. The 1/3 group will offer more insights on intervention experiences as recall will be fresher, and the latter 2/3 group will be able to help us understand longer term impacts and the multiple factors that influence outcomes (including but not limited to intervention).

The research assistant will ask them about their experience with and perceptions of the trial as well as the different components of the intervention. The interview will last about 60 minutes and will take place either at a private location. We will audio-tape the individual interview and the recordings will be transcribed. The recordings will be transferred to a computer where they will be secured by a password, and the recordings will be destroyed following transcription.

Retention: We have had 90% six-month retention in our previous studies in this setting.[7] As in the past, we will collect contact information such as cell phone numbers of participants and their friends and family that will be stored in a database that generates automated tracking reports and lists. We will obtain permission to access the participants' medical records to determine the date of their next clinic appointments, and their charts will be flagged so that the RAs will be notified when they come to the clinic so they may receive the study visit. We will provide air time to clinic staff so they can call us if a participant returns to clinic. Follow-up tracking will be conducted by phone calls and home visits (if other methods fail) to participants and their contacts. The RA will call participants at month five to remind them to attend the 6-month study appointment.

Table 3. Quantitative survey variables

Domain	Base-line	6 Months	9 Months	Individual variables
Demographics	X			Age, sex, religion, household assets (as a measure of SES),[130] occupation
Health	X	X	X	Medical Outcomes Study-HIV scale for quality of life and overall physical and mental health functioning,[131-135] body mass index, ART adherence Single Item Rating Scale.[136,137] From Clinic: CD4 cell count, ART status, and MUST pharmacy pill count.
Literacy, cell phone use	X			Ability to read this sentence when shown ("Please read this sentence out loud"), hours phone turned on and charged, SMS use, phone sharing
Alcohol use	X	X	X	AUDIT-C, drinking patterns, beverage-specific typical and maximum drinking,[138] 3 week timeline follow-back[139]
Psychosocial variables/scales	X		X	Social support,[140] HIV stigma,[141] Center for Epidemiologic Studies Depression Scale (16 items),[142] Stages of Change Treatment Eagerness Scale (19 items),[143] Marlowe Crowne Social Desirability Scale (11 items, baseline and follow-up)[144]
Intervention characteristics			X	Client Satisfaction Scale-8 (8 items)[145], System Usability Scale (10 items)[146,147] Perceived Awareness of the Research Hypothesis Scale (demand characteristics; 4 items)[148]

5.6. Specimen collection and laboratory procedures

DBS collection and testing. DBS collection will occur at the baseline, 6-month, and 9-month study visits. Six 50 µl drops of blood will be collected onto two Whatman 903 filter papers (3 spots each), which will be allowed to dry for ≥24 hours, and then stored packaged with a desiccant in a -80C freezer at the MUST laboratory.[127]

Viral suppression: Plasma HIV viral load will be measured at baseline and 9 months using the Cepheid Xpert HIV-1 RNA assay, run on an existing GeneXpert platform in Mbarara, Uganda, that has been in use for our ongoing trials.

PEth levels: The DBS card will be tested for PEth level at the United States Drug Testing Laboratories using liquid chromatography-tandem mass spectrometry (LC/MS/MS) as described.[129] We will obtain a Materials Transfer Agreement to ship the DBS to the U.S.; no laboratories in Africa conduct this test.

5.7. Measurements

5.7.1. Outcome variables

Efficacy analyses Outcome variables The primary outcome variable will be the number of days drinking (prior 3 weeks, TLFB) at 6 and 9 months. We chose this variable because (a) days drinking was the main outcome in the HWHL trial,[16] (b) of several self-reported drinking variables, the number of drinking days was most highly correlated (Spearman r=0.74) with PEth level in a validation study in Uganda,[95] and (c) this variable may also be the least susceptible to bias because it does not require reporting the number of drinks, which can be challenging where non-standard drinks are common.[9] We will use PEth level as an objective measure of prior 21-day alcohol use to confirm the findings obtained using self-report. Another main outcome variable will be HIV viral suppression at 9 months. Secondary outcomes will include the AUDIT-C score, which was associated with increased mortality in HIV-infected drinkers,[13] and the number of heavy drinking days (≥4/≥5 drinks per occasion by females/males, respectively), the standard measure for pharmacotherapy trials. Other exploratory outcomes will include CD4 cell count and ART adherence.

Booster uptake and satisfaction Outcome variables Tech booster uptake will be measured from data extracted from the technology databases that record the SMS and IVR interactions. Uptake will be the proportion of sessions in which the participant answered all the questions prior to the final sign-off message; the denominator for this will be the number of tech booster sessions initiated by the system. Live booster call uptake will be tabulated from the counselor's call record forms that will be entered weekly into the study database. We will also determine the proportion of participants who request a counselor call back. We will also calculate intervention satisfaction in each arm using the Client Satisfaction Scale-8.[145] Among those in the tech booster arm (Arm 2), we will calculate usability via the System Usability Scale, used to evaluate new technology,[146,147] and the proportions that chose SMS over IVR, overall and by reading literacy (yes/no).

Independent variables The predictor variable will be study arm by month (6 or 9 months).

5.7.2. Other measures

Cost methodology To determine costs, we will collect data to capture all relevant direct (e.g. equipment) and indirect (e.g. administrative), fixed (or 'start-up') and variable (or 'recurring') costs related to the intervention and control groups (Table 4). Costs will be differentiated by intervention component (e.g. clinic-based counseling versus remote booster sessions) and by booster session mode of delivery (i.e. live booster versus tech booster, and between SMS and IVR tech boosters). The data collection for costs and the analyses will be conducted using Excel-based worksheets previously developed by Mr. Kevany and UCSF teams for related settings.[155,156] The Ugandan project coordinator will collect these costs in years 2-4 with consultation from Mr. Kevany. We will estimate the marginal cost per unhealthy drinker (i.e. the change in the total cost of the intervention when one additional person is added to the program), overall and by study arm.

Table 4. Cost data collection

Cost category	Description	Source
Personnel – Ongoing	Personnel needed to conduct the in-person counseling, the live and tech boosters, to train patients to receive and respond to the tech boosters, to respond to queries by patients receiving the tech boosters, and to enter new patients and their information into the tech booster system.	MUST contracts and grants office
Personnel – Start up	Personnel needed to set up the tech booster system	As above
Space -- Ongoing	Space needed at the ISS clinic for each intervention arm	ISS Clinic
Equipment/services – Start up	Cell phones, computer and internet needed for setting up and maintaining the tech booster system, tech booster call costs, air time reimbursement,	MUST contracts and grants office

	internet time, office supplies, furniture, data storage.	
Organizational	Costs of meetings and trainings conducted in the clinic	ISS Clinic
Client time	Client time for receiving in-person components of intervention, plus training on the 2-way tech boosters	Counselor records

5.8. Data management

We will build on our previous data collection, tracking, and specimen bar-coding systems used in Uganda. The surveys will be RA-administered using the RedCap program for offline data collection on laptop computers. The field coordinator will observe 10% of the quantitative surveys and qualitative IDIs to assure that data are being collected in a systematic, unbiased method. The electronic data will be uploaded daily and monitored by the UCSF statistician who will check all data for completeness and range monthly. Discrepancies will be investigated and resolved by the UCSF statistician and the Uganda data manager.

5.9. Statistical analysis plan

The analyses below will provide effect sizes to inform a future large-scale trial.

5.9.1. Primary analyses

Efficacy analyses

The analysis for primary outcome variable 1 (alcohol reduction) will measure the number of drinking days (of the prior 21) at six months and nine months, in pairwise comparisons of the study arms, controlling for baseline days drinking (of the prior 21).[149] The analyses will be conducted as intention-to-treat, and we will use Poisson or negative binomial regression for the count data, i.e. the number of drinking days at 6 and 9 months, controlling for baseline days drinking. The PEth level will be transformed to log10 PEth before analyses, based on PEth's highly skewed distribution and we will use linear regression for this outcome.

The analysis for primary outcome variable 2 (HIV viral suppression) will use logistic regression to compare the proportions with viral load<500 copies/ml, controlling for baseline viral load. We will adjust these analyses for baseline characteristics that exhibit imbalance between groups (based on a p-value ≤0.1 in comparisons of potential confounders listed in Table 3).

Secondary outcomes: Other exploratory outcomes will include CD4 cell count and ART adherence.

Missing data We will evaluate differences in baseline characteristics between those lost to follow-up versus those who are retained.[152] If it is reasonable to assume that data are missing at random, multiple imputation methods will be applied to account for the missing data.[152,153] We will also consider pattern mixture models,[154] which are applicable when the data are missing not at random.

Statistical power: With a sample size of 90 in each arm, assuming 90% 9-month retention, using a simplifying t-test for power calculations, we will have 80% power to detect a difference in the number of drinking days in the prior 21 between two study arms at nine months of ≥2.4 days, i.e. nearly 1 fewer day per week, as statistically significant (α=0.05) assuming that the mean number of drinking days in the prior 21 in the control group is 7 (standard deviation is 5.5, based on prior data). Given that this is a pilot study we will not adjust for multiple comparisons.

Booster uptake and satisfaction analyses

Analyses We will calculate 95% confidence intervals for the outcomes listed above. We will conduct preliminary tests of whether the mean completion proportions and satisfaction scores differ by booster arm (live versus tech) by conducting 2-sample tests (t-test or Mann-Whitney).

Statistical power We will have 80% power to detect a difference of completion proportion of 11% or greater if the mean completion in one group is 50%. Power will be greater for mean proportions completing closer to 1.

5.9.2. Additional analyses

Exploratory analyses will examine the exposure to the boosters, in an as-treated analysis. For example, within the tech arm, we may examine whether the number of completed booster sessions is associated with the number drinking days in the prior 21, at six and nine months. Because these are non-randomized exposures, we will explore using propensity score analyses[150] to attempt to balance the groups. We will also examine effect moderation by variables found to impact intervention efficacy, such as gender and depression[151] and by literacy.

PEth versus self-report We will consider findings that are concordant by self-report and PEth (i.e. both analyses statistically significant or both not reaching statistical significance) to be conclusive. If the findings are discordant, we will examine the pattern of SDS scores and demand characteristics (Table 3). We found in our previous studies that, after controlling for PEth level, adjusted SDS means were 0.88 points lower ($p<0.01$) for those reporting versus those denying recent unhealthy alcohol use, while PEth levels were not associated with SDS ($p=0.28$, unpublished analyses). We will conclude in favor of the PEth results if the patterns are consistent with under-report (i.e. associations of higher SDS and demand scores with lower self-reported alcohol use at the same PEth level, suggesting under-reporting).

Missing data We will evaluate differences in baseline characteristics between those lost to follow-up versus those who are retained.[152] If it is reasonable to assume that data are missing at random, multiple imputation methods will be applied to account for the missing data.[152,153] We will also consider pattern mixture models,[154] which are applicable when the data are missing not at random.

6. Safety considerations

6.1. Potential Risks

Potential risks to participants, and their likelihood and seriousness to the human subjects: The main risk of participating in this study is the loss of confidentiality. While many participants may have disclosed their HIV status to their family, we consider loss of confidentiality an important risk of the study. The loss of confidentiality may lead to disclosure of HIV infection or disclosure of drinking status. Stigma associated with such disclosure may include social harms such as disruption of family (e.g., breakup of couples following HIV detection in one spouse), discrimination (e.g., a loss of employment or status in community), physical harm such as domestic violence (e.g., acts of physical violence directed at people who have been diagnosed with HIV), and psychological harm such as embarrassment (e.g., being questioned by family members about alcohol use). There may be some discomfort with the nature of the interviews, since alcohol use will be discussed. There is also the very slight but present chance of a breach of confidentiality inherent in any study that handles confidential data.

Other potential risks of participating in the study include:

- Psychological stress could be caused by the interview in which participants will be asked sensitive questions regarding substance use and HIV status and progression. Distress caused by the length of the interview is also possible.
- Phlebotomy associated risks include bruising, bleeding, infection, phlebitis, and pain. Bruising is common, minor pain with needlestick is universal, the other risks are rare.
- Biohazard containment is an additional risk, as the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products.
- There is a risk of a 3rd party (including makers of the computer software and others) intercepting both research and non-research data.
- There is a risk of additional costs to cell phone usage for participants that are not anticipated.

Alternative procedures: The alternative is to either not consent to the study or to withdraw from the study at any time after consented. We will be clear with participants that there is no obligation to enroll in or continue with the study. Any participant may decline any study procedure at any time—this will not affect the person's ability to receive

care at any HIV clinic. Any potential study participant who does not wish to enroll in the study but wishes to learn more about their alcohol consumption will be referred to their doctor.

6.2. Protection against risks

Planned procedure for protection from risks due to loss of confidentiality: We will implement the following procedures to protect participants against the risks of loss of confidentiality:

- We will discuss the possibility of HIV, or alcohol-related stigma with the potential participants during the informed consent process for the study. We will ask potential participants to think about persons in their family, group of friends, neighborhood, or workplace, who don't know their HIV status, and how they might react to discovering that the participant is infected with HIV, or drinks alcohol. Enrollment will be deferred for those who are unsure about ramifications of participating. Persons who decline or defer enrollment in the study will be assured that this will not affect their HIV care.
- We will ensure that all study visits and telephone calls for tracking or study visit reminders, may be deferred for any reason and that participation in the study may be ended at any time. Telephone calls may be ended at any time with a pre-agreed upon word or action. Study staff will be trained to apply the same measures of confidentiality and sensitivity during phone calls as they do with all other data collection activities.
- We will provide referrals to all participants and persons considering enrollment to social support services provided by the MRRH Counseling Program, as desired. These services include the option of participating in support groups where issues of disclosure can be discussed, and the individual can learn from peers about high-risk disclosure situations and how to minimize risk.
- To ensure confidentiality of participation, all instruments, forms, and biologic specimens will be coded with a unique participant identifier that renders the data anonymous to persons outside the study. All data will be kept in locked cabinets and on secure servers. Research records will be kept confidential to the level allowed by law. Records with identifying information, such as contact information and consent forms, will be stored separately from survey information. No individual identities will be used in any reports or publications.
- All staff in contact with participants and/or data will be trained on procedures for maintaining privacy and will sign a pledge of confidentiality. They will also take the NIH online human subjects training courses.
- We will provide participants with a small card containing information on how to contact the local field staff to report incidents such as HIV-related disruption of families, acts of discrimination, and physical harm. These cards will not identify the study as a study of alcohol use, or of persons with HIV. This information will also be written on the take-home consent form.
- Study activities will be conducted in English or Runyakole (the local language) in the language that the participant feels most comfortable with.

Planned procedure for protection from risks due to psychological distress: The RAs will be trained to address these issues with a calm, non-judgmental attitude. Study activities will be conducted in English or Runyakole (the local language) in the language that the participant feels most comfortable with. At the participants' request, we will refer patients for medical alcohol detoxification and support groups conducted by the Department of Psychiatry at MUST. These referrals are a standard part of care at the ISS clinic. These minimal risks are not likely and will be minimized further by only selecting participants who understand the study and are willing to participate.

Planned procedure for protection from risks due to phlebotomy: Trained RAs or laboratory technicians will collect all specimens using standard sterile procedures. The phlebotomist will report any complications resulting from blood draws to the field study coordinator, who will make an immediate report to the Principal Investigator. The Principal Investigator will take responsibility for reporting such AEs to the relevant IRBs and NIH within ten days.

Planned procedure for protection from risks due to lack of biohazard containment: As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and

handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention and the NIH. Personnel will be trained in and follow standard laboratory procedures to minimize the risk of contamination.

Planned procedure for protection from risks due to 3rd party intercepting participant's data: We plan to institute the following data security controls that prevent interception of information issues as follows:

- The cell phone data will be kept only by cell phone number and unique study identifier that renders the data anonymous to persons outside the study. All SMS/IVR messages will require authentication codes for access. The web-based databases will be password protected and encrypted. All data transfers to servers at UCSF or MUST will occur via an encrypted internet connection and data will be stored on secure UCSF servers that are password-protected and encrypted.

- We plan to institute the following data security controls in general:
    - Data storage safety: The SMS/IVR data (accessed only with an authentication code) will be stored temporarily on participant's phones until the participant deletes them. The SMS/IVR data will also be stored temporarily on secure, password-protected and encrypted web-based databases until they are transmitted to our research team at UCSF. All servers storing EXTEND study data will be encrypted. Thus, all data transfers of study data, from Uganda to servers at UCSF, will occur via this encrypted internet connection, and data will be stored on secure UCSF servers that are also password-protected and encrypted. Once transmitted, data will be stored via secure, password protected, and encrypted files, identified only by the study ID, on a password protected network computer at the research study offices at UCSF. All data transfers to servers at UCSF will occur via an encrypted internet connection and data will be stored on secure UCSF servers that are password-protected and encrypted.
    - All data transfers to servers at UCSF will occur via an encrypted internet connection and data will be stored on secure UCSF servers that are password-protected and encrypted.
    - UCSF IT risk assessment and data safety measures: We will have a contract with any entity engaged in implementing our research study prior to commencing their services. The contracts will include Terms of Agreement and/or Privacy Policy to be reviewed by the UCSF IT department as well as the UCSF contracts and grants offices. These offices will continue to review updates of the agreement as needed. We will defer to the MUST IRB in Uganda on determining how the study participants will be informed that the data is subject to the set terms of agreement, which may change over time. However, we will address these issues broadly in the informed consent process.
    - Data will not be shared including contacts, texts, geo-location information, photos or other data from any of the devices used during our research study by the research team or by the study participants, with 3rd parties in both Uganda and the United States.
    - We will discuss the risks to confidentiality in engaging in SMS/IVR system in the informed consent processes and again during SMS/IVR training with participants. The SMS/IVR system will include authentication codes (PIN#s) so that only the intended participant will access the SMS/IVR messages. In addition, we will train participants to delete the SMS at the end of each session so they cannot be viewed by others using the phone. We will not identify the study as associated with the HIV clinic in any message. The cell phone data will be kept only by cell phone number and unique study identifier that renders the data anonymous to persons outside the study. All data transfers to servers at UCSF or MUST will occur via an encrypted internet connection and data will be stored on secure UCSF servers that are password-protected and encrypted.

Planned procedure for protection from risks due to additional costs to participant's cell phone use: We do not anticipate that participants will incur additional costs in cell phone charges as a result of our study. It is free to receive calls and SMS messages on Ugandan phones, thus the IVR sessions will be free, and participants can receive calls and SMS messages even if the phone has no “air time” (pre-loaded credit). The SMS sessions will require a small amount of air time to enable participants to send answers to the SMS questions, but we will automatically load (“top up”)

participants' phones with air time before SMS sessions. The expected value of the cell phone credit will not exceed the expected cost of the SMS charges and will occur at the time of use so as not to be viewed as coercive. Our technology platform will be programmed to receive free text replies from participants via SMS, or a voice message from participants (as an MP3 file) via IVR, allowing for open-ended questions and responses. In addition, participants will be trained to 'flash' (calling a phone number and disconnecting the call before it is answered at no cost) the study staff if they need to reach them. Following a flashed call, the study staff will call participants back at no additional cost to the participant. Flashing is common practice in Uganda and will be utilized by the study participants as needed to reach study staff while in the study. These minimal risks are not likely and will be minimized further by only selecting patients who understand the study and are willing to participate.

6.3. Potential Benefits

Participants may benefit from a positive health outcome associated with a reduction in unhealthy alcohol use. Improved health due to lifestyle changes and/or knowledge gained about health and health conditions may occur as a result of participation. Closer follow-up than standard of care may lead to improved outcomes or patient engagement. Collateral benefits include receipt of refreshments, transportation reimbursements, and the receipt of results from laboratory tests (CD4 cell counts, HIV viral load). PEth biomarker results will not be disclosed to participants due to the lag in testing and the non-routine nature of this test in this population. Otherwise, participants are not promised any direct benefit. The risks to the participants are minimal in relation to the anticipated benefits to the participants and the results of this study could benefit both HIV and alcohol treatment and medical services in Uganda and worldwide.

6.4. Data safety monitoring plan

Day to day data and safety monitoring will be the responsibility of the Principal Investigator. We will follow guidelines set forth by the UCSF IRB regarding AEs. AEs will be reported to the IRBs within 10 days of awareness of the AE. Serious adverse events (SAEs) will also be reported to the NIH and will be reported to the IRBs and the NIH within 2 days.

AEs will be monitored for each subject participating in the study and attributed to the study intervention by the Principal Investigator with review by the physicians/co-investigators according to the following categories:

1. Definite: Adverse event is clearly related to the intervention.
2. Probable: Adverse event is likely related to the intervention.
3. Possible: Adverse event may be related to the intervention.
4. Unlikely: Adverse event is likely not to be related to the intervention.
5. Unrelated: Adverse event is clearly not related to the intervention.

The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event
2. Moderate adverse event
3. Severe adverse event

In addition to grading the AE, the Principal Investigator will determine whether the AE meets the criteria for a SAE. An AE is considered serious if it:

1. is life-threatening
2. results in in-patient hospitalization or prolongation of existing hospitalization
3. results in persistent or significant disability or incapacity
4. results in a congenital anomaly or birth defect
5. results in death
6. may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition, based upon appropriate medical judgment, or
7. adversely affects the risk/benefit ratio of the study

An AE may be graded as severe but still not meet the criteria for a SAE. Similarly, an AE may be graded as moderate but meet the criteria for a SAE. The Principal Investigator and the study physicians/co-investigators will determine the grade of the event as well as its "seriousness."

Risk assessment

Participation in the EXTEND Study may present minimal risks, including social harm due to loss of confidentiality, disruption of family (e.g., breakup of couples following HIV detection), discrimination (e.g., loss of employment or status in community), physical harm (e.g., acts of physical violence directed at people who have been disclosed as HIV-infected) and embarrassment (e.g., being questioned about alcohol use). Should any of these or other incidents occur, the on-site Field Coordinators will immediately report them to the Principal Investigator, who will in turn report them to the appropriate IRB(s) and to the NIH within ten days of learning of the incident, and notify all study co-investigators. We will ask study participants to return to the research field site as well as provide participants with a palm card containing information on how to contact the local field staff to report such incidents.

The Field Coordinators will be trained to complete descriptions of AEs on an AE reporting form that will then be sent electronically to the US PI. The PI will also report any instances where a US or international IRB takes any action relating to the study. The PIs will make at least two site visits per year to inspect the quality assurance protocol and to review study procedures, including recruitment and data collection.

Interim analyses

No interim efficacy or futility analyses are planned, however, the study team, including the project directors, statistician, co-investigators, field coordinators, and RAs, led by the Principal Investigators, will monitor the progress of the study, participant recruitment, accrual and retention at twice monthly conference call meetings. They will also examine factors external to the study when interpreting the data, such as scientific developments or the new availability of information that could impact the safety of the participants, the performance of the study, or the ethics of the study.

Data Management and Security to Protect Privacy

UCSF, in collaboration with the MUST data management teams, will ensure high quality forms, monitor data quality, and track and link the multiple data sources. The team will jointly develop data collection forms, design the database management system for data entered and for participant tracking, implement procedures for quality control, and provide statistical programming and collaborate in report writing and presentation of study results.

Electronic data will be collected using password-protected laptop computers. The data team will design, develop and maintain the electronic data collection forms, participant and data tracking, and underlying SQL database systems, and implement procedures for data quality control, including multiple checks for entered data. Electronic data collection forms will be designed to read easily, have clear instructions, preprogrammed skip patterns, real-time range checks and internal logic to minimize missing data and resulting in "cleaner" data at capture. The databases will be located on secure, password-protected servers in Uganda and the US.

7. Publication of Research Findings

The findings from this study may be published in a medical journal. No individual identities will be used in any reports or publications resulting from the study. The researchers will publish results of the study in accordance with NIH, UCSF, UNCST, and MUST guidelines.

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MBARARA UNIVERSITY OF SCIENCE AND TECHNOLOGY

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INFORMED CONSENT DOCUMENT for RCT participants

Study Title: Mobil technology to extend clinic-based counseling for HIV+s in Uganda (The EXTEND study)
Principal Investigator(s): Dr. Judith Hahn, Dr. Winnie Muyindike.

INTRODUCTION

What you should know about this study:
You are being asked to join a research study.

- This consent form explains the research study and your part in the study.
- Please review it carefully and take as much time as you need.
- You are a volunteer. You can choose not to take part and if you join, you may quit at any time. There will be no penalty if you decide to quit the study.
- After this consent form is read to you, and your questions have been answered, we will ask if you want to be in the study. If you agree, we will ask you to sign this consent form. You will get a copy of this form to keep.

Brief background to the study:
Unhealthy alcohol use is a significant barrier to suppressing HIV. About one out of every 4 persons with HIV in the world is an unhealthy drinker and interventions are needed. Multi-session counseling can be effective in reducing unhealthy drinking. This study will test an intervention of multi-session counseling delivered in-person, followed by either a live person phone call or phone text and voice messages, to reduce unhealthy alcohol use.

Purpose of the research project:
The goal of this study is to test a brief alcohol intervention to reduce unhealthy drinking among persons with HIV in Uganda. The intervention is composed of an initial in-person counseling session followed by booster sessions delivered by cell phone voice and text messages. The study is being conducted by researchers at the Mbarara University of Science and Technology (MUST) and the University of California San Francisco (UCSF) in the United States.
Approximately 270 people will participate in this randomized controlled trial (RCT). After you have completed the RCT you may also be invited to participate in a follow up one-on-one interview lasting about 60 minutes.

Why you are being asked to participate:

You are being asked to participate in this study because you are an adult patient at the Mbarara Regional Referral Hospital, you stated that you drink alcohol, you are not currently participating in any other research study but you may have participated in a previous research study conducted by our team.

Procedures:

If you agree to participate in the study the following will occur:

We will ask you to take part in a randomized controlled trial (RCT) to test an alcohol use reduction intervention. Your participation in the RCT will last 9 months and include the following procedures:

Interview: A research assistant will interview you about your health, use of alcohol, at the beginning of the study, and at your 6-month and 9-month study visits. We will talk about matters that may be personal to you. If we ask any questions that you do not want to answer, you can simply say, "I do not want to answer that." This interview will occur in a private location and will take about 60 minutes each time. The interviewers will not be able to answer questions about your health or your health care. However, you may consult health care practitioners at the Mbarara Regional Referral Hospital for additional information about alcohol or your health at any time.

Blood draw for test: A research assistant will draw approximately 5 mls (1 tablespoon) of your blood at your first study visit and also at your 6-month and 9-month study visits. Your blood will also be used for a laboratory test that will measure the amount of alcohol you have taken in the last month. You will not be told the results of the blood test for alcohol. The researchers will store the specimens until the testing has been completed. Each blood draw will take about 20 minutes to complete.

Randomization to one of three groups: You will be "randomized" into one of the three study groups that I will describe to you. Randomization means that you are assigned to a group by chance. A computer program will make this assignment. Neither you nor the research assistant can choose the group you will be in. You will have an equal chance of being placed in each group.

- **If you are in group one** will be asked to complete study activities now, and every three weeks for 3 months, and then at 6 months and 9 months after your enrolment in the study.
- **If you are in group two** will be asked to complete study activities now, and once to twice a week for 3 months, and then at 6 months and 9 months after your enrolment in the study.
- **If you are in group three** will be asked to complete study activities now, and again at 9 months after your enrolment in the study.

I will now tell you about the study activities, and when they will take place. The schedule for the study activities will be dependent on whether you are put in group 1, group 2 or group 3.

In-person Counseling for Group 1 and Group 2: You will receive an in-person counseling session about your drinking from a study counselor. The counselor will discuss options for reducing your drinking and develop a plan with you to achieve your drinking goals. The in-person counseling session will last about 30-60 minutes and will take place at our offices in Mbarara Regional Referral Hospital or at any location of your choosing.

Cell phone use for Group 1 and Group 2: You will be required to own or have access to a working cell phone for use during your participation in this part of the study.
Follow-up counseling sessions via telephone for Group 1 only: You will be required to own or have access to a working cell phone for use during your participation in this part of the study, to enable you receive phone calls

at no additional cost to you. You will receive a phone call from a counselor for counseling booster sessions over the phone. You will receive one phone call every three weeks for 3 months after your in-person counseling session. These phone calls will last approximately 20 minutes.

IVR/SMS training for Group 2 only: You will be trained by a research assistant on how to operate your cell phone for purposes of the study including training on how to receive and send messages via text or voice. You will also be shown how to protect your privacy by using a selected password to access the phone messages. This training will last about 30 minutes.

Follow-up counseling sessions via telephone for Group 2 only: You will be required to own or have access to a working cell phone for use during your participation in this part of the study, to enable you receive and send phone voice and text messages at no additional cost to you. You will receive either a phone voice or text message once to twice a week for 3 months after your in-person counseling session. You will be asked to respond to the messages when you receive them.

Standard of Care for Group 3 only: You will continue to receive the normal care that you get at the Mbarara Regional Referral Hospital for 9 months after your enrolment in the study.

Follow-up Interview for Group 1, Group 2, and Group 3: After you have participated in the RCT, you may be invited to participate in a follow-up one-on-one interview with a research assistant. The interview will be informal, like a conversation. We will talk about your experience with the RCT as well as all aspects of the intervention, including the in-person counseling sessions, the use of the telephone text and voice messages. The interview will last about 60 minutes and will take place either at the offices of the Global Health Collaborative Mbarara, in a private room at Mbarara Regional Referral Hospital, or at a private location that we agree upon.
We will audio-tape the individual interview and the recordings will be used in writing up the discussions, to ensure our notes are complete and accurate. Only members of the research team will have access to the recordings. The recordings will be transferred to a computer where they will be password-protected, and the recordings will be destroyed when we have finished analyzing the data.

Collection of tracking information and tracking activities: We will ask that you give us information about where you live and phone numbers so that we can contact you. We will call you to remind you when it is time to come in for your 6-month and 9-month study visits and also try to locate you by phone or in person if you miss a study visit. We will not disclose any of your private information to anyone we speak to when we try to find you**.** We may also contact you for future studies during this study or after it is over.

Referrals for mental health and alcohol evaluation: Based on what you tell us or if you request, we will refer you for optional alcohol and mental health services available at Mbarara Regional Referral Hospital to help you cope.

Risks / discomforts:

Risk of blood draw: During the blood draw, mild pain, bruising, bleeding and fainting may happen. Study staff will be properly trained in blood draws to minimize such happenings.

Risk of discomfort: Some of the interview questions may make you feel uncomfortable or raise unpleasant memories. You are free to refuse to talk about any topic without jeopardizing your participation in the study.

If you are in Group 1 or Group 2, it is possible that you may become frustrated if you find the telephone difficult to use or the voice and text messages difficult to understand. You are free to discuss this with the research assistant and ask for help.

Potential loss of privacy or confidentiality: One potential risk of participating in the study is loss of privacy. Your information will be handled with as much privacy as possible. In order to protect your name, only your ID number will be used. All text and voice messages will require a passcode that you have selected to enable access to them. You will also be trained on how to delete messages from the study phone after you have received them. When the study team visits your home, they will not tell anyone outside your household why they are visiting and the vehicle will not have a name on it.

The research assistant will not talk about your responses and comments with anyone other than the study investigators. Although the study staff will do their best to protect your privacy, it is possible that others will find out that you are participating in this study.

Refusing to participate at any time will not affect healthcare services or medicines that you are currently receiving. For more information about risks and side effects, ask one of the researchers.

Benefits:

There will be no direct benefit to you from participating in this study. However, you will help the researchers conduct their research. In the long term, this research may improve the care of patients.

Incentives / rewards for participating:

You will not be paid for your participation, but you will be given refreshments and we will give you a small amount of food staples, such as 1 kilogram of sugar or 1 bar of soap, to compensate you for your time. If you need to come for a study visit on a day that you have no other clinic activities, we will reimburse your transport costs. If you live within 20km, we shall reimburse you ten thousand Uganda shillings (10,000 only), if you live farther than 20km from the clinic, we shall reimburse you twenty thousand Uganda shillings (20,000 only) and if you live farther than 60km from the clinic, you will be reimbursed up to forty thousand shillings (40,000) only.

Protecting data confidentiality:

We will do our best to make sure that the personal information gathered for this study is kept private and confidential. All study forms will be kept in a locked file cabinet in a locked research office; electronic data will be saved on password-protected computers. Only members of the research study team will have access to these data. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. We will destroy information that could identify you such as your name, address, and phone numbers ten years after the study has ended. All information will be handled in compliance with Uganda and U.S. law for confidential information. In unusual circumstances, your research records may be looked at by appropriate government agencies or be released in response to an order from a court, but the records will not contain your name or identification. These organizations include the U.S. Office for Human Research Protections, Committee for Human Research of the University of California, San Francisco, the Institutional Ethical Review Committee of Mbarara University of Science and Technology, and the Uganda National Council on Science and Technology (UNCST).

Protecting subject privacy during data collection:

We will carry out the individual discussions in a private room at the clinic or the research offices. Alternatively, if you select an alternative location that is convenient for you, we will carry out this discussion from that alternative location. We will record your voice during the discussion, and then we will listen to the recording of the discussion and change it into written words later. We will not include your name or any information that identifies you in the written notes.

Right to refuse / withdraw:

Your participation in this study is voluntary, and you can decide to stop at any time. Just tell the researcher or study staff person right away if you wish to stop being in the study. Your decision will have no impact on your medical treatment at Mbarara Regional Referral Hospital or any other services you receive.

What happens if you leave the study?

If you decide to leave the study, there will be no penalty to you in any way. You will not lose any of your regular benefits, and you can still get your care from Mbarara Regional Referral Hospital the way you usually do.
Also, the study researcher may stop you from taking part in the study at any time if he or she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped. If this happens, you will not lose any of your regular benefits, and you can still get your care from the Mbarara Regional Referral Hospital the way you usually do.

Who do I ask/call if I have questions or a problem?

If you have questions about this research, you may contact Dr. Winnie Muyindike (Tel. 0772-52-1619). Dr. Muyindike is a medical doctor at the Mbarara Regional Referral Hospital. You may also call or visit the assistant study coordinator, Naomi Sanyu (Tel. 0759 584256).

If you have questions about your rights as a research subject, you may call the Dr. Francis Bajunirwe, the chairperson of the Institutional Ethical Review Committee of Mbarara University of Science and Technology. (Tel. 256-4854-33795)

What does your signature (or thumbprint/mark) on this consent form mean?

Your signature on this form means;

- You have been informed about this study's purpose, procedures, possible benefits and risks
- You have been given the chance to ask questions before you sign
- You have voluntarily agreed to be in this study

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Print name of adult participant	Signature of adult participant/legally authorized representative	Date
_____	_____	_____
Print name of person obtaining Consent	Signature	Date
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Thumbprint/mark	Signature of witness	Date