Zambia Common Elements Treatment Approach Pilot Study (ZCAP)

Study Protocol with Analysis Plan

NCT03966885

Version Date: December 5, 2018

JHSPH IRB Research Plan for New Data Collection

Use this template for new data collection and if you also will analyze secondary data. Answer the questions below and for numbered sections that do not pertain to your study, retain the section numbers and bolded questions, and write "N/A". Please start typing in the gray boxes provided.

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Study Title: **Zambia Common Elements Treatment Approach Pilot Study (ZCAP)**

IRB No.: 8795

PI Version No. / Date: Version 1.2, December 5, 2018

I. Aims of the Study: Describe the aims/objectives of the research and/or the project's research questions or hypotheses.

Alcohol misuse is a major unaddressed barrier to ending the HIV/AIDS epidemic. Hazardous drinking increases HIV transmission, delays antiretroviral therapy (ART) uptake, reduces adherence and retention, and increases mortality. Concerningly, alcohol consumption is increasing in sub-Saharan Africa (SSA) where 65% of persons living with HIV (PLWH) reside. In preliminary studies in Zambia, we found that: (1) 47% of male and 16% of female PLWH had hazardous use during their first year on ART, (2) among Zambians who drank hazardously, over 50% had a more severe alcohol use disorder (AUD) and/or mental health problems, and (3) over 30% reported other substance use (most commonly inhalants). Comorbid mental health or substance misuse, similar to alcohol use alone, can also significantly undermine HIV treatment.

Brief alcohol interventions (BIs), the standard of care and typically only alcohol treatment available at most SSA HIV clinics (including Zambia), can be clinically and cost effective for reducing hazardous alcohol use. However, they were not designed to treat more severe AUD or comorbid mental health/substance use problems (hereafter referred to as 'comorbidities'). When BIs are ineffective in these settings, advanced treatments are virtually non-existent. A more comprehensive alcohol treatment approach is therefore needed to reduce the impact of alcohol misuse on the HIV/AIDS response.

Cognitive-behavioral therapy (CBT) is efficacious in treating AUD among adults in high income countries; however, scalability to SSA has been limited by a lack of trained personnel and concerns over fidelity to an evidence-based treatment model. Multi-session CBT was recently shown to be feasible and efficacious among PLWH in Kenya Current approaches focus solely on alcohol and cannot address comorbidities, creating a critical gap. Our team developed Common Elements Treatment Approach (CETA), a CBT-based intervention that is delivered by lay health workers and is *transdiagnostic*, meaning a range of comorbid mental and behavioral health problems that each negatively impact HIV outcomes can be addressed. CETA was feasible and effective for treatment of a range of mental health problems in previous trials, but it has not been used among PLWH in SSA to reduce alcohol use and associated comorbidities.

We propose a Stage 1 hybrid implementation-effectiveness behavioral intervention development study to investigate CETA for alcohol reduction at HIV care settings in Zambia. Our central hypothesis is that alcohol misuse among PLWH in SSA can be addressed through a stepped care approach that includes an evidence-based BI (for

hazardous use alone) and more advanced treatment such as CETA (for hazardous use + comorbidities and for severe AUD). We will specifically test the hypotheses that (1) CETA can be feasibly delivered at HIV care settings in SSA and (2) among PLWH with hazardous use + comorbidities and/or moderate-to-severe AUD, BI+CETA will improve alcohol, mental health, and HIV outcomes compared to BI alone.
Aims include:

Aim 1: Adapt CETA for delivery in an HIV care environment (Stage 1A). Grounded in the Practical, Robust Implementation and Sustainability Model and informed by focus group discussions with PLWH who drink and HIV health workers, as well as interviews with key informants in the HIV and mental health system, we will adapt the CETA manual and related standard operating procedures for delivery at HIV clinics in Zambia.

Aim 2: Pilot CETA delivery at two Zambian HIV clinics (Stage 1B). Hypothesis 1: *BI+CETA will be clinically* ($d>0.5$) *and statistically* ($p<.05$) *more effective in reducing alcohol use and comorbidities than BI alone.* Hypothesis 2: *ART retention and HIV viral load (VL) will improve among recipients of BI+CETA compared to BI alone* ($p<.05$). To test these hypotheses, PLWH who screen positive for hazardous alcohol use will be enrolled. Those with comorbidities and/or who meet criteria for moderate-to-severe alcohol use disorder (AUD) (n=160) will be randomized 1:1 to receive BI+CETA or BI alone. Participants who have hazardous alcohol use but do not have a moderate-to-severe AUD and do not have mental health comorbidities will receive a BI and be assessed but not included in the pilot RCT (they will be included in the 'cohort' study). We will measure the difference in change in alcohol use and comorbidities from enrollment to 6-months follow-up and use an Ethyl glucuronide test to confirm self-reported alcohol abstinence. ART retention and VL will also be measured at enrollment and 6 months.

Aim 3: Investigate feasibility, acceptability, and other implementation factors related to delivery of BI and CETA. We will describe the care cascade of this approach and identify demographic, clinical, and structural correlates of uptake, engagement, and completion of the BI and CETA. We will investigate implementation factors through mixed methods interviews with study participants and health workers.

II. Background and Rationale: Explain why this study is being done. Summarize briefly what is already known about the issue and reference previously published research, if relevant.

- Hazardous alcohol use is common and increasing among persons living with HIV (PLWH) in sub-Saharan Africa (SSA). Alcohol is the most commonly consumed and distributed substance in SSA and prevalence of alcohol consumption is increasing rapidly. PLWH face many adversities, including low social support, trauma exposure, and stigma that increase their risk for hazardous alcohol use and they are between two and four times more likely than the general population to have an alcohol use disorder (AUD).

- Hazardous alcohol use leads to poor HIV outcomes. A recent systematic review on alcohol and HIV found that 77% of included studies reported a deleterious impact of alcohol on one or more levels of the HIV care continuum, including HIV testing, linkage and retention, ART initiation and adherence, and virologic suppression. There is growing recognition in both the US and Africa that alcohol and other substance use undermines HIV prevention and treatment programs. Alcohol impacts HIV outcomes through both behavioral and biological mechanisms, including: (1) cognitive impairment (i.e., forgetfulness), which can lead to poor ART adherence and subsequent low viral suppression; (2) increased sexual risk behaviors, which can lead to a higher risk for transmission; (3) depression, which can be a comorbidity, cause and consequence of alcohol use and is associated with decreased ART adherence and retention; (4) immunocompromise with increased susceptibility to infections; and (5) nutritional deficiencies.

- Hazardous alcohol use is a major unaddressed barrier to achieving the UNAIDS 90-90-90 goals and ending the HIV/AIDS epidemic. The majority of PLWH globally reside in SSA (approximately 25.8 million); therefore, the implementation of evidence-based interventions to address alcohol use problems in SSA has significant

potential to increase the number of PLWH receiving appropriate care and improve HIV outcomes. Alcohol reduction is particularly important for those with tuberculosis and viral hepatitis coinfection. These coinfections are leading causes of mortality among PLWH. Alcohol both increases the risk of TB and reduces treatment outcomes, while alcohol use is also linked to advanced liver fibrosis among HIV-hepatitis patients. Unfortunately, there is a substantial treatment gap for alcohol use disorders in SSA (as high as 90% in some countries) and the vast majority of PLWH who require services for alcohol use problems do not receive them. Achieving the UNAIDS 90-90-90 targets will require a more comprehensive approach to hazardous alcohol use.

- Brief interventions (BIs) are potentially effective and low-cost treatments for hazardous alcohol use. BIs typically consist of a 5-15 minute single counseling session (with possible booster sessions) administered by a primary care physician or nurse and include components such as: feedback on use and the harm drinking may be causing, norm referencing, identifying coping strategies, and motivational enhancement for changing behavior. Literature from high income countries suggests that BIs delivered in primary care settings can be both cost and clinically effective in reducing alcohol consumption for hazardous/harmful drinkers and mild AUD, including among PLWH. Evidence for the effectiveness of single-session BIs in SSA among PLWH is limited; two studies conducted in Uganda and South Africa found that alcohol consumption decreased among PLWH who received a BI but not significantly greater than a control condition.

- In addition to BIs, multi-session psychological treatments, such as cognitive behavioral therapy (CBT)-based approaches, are needed to address more severe AUD. BIs were designed to address hazardous use and other sub-threshold alcohol problems but are not intended as a stand-alone treatment for moderate-to-severe AUD or comorbidities (defined in this study as mental health or non-alcohol substance use issues). Conversely, CBT is an evidence-based psychological treatment for AUD and mental health disorders. A review of AUD interventions among PLWH found that CBT was particularly promising.

- A *transdiagnostic* CBT approach is ideal for treatment of AUD and comorbid mental health and substance use problems among PLWH. AUD is known to frequently co-occur with psychiatric disorders. Baseline data from our team's ongoing study among Zambian families affected by domestic violence suggest that hazardous alcohol use among PLWH very frequently cooccurs with depression, trauma symptoms, and other substance use (most commonly, inhalants, marijuana, and cocaine). Although the Kenya CBT study referenced above is a significant advance in SSA alcohol treatment, the paraprofessional counselors were not equipped with the skills to address comorbid conditions. This is a critical gap because mental health and other substance use problems are also associated with poor retention and adherence. In SSA, referral to a specialist for treatment of comorbidities (e.g., depression) is infeasible (Zambia for example has only 5 qualified psychiatrists, none outside Lusaka). Therefore, an innovative common elements, or transdiagnostic, treatment approach is a preferred strategy. In a transdiagnostic approach, therapists are trained in common elements that exist across a number of evidence-based mental health treatments and are provided with the knowledge and skills to manage a wide range of mental and behavioral health problems and severities, thereby removing the 'silos' that exist within mental health care. Studies have indicated the effectiveness of transdiagnostic treatments in reducing common and co-occurring mental and behavioral health problems that each can impact HIV outcomes, however they have not yet been tested in SSA clinic settings among PLWH for alcohol reduction.

- A stepped care approach to the treatment of hazardous alcohol use and AUD within SSA HIV care settings has potential to efficiently provide targeted, evidence-based interventions. A stepped care approach, which has been utilized for alcohol use, mental health, and management of other chronic diseases in high income settings, involves the provision of interventions that range in intensity--and resources required--commensurate with symptom severity. Referral is made to the lowest-intensity level intervention

appropriate for presenting symptoms. If treatment fails, the patient is referred to a higher 'step' intervention. Applied to alcohol treatments in HIV care, this could involve a lower-intensity intervention, such as BI, for patients who present with hazardous use or sub-threshold AUD, and a higher-intensity intervention, such as transdiagnostic CBT, for patients who present with moderate-to-severe AUD or comorbidities. A third step may include referral to a specialist and consideration of pharmacotherapy, when available. Although recommended by the World Health Organization (WHO) to improve reach and efficient delivery of interventions,61 we are not aware of studies investigating a stepped care approach for the treatment of alcohol use problems in SSA.

- In summary, the scientific premise of this proposal is that alcohol use in Zambia and SSA is increasing and has a significant negative impact on HIV outcomes, yet treatments are severely lacking. Some hazardous drinkers may respond to BIs; however, HIV clinics need access to more advanced treatments for moderate-to-severe AUD and comorbidities. In this project we will adapt, integrate, and pilot a transdiagnostic CBT-based treatment (CETA) within HIV care in Zambia and test its preliminary effectiveness at addressing these higher step problems. This project will lay the foundation for a stepped care approach to alcohol reduction that can be tested in a larger follow-up study.

III. Study Design:

A. Provide an overview of your study design and methods. The study design must relate to your stated aims/objectives. Details will be requested later. If your study also involves analysis of existing data, please complete Section XI, "Secondary Data Analysis of Existing Data" in the last part of this research plan. If your study ONLY involves analysis of existing data, please use the research plan template for secondary data analysis (JHSPH IRB Research Plan for Secondary Data Analysis of Existing Data/Specimens).

Following the NIH Stage Model for Behavioral Intervention Development, we will conduct a Stage 1 study in two phases: (1) adaptation and refinement of an existing behavioral intervention in new and 'real-world' settings (Stage 1A) and (2) pilot testing of the adapted intervention to assess feasibility and preliminary effectiveness (Stage 1B). In Stage 1A (Aim 1), we will adapt CETA for use in HIV clinics through formative research, including a review of national HIV care protocols and focus groups with PLWH who drink and HIV clinic staff at the study sites. We will also conduct key informant interviews with policy-level officials. We will adapt and tailor the CETA manual for use with PLWH, with input from stakeholders. In Stage 1B (Aims 2/3), we will conduct a pilot RCT of BI+CETA compared to BI alone for PLWH with moderate-to-severe AUD and/or hazardous use with comorbidities. We will collect mixed methods implementation data and clinical outcomes data on alcohol, comorbidities, and HIV (ART retention and VL collected through routine care).

B. Provide a sample size and a justification as to how you arrived at that number. If you use screening procedures to arrive at a final sample a table may be helpful.

The total sample size for the study is 400. This includes a maximum of 80 participants in Stage 1A and 320 in Stage 1B.

Stage 1A: There are no formal sample size calculation for this qualitative, formative stage of the study, in which we will conduct focus groups and in-depth interviews. We will conduct 4 focus group discussions (FGDs) with PLWH who use alcohol. Each group will have a maximum number of participants of 8. Therefore, the maximum

number of PLWH participants in Stage 1A will be n=32. Additionally, we will conduct 4 FGDs with health workers at our study clinics. These FGDs will also have a maximum number of 8 participants per group, thus the maximum number of healthcare worker participants will be n=32. Finally, we will conduct up to 16 key informant interviews with policy officials and relevant program leaders.
Stage 1B: This stage will enroll n=320 participant who have hazardous alcohol use: n=160 will formally be enrolled in the RCT (participants who meet criteria for a moderate-to-severe AUD or have hazardous alcohol use plus comorbidities) and n=160 who will not be enrolled in the RCT but will receive the BI and will be tracked for follow-up in a cohort study (participants with hazardous use but do not have a moderate-to-severe AUD and have no comorbidities).

The primary endpoint of the pilot RCT is the difference in change in AUDIT score from baseline to 6-month follow-up between BI+CETA and BI alone (see assessments section below). We believe that an effect size of CETA ≥0.5 would be clinically significant and justify further investigation in a subsequent latter Stage trial. Further assuming α=0.05 and β=80%, we will require a total sample size of 128 (n=64 per arm). To account for possible loss-to-follow-up/drop-out of 20% based on our previous studies with HIV-affected populations in Zambia, we will inflate the sample size to 160 (n=80 per arm). Based on Preliminary Studies, we anticipate that 20% of female and 40% of male patients at the study sites will report hazardous drinking and that 50% of hazardous drinkers will qualify for the RCT. Therefore, we expect to enroll n=320 hazardous drinkers to reach the RCT target sample size. There is no sample size calculation for cohort study participant; however, the anticipated sample of n=160 should be sufficient to detect even a small within-group change in outcomes after receipt of BI.

IV. Participants:

Describe the study participants and the population from which they will be drawn. Specify the inclusion and exclusion criteria. If you plan to include children, note their ages and whether you will include children in foster care. Note if the participants are particularly vulnerable in terms of cognitive limitations, education, legal migration status, incarceration, poverty, or some combination of factors.

- **Inclusion Criteria:**

Stage 1A:

Data will be collected from three participant types in Stage 1A.

(1) PLWH who have a history of alcohol use while on ART.
- 18 years of age or older
- HIV-infected
- Currently a patient receiving care in one of the study HIV clinics
- Current or previous use of alcohol while on ART
- Provides informed consent

(2) Health workers/clinic staff at our two study clinics
- 18 years of age or older

- Currently works in one of the study HIV clinics in a position that will be relevant for CETA integration
- Provides informed consent

(3) Policy and program-level stakeholders (e.g., Ministry of Health officials)

- 18 years of age or older
- Works for MoH or is a key informant in the Zambia HIV Health system or is a key informant in the area of alcohol policy and treatment.
- Provides informed consent

Stage 1B:

Study participants will be PLWH who are currently receiving care at one of the two study clinics. Participants will be recruited by their regular care providers (i.e., peer educators, counselors, nurses, physicians) and referred to study staff if they are interested. We anticipate enrolling a total of 320 participants, all of whom have hazardous alcohol use. 50% of them will be lower-risk drinkers who do not have moderate-to-severe alcohol use disorders (AUD) or mental health comorbidity. These participants will be part of the 'Cohort Study'. These will not be randomized. The other 50% will be high-risk drinks due to having either moderate-to-severe AUD or mental health comorbidities, or both. This second group will be randomized into the RCT Study. The minimum age of research subjects will be 18. All subjects will be recruited from our two study clinics. Eligibility will be assessed via audio computer assisted self-interviewing (ACASI).

Initial inclusion criteria for overall enrollment (into either the Cohort or RCT study) will be:

- HIV positive
- Receiving HIV treatment services at one of the two study clinics
- Current hazardous alcohol use, defined as an AUDIT score of ≥8 for men and ≥ 4 for women
- Provides informed consent

Secondary inclusion for enrollment into the RCT will be:

- AUDIT scores that indicate a moderate-to-severe AUD (≥12 for women; ≥16 among men)
- AND/OR: meeting validated symptom criteria for depression (≥16 on CES-D), trauma/anxiety (≥2.5 on HTQ), and/or substance use (≥27 for any non-tobacco/alcohol substance on ASSIST)

Participants who meet initial inclusion criteria AND secondary inclusion criteria will be eligible for the RCT. Participants who meet initial inclusion criteria but NOT secondary inclusion criteria will be eligible for the Cohort study.

- **Exclusion Criteria:**

Stage 1A: No formal exclusion criteria.

Stage 1B: Study exclusion criteria for Stage 1B (applies to the Cohort study and the RCT) will be:

- HIV negative

- Not receiving care at one of the study clinics
- Currently psychotic or on an unstable psychiatric drug regimen
- Actively suicidal: Suicide attempt or suicidal ideation with intent or plan, or self-harm in the past month.
- Unable to provide informed consent

NOTE: If you are recruiting participants or receiving, accessing, or using data from a U.S. health care provider, HIPAA review is likely to be required. If you plan to bring identifiable health information from a foreign country to a U.S. covered entity (e.g., lab at the Hopkins SOM), HIPAA may be triggered. Check "yes" to the HIPAA question in the PHIRST application.

V. Study Procedures:

In this section, provide details of your procedures, particularly as they relate to human subjects. If this is a multi-center study, make the role of JHSPH clear. If the JHSPH will serve as **data coordinating center**, indicate in the sections below which procedures JHSPH will not be performing. Additional information regarding data coordinating centers is requested in a later section. If your study will develop in phases, address each item below by phase.

A. Recruitment Process:

1. Describe how you will identify, approach, and inform potential participants about your study. Include details about who will perform these activities and what their qualifications are.

   Before any data collection begins, community meetings will take place at each site in order to explain the procedures of the study, the risk and benefits, the confidentiality of results, and to allow for any questions. Based on our prior experience using this approach in Zambia, which has featured good relationships with the local population, we do not anticipate difficulties in obtaining community approval.

- *Stage 1A: CETA Adaptation*

  PLWH study participants for Stage 1A will be recruited from their regular care providers at the study HIV clinics in Lusaka. Care providers will be asked to inform their adult patients with a history of alcohol use while on ART about the presence of the qualitative study using a recruitment script (included with this IRB application). Interested participants will be referred to our on-site study assessor. The assessor will explain the study in full and obtain informed consent if the participant is interested. The assessor will obtain contact information from the participant to schedule the focus group discussion, which will happen at a later date. This method will ensure that only patients who express interest in the study to their usual care provider will have any contact with research staff.

  Health worker and policy level participants will be contacted by a study assessor and informed about the qualitative study. Due to our team's ongoing collaborative work with the study clinics and the Ministry of Health, we have an existing sampling frame of stakeholders who we will ask to participate in focus group discussions and key informant interviews. Our study team will contact these stakeholders about participation and explain the purpose of the study. If potential participants are interested, the assessor will obtain informed consent and participant contact details to set up the focus group discussion or key informant interview.

- *Stage 1B: Pilot RCT of CETA*

  Study participants for the pilot RCT will be recruited from two HIV clinics in Lusaka. Participants will be recruited from the general HIV+ patient population at these clinics. While receiving regular care at these HIV clinics, clients will be informed of the pilot RCT by a care provider, which may be their physician, nurse, a

peer educator, or a counselor. We will provide training to these care providers in the background of the study and human subjects research. We will provide them with a recruitment script (included in this IRB application) to ensure that their description of the study is consistent. Staff will emphasize at the outset that participation in the pilot RCT will not affect whether or not the participant receives HIV care as usual. Interested participants will be referred to our on-site study assessor, who will be stationed in a private room within the clinic.

All recruitment activities will be conducted by HIV care providers working in the study clinics and/or personnel of the study implementing organization, Centre for Infectious Disease Research in Zambia (CIDRZ). All personnel working on the study will receive training on study procedures, human subjects research, and research ethics. They will also have certification in human subjects research from relevant NIH modules.

2. Address any privacy issues associated with recruitment. If recruitment itself may put potential participants at risk (if study topic is sensitive, or study population may be stigmatized), explain how you will minimize these risks.

Recruitment for PLWH (both Stage 1A and Stage 1B) will be conducted by physicians, nurses, peer educators, and counselors who provide them with regular HIV care. These providers will identify PLWH under their care who they think would meet inclusion criteria for the study. This conversation will take place in private and include only the provider and the potential participant, and will be facilitated by a standardized recruitment script. Only if the potential participant agrees to hear more about the study will the provider contact and invite research staff to fully explain the study and obtain informed consent. Therefore, potential participants will have no contact with research staff unless they express an interest in hearing more about the study. Potential participants will be counseled that they can refuse to participate in the study and still receive HIV care at the treatment site. Providers will be highly trained and will receive specific training in human subjects research.

Provider, staff, and policy-level participants for Stage 1A are employees currently working in clinics or relevant programmatic or MoH offices. All potential participants will be contacted by a study assessor who will explain the purpose of the study. If the potential participant is interested in participating, the assessor will set up a time to obtain informed consent and schedule the subsequent focus group or interview. The assessor will additionally counsel potential participants that their participation is completely voluntary, and that whether or not they participate, and regardless of the data they provide during the FGD/KII, their position with MoH or CIDRZ will not be impacted in any way. Senior MoH and CIDRZ officials will not have access to individual FGD/KII data and all data provided from participants will be de-identified and only presented in aggregate to maintain confidentiality of participants.

B. **Consent Process**:

1. Describe the following details about obtaining informed consent from study participants. If a screening process precedes study enrollment, also describe the consent for screening.

A. Who will obtain informed consent, and their qualifications:

All informed consent activities for all participant types and research phases will be obtained by our trained CIDRZ study assessors. The assessors will be highly trained in human subjects and responsible conduct of research and will have the appropriate certifications (e.g., NIH).

B. How, where, and when the consent discussion(s) will occur:

Consent for participants in Stage 1A will be done in a private room within the HIV clinic or office building where the participant works.

Informed consent from PLWH in Stage 1B will be obtained within a private room within the HIV clinic. This will be done after the patient has been referred to our on-site study assessor by one of their care providers following the recruitment process. Consent will first be obtained for screening. If the participant is eligible following screening, the assessor will then obtain informed consent for the remaining study activities. The second informed consent will be specific to either the cohort or trial study, whichever the participant screened eligible for.

For all consent activities with all participant types, the following information about the study will be discussed:

- Purpose;
- Locations where research will be conducted;
- Points of assessment and the types of questions that will be asked;
- Random assignment to treatments;
- Description of each treatment;
- How privacy will be protected;
- Incentives for research visits and schedule;
- Potential risks;
- Potential benefits;
- The circumstances in which mandated reporting will be required; and
- The participant's rights.

The consent forms will be available in English and two common Zambian languages and consent will occur in the language (among the 3) chosen by the participant. If the participant is not literate in one of the 3 languages, an independent witness (either family member, friend, or clinic staff not working on the study) who is literate in the chosen language will be present and will co-sign the consent. Study procedures will allow for potential participants to take time to make a decision about whether or not to participate and a follow-up appointment within 48 hours of the initial meeting can be scheduled, if desired. The participants will be encouraged to ask questions throughout the consent process and also throughout their entire participation in the study.

C. The process you will use to determine whether a potential participant meets eligibility criteria:

1. Screening for eligibility into the overall study. Participants will provide informed consent for the screening activity. They will then complete a screener that consists of demographic information and the Alcohol Use Disorders Identification Test administered via the audio computer assisted self-interviewing (ACASI). Eligibility criteria for this stage are:

- HIV positive
- Receiving HIV treatment services at one of the two study clinics
- Current hazardous alcohol use, defined as an AUDIT score of ≥8 for men and ≥ 4 for women

Following the ACASI screener, the ACASI system will alert the assessor if the participant is eligible or not. If not eligible, the participant will exit the study. If eligible, the participant will conduct the secondary screening to determine whether they will be part of the cohort or the RCT. The additional screening questions will also be administered via ACASI. Participants will be enrolled into the cohort study unless one or more of the following conditions are met:

- AUDIT scores that indicate a moderate-to-severe AUD (≥12 for women; ≥16 among men)
- AND/OR: meeting validated symptom criteria for depression (≥16 on CES-D), trauma/anxiety (≥2.5 on HTQ), and/or substance use (≥27 for any non-tobacco/alcohol substance on ASSIST)

If any of these conditions are met, the participant will be eligible for and enrolled into the RCT.

Cohort study participants (i.e., lower risk participants) will not be randomized. They will receive the brief alcohol intervention and we will conduct a 6 month post-baseline assessment. The purpose of including them in the study is to gain some preliminary data on whether the brief intervention may be helpful in reducing alcohol consumption among these participants that have a lower level alcohol use problem and no significant mental health or other substance use comorbidities. They are not formally included in the RCT because we did not have the resources to do so in this pilot grant.

RCT participants (i.e., higher risk participants) will be randomized to receive either the brief intervention alone or the brief intervention + CETA. Similar to the cohort participants, we will conduct a 6 month post-baseline assessment among all RCT participants. The purpose of the RCT is to assess whether the BI

alone is effective or whether a more substantial intervention (BI +CETA) is necessary for these higher risk participants.

D. Whether you will obtain a signature from the participant or will use an oral consent process:

As with previous studies conducted among HIV-populations by CIDRZ, we will obtain a signature from the participant.

E. Whether you will obtain a legally authorized representative's signature for adults lacking capacity:

We will not include adults who lack capacity to provide consent in the study.

F. If children are included in the study, if and how you will obtain assent from them:

N/A

G. If children are included in the study, how you will obtain permission for them to participate from their parent, legal guardian, or other legal authority (if child is in foster care or under government supervision):

N/A

H. If you are seeking a waiver of informed consent or assent, the justification for this request:

We are not seeking a waiver.

I. Whether you will include a witness to the consent process and why:

J. If a person is not literate, we will ask them to choose 1 of the 3 languages (English, bemba, Nyanja) and we will conduct consent orally in that language with a witness present who is literate in that language. Witness cannot be someone employed by the study. After consent the witness will sign the form if the participant agrees.

K. If the language is unwritten, explain how you will communicate accurate information to potential participants and whether you will use props or audio materials:

N/A

2. Identify the countries where the research will take place, and the languages that will be used for the consent process.

Country	Consent Document(s) (Adult Consent, Parental Permission, Youth Assent, etc.)	Languages
Zambia	Stage 1A Qualitative consent	English, Nyanja, Bemba
	Stage 1B Screening consent	English, Nyanja, Bemba
	Stage 1B Cohort consent	English, Nyanja, Bemba
	Stage 1B RCT consent	English, Nyanja, Bemba

a. **Study Implementation**:

1. Describe the procedures that participants will undergo. If complex, insert a table below to help the reviewer navigate.

Stage 1A: Adaptation of CETA for use in HIV settings

There will be two key adaptations of the CETA intervention: (1) integration of CETA within regular HIV care; and (2) modification/tailoring of CETA for use with PLWH. The output of Stage 1A is an adapted CETA protocol and standard operating procedure that will be piloted in Stage 1B.

Integration of CETA within HIV care services. We will explore perceived barriers and facilitators of CETA integration within HIV care to inform the protocol. As a preliminary step, we will review the most recent HIV care protocols in our two study clinics to identify possible integration points. We will conduct a series of focus group discussions (FGDs) and key informant interviews (KIIs) with stakeholders on implementation factors.

Stage 1A Participants and Procedures.

Three levels of stakeholders will be convened for this phase:

- ***PLWH who are 18+ years of age and have a documented history of drinking while on ART* (4 FGDs; N=5-8 participants per FGD; 50% female)** will be referred to this qualitative study by care providers in the two study clinics. Discussions will build on our previous qualitative study that explored motivations to drink and abstain among HIV-infected individuals taking ART. In FGDs, a facilitator will introduce the concept of CETA using vignettes, which are an effective tool to engage participants and elicit responses on barriers and facilitators to HIV programs in SSA. As the PLWH have not experienced cognitive behavioral therapy before, vignettes that illustrate CETA being used will be developed in collaboration with existing CETA counselors in Zambia and based on our initial review of the HIV care protocols. They will describe hypothetical CETA sessions and facilitators will probe for feedback from participants on perceived acceptability, appropriateness, and feasibility of CETA using an interview guide (included in this IRB application).
- ***Health workers at HIV clinics* (4 FGDs; N=5-8 participants per FGD)** will also be invited to participate in FGDs. Through our previous studies in these clinics, we already have a sampling frame of providers and staff who will be essential for CETA integration. Additional participants will be recruited through a snowball sampling approach. Similar to the PLWH FGDs, a facilitator will introduce the concept of CETA using vignettes. Discussions will focus on acceptability, appropriateness, and feasibility of delivering CETA within the clinics with an emphasis on logistical hurdles to integration.
- ***Policy- and program-level stakeholders* (10-15 KIIs)** will be recruited with the assistance of John Mayeya, a longtime collaborator of our team, senior-level MoH official, and Significant Contributor on this study. These will include MoH officials and key informants in the HIV health system, such as clinic in-charges, district and national coordinators, clinical care specialists, and community advisors to the Zambian ART program. These interviews will inform adoption, integration, and sustainability from a policy perspective.

Stage 1A: Data Collection and Analysis. All qualitative research activities will be audio recorded and transcribed (and translated to English when necessary) and FGDs will include both a facilitator and a note taker. Recordings and notes from the FGDs and KIIs will be analyzed by coding emergent themes using grounded theory, an inductive approach to explore similarities and differences of perceptions to barriers and facilitators for CETA integration across study participants and both clinics. Coding will be done using an *in vivo* method to explore these emergent themes. Results will be used to generate a draft pilot protocol for CETA provision within the HIV clinics. The protocol will be circulated to stakeholders with a chance for review and comment before finalization.

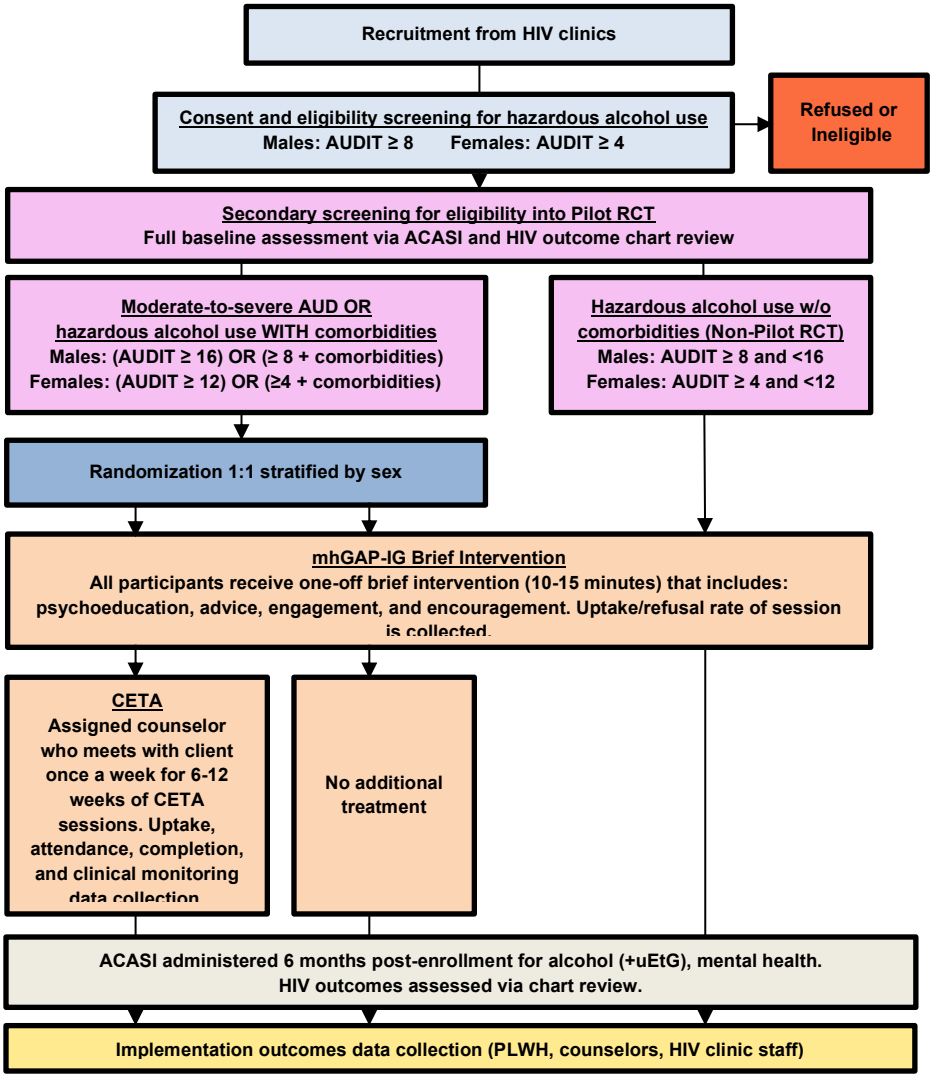
Stage 1B: Piloting of CETA referral and treatment in HIV clinics.

Stage 1B of the study will be a pilot RCT of CETA delivery in HIV clinics. Our hypothesis is that BI+CETA will be more effective than BI alone at treating severe AUD, mental health, and substance use problems. As such, the two populations targeted for this pilot RCT are those that are 'higher risk', namely: (1) PLWH with hazardous drinking and comorbidities; and (2) PLWH with moderate-to-severe AUD (with or without comorbidities). BI alone is currently the standard of care and only alcohol treatment in Zambia HIV clinics and therefore an appropriate comparison to BI+CETA. Participants in these two groups will be randomized 1:1, stratified by sex, to receive BI+CETA or BI alone. Alcohol, substance use, and mental health outcomes will be assessed at baseline and 6-months post-baseline. Retention on ART and HIV viral suppression will also be assessed at baseline and 6-months post-baseline. These HIV outcomes will be assessed as part of usual HIV care. We will also systematically capture data on intervention uptake, attendance, and completion, clinical monitoring, and implementation factors.

Although our focus is on the feasibility of delivering a higher intensity and potentially more effective therapy (i.e., CETA) for individuals at higher risk, we will also provide BI alone for PLWH who report hazardous alcohol use *without* comorbidities and do not meet criteria for a moderate-to-severe AUD (individuals at 'lower risk', referred to as 'cohort' participants in the consent form) and evaluate their outcomes to lay broad foundation for a stepped care intervention in the future. That is, in a real-world program, these are PLWH who would be initially targeted by BI alone. Although enrolling these participants into an RCT is beyond the scope of this study, we will collect pre/post data on the same outcomes as the pilot RCT participants to estimate within group effects of the BI alone for these lower risk drinking problems.

Baseline data collection. The baseline assessment will be conducted via ACASI. The participant will first complete the Alcohol Use Disorders Identification Test (AUDIT) to assess eligibility into the study. The ACASI will automatically alert the assessor if the participant is eligible based on the hazardous alcohol use criteria. If eligible, the participant will complete the remaining measures: (1) Center for Epidemiological Studies-Depression Scale (CES-D)[91]; (2) Harvard Trauma Questionnaire (HTQ); and (3) the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST). All of these measures have previously been translated and used by our team in Zambia and the AUDIT, CES-D, and ASSIST measures have been formally validated. A research assistant will be available if there are any challenges with the ACASI. Additionally, we will use HIV clinic files to extract HIV-related data. These data are captured as part of HIV routine care in Zambia and include: (1) ART initiation date, (2) hepatitis B surface antigen, (3) most recent CD4+ count, (4) cumulative and past 6-month ART retention, defined by medication possession ratio (MPR; an objective pharmacy record metric that we have used previously) and (5) plasma HIV viral load (measured at CIDRZ Central laboratory using the Roche COBAS/Ampliprep platform).

Secondary eligibility criteria for the RCT. Following completion of the baseline assessment, ACASI will automatically alert the assessor if the participant is eligible for the pilot RCT via a built-in algorithm. Criteria for the RCT will be (a) AUDIT scores that indicate a moderate-to-severe AUD (≥12 for women; ≥16 among men) and/or (b) meeting validated symptom criteria for depression (≥16 on CES-D), trauma/anxiety (≥2.5 on HTQ),[92] and/or substance use (≥27 for any non-tobacco substance on ASSIST).



Randomization. Participants eligible for the pilot RCT will be randomized 1:1, stratified by sex, to receive the BI alone or BI+CETA. Participants who are NOT eligible for the pilot RCT will be provided with a BI but will not be randomized.

Interventions

- *World Health Organization mhGAP BI.* All participants (regardless of whether RCT criteria are met) will receive a BI. We will provide training to lay counselors (e.g., counselors/nurses already working in the HIV clinics) based on World Health Organization (WHO) mhGAP-Intervention Guide (mhGAP-IG). The mhGAP-IG was developed to provide non-specialists in LMIC with knowledge and skills to deliver low-intensity interventions with fidelity in primary care to treat mental, neurological, and substance use problems. WHO has developed modules to train health care workers. The JHU clinical team in Zambia will adapt these modules to provide a 2-day workshop for counselors at our two clinics. Training will cover components such as: (1) psychoeducation (e.g., examples of ways that hazardous use can be reduced); (2) engagement (e.g., discussing motivations for drinking); (3) personalized feedback and advice (e.g., helping the participant reflect on how use is impacting their life); and (4) encouragement for the participant to change their pattern of use.[100]

  Following the baseline assessment, the assessor will notify the on-duty counselor who has been trained in the BI. The BI, which is expected to take 10-15 minutes, will be offered to participants the same day and provided in a private room.

- *Common Elements Treatment Approach (CETA).* Lay counselors (e.g., HIV peer educators, counselors in the HIV clinics) will be trained to deliver CETA to participants randomized to BI+CETA (i.e., n=80). After enrollment, participants receiving CETA will flexibly meet with their counselor weekly for approximately one-hour sessions, for 6-12 weeks depending on presentation and symptom level. Core elements of CETA sessions are described in Table 2 and will be adapted as needed in Stage 1A.

Table 2. Common Elements Treatment Approach

Component	Content	Target
Engagement	Discuss how program helps Identify obstacles to engagement	Promote client buy-in
Safety	Assess client risk for harm to self/others Domestic violence/abuse assessment Initiate safety plan as needed	Assess and address client safety
Empirically-supported cognitive-behavioral elements		
Psychoeducation/Introduction	Program information, normalize symptoms, goal setting	Psychoeducation Reduce stigma
CBT for alcohol and other substance use	CBT and MI integrated element to set goals and reduce use; Identification and strategies for addressing drivers of use	Reduce alcohol/substance use Increase social support
Behavioral Activation	Identify and engage in pleasurable activities	Reduce depressive symptoms; Facilitate engagement in helpful programs
Cognitive Coping/Restructuring	Identify and correct thoughts, feelings, and behaviors Replace unhelpful thoughts with helpful ones	Reduce depressive, anxious, and trauma-related symptoms; Reduce self-blame and stigma; Reduce negative thoughts on HIV care
Relaxation	Breathing exercises, imagery	Reduce anxiety and stress-related symptoms
Exposure	Talk about trauma memories or confront fears using gradual desensitization	Reduce trauma and anxiety symptoms
Problem Solving	Teach a process of steps to solve problems and make healthy decisions	Promote health decision making Skills training for problem solving

CETA will be delivered within the clinic with an option for community-based delivery (i.e., in a local church or community center) if preferred by the participant, similar to previous Zambia studies. To estimate uptake of CETA in a "real-world" HIV clinic setting, if participants do not attend their initial meeting, counselors will make several phone follow-ups for up to a maximum of 1 month after enrollment. If the participant does not start treatment within one-month post-enrollment, the counselor will cease efforts to engage them in CETA as additional retention efforts would be impractical in a non-research setting. After the initial session, if a client misses a follow-up appointment, the counselor will again follow-up by phone up to three times in a week and make a one-time home visit to re-engage the client. The research team will not contact the participant during the active intervention phase so as not to artificially influence the participant to attend CETA sessions.

Tracking of treatment uptake and completion. We have developed rigorous and sophisticated participant tracking systems through our previous Zambia studies. We will systematically track throughout the course of the study: (1) the number of participants who successfully complete and decline BI; (2) the number of participants who successfully link to CETA, defined as attending the first CETA session; (3) the amount of time counselors dedicate to client tracking/retention; and (4) the number of clients who successfully complete CETA. Counselors will attempt to track clients to the extent that this would be practical in a real-world setting.

Clinical monitoring data collection. During CETA sessions, the counselor will administer a brief clinical symptom checklist (Client Monitoring Form; CMF) and a past 7-day Alcohol TLFB. These data guide clinical care by informing the choice of CETA elements to be delivered in session and will also be used in analyses. These forms will only be administered to CETA participants during their CETA sessions. (Neither RCT participants randomized to the BI alone nor Cohort study participants will complete the TLFB).

Follow-up assessments. Alcohol and comorbidities will be assessed in all participants at 6 months (i.e., endline) after baseline. The ACASI questionnaire that was used at baseline will again be administered at this follow-up visit (i.e., the questionnaire at this visit is the same as at baseline). In addition to ACASI assessments, we will confirm self-reports of alcohol abstinence on the AUDIT by conducting a urine-based rapid alcohol biomarker test, ethyl glucuronide (uEtG). Finally, at the 6-month post-assessment, which coincides with a regularly scheduled clinic visit, we will extract relevant information from the client's HIV clinical record (this will be the same information that is collected at baseline), including: , (1) hepatitis B surface antigen, (2) most recent CD4+ count, (4) cumulative and past 6-month ART retention, defined by medication possession ratio (MPR; an objective pharmacy record metric that we have used previously) and (4) plasma HIV viral load (measured at CIDRZ Central laboratory using the Roche COBAS/Ampliprep platform. We will not collect any additional biospecimens for purposes of the study—all HIV-related data will be captured via chart extraction. To supplement retention data captured through MPR measurement, we will also assess visit adherence, the percentage of assigned pharmacy and clinical visits that were made (coming to clinic within 3 days).

Implementation data collection. We will conduct a mixed methods process evaluation with stakeholders involved in the CETA referral and treatment process, including follow-up FGDs and KIIs with participants from Stage 1A and CETA counselors. We will also conduct mixed methods interviews with approximately N=30 PLWH who participated in the Stage 1B pilot RCT. This will include a purposeful sample of PLWH from a range of ages and both sexes who did and did not complete the BI and CETA. Implementation factors to be explored will include: acceptability, appropriateness, reach, cost, feasibility, and sustainability and will explore the attitudes, thoughts, feelings, and barriers and facilitators related to implementation. Interviews will include an in-depth interview component and JHU quantitative implementation measures.

Data management. All uptake/completion, clinical monitoring, HIV outcome, and UEtG data will be double entered into password protected databases by research staff weekly. ACASI data will be electronically transferred from field laptops at the HIV clinics into the study database at CIDRZ headquarters daily. De-identified data will be transferred to JHU weekly. Dr. Kane will run data checks and return queries for resolution. Dr. Kane and Dr. Vinikoor will hold weekly calls with the Zambian data team.

2. Describe the number and type of study visits and/or contacts between the study team and the participant, how long they will last, and where/how they will take place.

Stage 1A: We expect to have two study visits with focus group participants (PLWH and healthcare workers). The first visit will be the recruitment/consent visit. The second visit will be the actual focus group session. The first visit we expect to take approximately 30 minutes. We expect the focus groups to be between 60-90 minutes. We expect to have one study visit for key informants in which we will conduct both the consent and interview. We expect these sessions to be approximately 60-90 minutes. A third contact may be conducted with some of the healthcare workers and key informants at the end of the study to discuss implementation factors in an in-depth interview or focus group. This third visit will be approximately 60-90 minutes in length.

Stage 1B: Participants in the pilot will have an initial study visit for consent/screening/baseline/BI. The initial visit, which includes informed consent and baseline ACASI to capture data, may take up to 120 minutes. If they are randomized to CETA they will have an additional 6-12 weekly therapy sessions (approximately 60 minutes each). All participants will have a post-assessment visit approximately again 6 months post-baseline (we will attempt to have the 6 month assessment align with a regular HIV care visit). The follow-up study assessments we expect to take approximately 45 minutes. We will also ask a sample of participants to participate in a mixed methods interview following the study on implementation outcomes.

3. Describe the expected duration of the study from the perspective of the individual participant and duration overall.

From the perspective of participants, the study will be approximately 6 months. Overall, we expect the study to take 3 years, including final data analysis. An estimated timeline is provided below.

Table 4. Study timeline

Study Phase	Activity	Year 1				Year 2				Year 3			
		Q 1	Q 2	Q 3	Q 4	Q 1	Q 2	Q 3	Q 4	Q 1	Q 2	Q 3	Q 4
Planning	Study protocol finalization and ethical approval												
	Staff hiring and site preparation												
	Training of qualitative data staff												
Stage 1A	Focus groups and key informant interviews												
	Adaptation of CETA for PLWH												
	Development of CETA protocol in HIV care based on Stage 1A												
	CETA/mhGAP-IG trainings, assessor trainings, M&E trainings												
	CETA pilot cases												
Stage 1B	Recruitment, consent, screening and baseline assessments (ACASI, HIV)												
	Interventions active												
	Post-treatment assessments (ACASI, UEtG)												
	6-month outcomes assessment (ACASI, UEtG, HIV outcomes via chart review)												
	Implementation data collection (PLWH, clinic staff, policy officials)												
Analysis, dissemination, and next steps	Data analysis												
	Report/manuscript writing and dissemination at conferences												
	Preparation and submission of follow-up R01												

4. Provide a brief data analysis plan and a description of variables to be derived.

Analysis of treatment uptake and completion. We will estimate a logit model with a binary outcome (1=completer; 0=non-completer) to assess predictors of treatment completion. Predictors will be demographic (e.g., sex, age), clinical (e.g., symptom severity), and structural (e.g., distance from clinic) level factors.

Analysis of ACASI outcome data. Analyses will be intent-to-treat. AUDIT score, along with other continuous secondary outcomes (Past 30-Day TLFB [% days drinking and mean drinks per day], CES-D, HTQ, ASSIST scores) will be modelled with linear mixed models. Fixed effects will include treatment arm (0=BI; 1=BI+CETA), time (0=Baseline; 1==6-months post-baseline), and interaction terms between treatment arm

and time. This will allow estimation of the mean difference in change in score between arms and 95% confidence intervals. Cohen's D will be calculated to estimate effect size. Covariates will be included if they differ meaningfully at baseline or predict significant change in the outcome. For dichotomous outcomes or non-normally distributed continuous outcomes, generalized linear mixed effects models will be estimated. Paired t-tests will be used to assess within group change among the non-Pilot RCT hazardous drinkers.

Analysis of CETA clinical monitoring data. We will conduct longitudinal data analysis with CMF and TLFB daily estimates of drinking during CETA. Exploratory analysis will examine trajectories of weekly symptom change based on CMF score and number of drinks per day using spaghetti and scatter plots. We will explore the association between baseline client characteristics on symptom trajectories. We will use survival analysis to calculate the number of sessions required for 25%, 50%, and 75% of clients to achieve one or two standard deviation(s) in symptom improvement from baseline. We will also calculate the percentage of clients that achieve these changes by the end of treatment. Collectively, these analyses will provide insight into *when* symptoms change over the course of treatment, which may be useful in refining CETA in future studies.

Analysis of HIV outcome data. In both RCT and non-RCT participants, we will use a linear model to investigate changes to MPR during the period before and after the intervention and a logistic model for changes to the proportion with HIV viral suppression (defined as <1000 copies/ml, the standard in SSA). We will compare visit adherence between those randomized to BI+CETA versus BI alone. Because of the relatively small sample sizes in this pilot study, these data will be primarily descriptive; however, these data will inform a follow-up grant.

Analysis of uEtG results. The purpose of uEtG testing is to confirm abstinence and not to validate AUDIT scores >0. Based on Preliminary Studies we expect to identify 'under-reporters,' defined as participants who report abstinence on AUDIT or TLFB and test uEtG-positive. In a secondary analysis, we will exclude under-reporters and re-assess the impact of the intervention on alcohol use and other outcomes.

Analysis of implementation data. Mixed methods analysis based on NIH best practice guidelines will be used to integrate findings from the quantitative and qualitative data. Descriptive analyses will be used to investigate the quantitative data on constructs of acceptability, appropriateness, reach, feasibility, and cost. The qualitative data will provide in depth understanding of factors related to (1) mechanisms of change; and (2) barriers and facilitators to program implementation in the Zambian context. Findings will be shared with local (HIV clinics, Lusaka district, and Zambia MoH) and international stakeholders (PEPFAR/CDC, UNAIDS, etc.) to inform future programming efforts.

5. Answer the following **if they are relevant to your study design**:

1. If the study has different arms, explain the process for assigning participants (intervention/control, case/control), including the sequence and timing of the assignment.

The assessor will have two locked cabinets at the clinic with sealed envelopes. One cabinet will contain randomization assignments for female participants, the other for male participants. Printed on the outside of the sealed envelopes will be a Randomization ID. When a participant is eligible for the pilot RCT, the assessor will retrieve the next available envelope and record the Randomization ID and Screening ID on a Screening Information Sheet, thus linking the two IDs to the participant. Randomization IDs will be assigned to BI+CETA or BI alone using *randomize* in Stata *a priori* by a U.S.-based statistician not affiliated with the study. Randomization IDs will be randomized 1:1 in blocks of 20 stratified by sex. The assessor will inform the participant of their assignment by opening the envelope

immediately after the baseline assessment. This ensures that the assessor is blinded to the participant's randomization status during the assessment itself. Follow-up assessments will be conducted by a different assessor.

2. If human biospecimens (blood, urine, saliva, etc.) will be collected, provide details about who will collect the specimen, the volume (ml) and frequency of collection, how the specimen will be used, stored, identified, and disposed of when the study is over. If specimens will be collected for use in future research (beyond this study), complete the "Biospecimen Repository" section below.

   The only biospecimen being collected in this study will be a urine ethyl glucuronide (ETG) test to confirm alcohol abstinence. In previous alcohol research conducted by our team in Zambia, we have found that it is important to compare self-reported alcohol use to an objective biomarker. This urine specimen will only be collected at one timepoint among cohort and RCT participants: at the 6-month post-baseline assessment. The test requires the participant to provide a small urine sample (appx. 100ml). During the study visit we will provide participants with a urine cup and ask them, in a private bathroom at the clinic, to provide us with a 100ml sample of urine. Following the sample collection, a study assessor will insert a dipstick into the sample and within 1 minute the test provides a qualitative (positive/negative) result for alcohol consumption within the past 2-5 days.

   We will provide participants with results of the EtG test at the visit. No additional tests except the dipstick will be conducted with the sample. Following testing, the sample will be destroyed. We have used EtG tests previously with similar patient populations and it was found to be feasible and acceptable (Vinikoor et al., 2018).

3. If genetic/genomic analyses are planned, address whether the data will be contributed to a GWAS or other large dataset. Address returning unanticipated incidental genetic findings to study participants.

   N/A

4. If clinical or laboratory work will be performed at JHU/JHH, provide the JH Biosafety Registration Number.

   N/A

5. If you will perform investigational or standard diagnostic laboratory tests using human samples or data, clarify whether the tests are validated and/or the lab is certified (for example is CLIA certified in the U.S.). Explain the failure rate and under what circumstances you will repeat a test. For all human testing (biomedical, psychological, educational, etc.), clarify your plans for reporting test results to participants and/or to their families or clinicians. Address returning unanticipated incidental findings to study participants.

   The urine dipstick ETG test has been FDA-approved and validated.

Urine dipstick results (positive or negative) for ETG will be discussed with participants as soon as they are available (within 1 minute of sample collection).

6. If your study involves medical, pharmaceutical or other therapeutic intervention, provide the following information:

1. Will the study staff be blind to participant intervention status?

   Assessors will be blind to participant intervention status. Due to the nature of the interventions, counselors will not be blinded. Data Analysts will also be blinded.

2. Will participants receive standard care or have current therapy stopped?

   Participants are already receiving standard of HIV care in Zambia and this will be continued during and after the study. Participants will not be asked to stop any current therapy.

3. Will you use a placebo or non-treatment group, and is that justifiable?

   We will not have a non-treatment group. The control group will receive the BI, which is the current standard of care at HIV clinics in Zambia.

4. Explain when you may remove a participant from the study.

   Participants will be temporarily removed from the study if they demonstrate actively suicidal or homicidal thoughts. Anyone who develops psychosis in need of hospitalization will also be removed. In any of these events, research assistants, counselors, and supervisors will work together to get appropriate psychiatric assistance for the individual. The study PI and our clinical supervisory team will consult with psychiatric providers in Zambia to determine whether the participants may return to the study following appropriate treatment.

   Participants will be removed from the study at their request if they express to us that they do not feel safe.

5. What happens to participants on study intervention when the study ends?

   Study interventions will be completed before the end of the study. Following the end of the study, participants who request additional services will be referred to appropriate care.

6. Describe the process for referring participants to care outside the study, if needed.

   Some participants may experience emotional distress as a result of participation. Many therapeutic interventions deal with small degrees of stress within a session as part of the treatment. Based on research and experience, the expected degree of distress will be minimal and expected as part of the therapeutic process. In cases where distress does occur during treatment, the participant would be with a trained counselor who will be trained at handling such situations. In addition, these

counselors will have local supervisors; and access to Ms. Stephanie Skavenski (co-I; Licensed Clinical Social Worker) and Dr. Laura Murray (co-I; Clinical Psychologist) and Dr. Ravi Paul (consultant; psychiatrist, University of Zambia). Our team has run multiple trials with CETA, including in Zambia, and have not found this to be a problem. We are prepared to handle more significant issues that could arise and have established relationships at Chainama Hills Hospital in Lusaka, which has inpatient psychiatric services. Should it be necessary, participants can be referred and receive treatment there.

VI. Data Security and Confidentiality Protections:

a. Personally Identifiable Information (PII):

Please identify the Personally Identifiable Information (PII) that you may be collecting and using at any of the following stages of your study: ***Recruitment***, ***Consent,*** *and* ***Study Implementation***.

Name, signature, initials, or other identifiable code	☒
Geographic identifier: address, GPS location, etc.	☒
Dates: birth, death, clinical service, discharge, etc.	☒
Contact information: phone numbers, email address, etc.	☒
ID: Social Security Number, driver's license number, etc.	☐
Health record identifiers: medical record, insurance plan number, etc.	☐
Account numbers	☐
Device identifiers: e.g., implants	☐
Internet identifiers: IP address, social media accounts	☐
Biometric identifiers, including finger and voice prints	☐
Audio recordings	☒
Video or full face photographic images	☐
Genomic/genetic data	☐
Any other unique identifying number, characteristic, or code (note: this does not mean the unique code assigned by the investigator to code the data)	☐
Other: Click here to enter text.	☐

b. Recruitment:

Will you collect identifiers for the purpose of contacting potential participants? Yes ☒ No ☐

If **yes**, will you retain the identifiers after the recruitment contact has been made? Yes ☒ No ☐

c. Data Collection:

Collection of data for a research study can take on many forms. It can be as simple as gathering the data with pen and paper or developing an on-line adaptive survey that changes based on the participant's answers. Regardless of the method, PII for the purposes of identifying the participants will

most likely be collected. Once collected, the raw data should go through a de-identification process to further protect PII.

In what form will you collect and store PII? When you respond, think of PII collected for recruitment, consent, and other study purposes.

a. **Hard Copy/Paper:** Yes ☒ No ☐

If yes, please answer the following:

1. How will the data be kept secure during transfer from study collection site to storage site?

All data collected on paper forms will include only the participant's ID number. Paper forms will be transferred securely in study vehicles to the storage site where they will kept in locked filing cabinets within locked offices.

2. Will the data be secured in a locked cabinet or room? Yes ☒ No ☐

3. If study IDs/Codes are used, will they be stored separately from the study data? Yes ☒ No ☐

4. Will the hard copy/paper be destroyed after data abstraction and cleaning are complete?
Yes ☒ No ☐
If No, when do you plan to destroy the hard copies?

b. **Electronic:** Yes ☒ No ☐

If yes, please answer the following:

1. Will the data be collected/stored on a portable device (laptop, mobile phone, tablet, PDA) protected by encryption? Yes ☒ No ☐

2. Will study participants use personally owned devices or study-provided devices?
Personally owned ☐ Study provided ☒

3. Is the application/website used for data collection being developed in-house (Hopkins) or by a 3rd party vendor?

In-house ☐ 3rd party ☒

If 3rd party, provide the name of vendor and URL:
Identify Mobile Ecosystem (check all that apply) Apple ☐ Google ☐ Website ☐

Tufts University: http://medicine.tufts.edu/Education/Academic-Departments/Clinical-Departments/Public-Health-and-Community-Medicine/Nutrition-and-Infection-Unit/Research/Implementation-Science/ACASI-CASI-CAPI

4. Will the data be stored on a secure server (@JHSPH/on-site)? Yes ☒ No ☐

5. Will the data be stored in the Cloud/Web? Yes ☒ No ☐

6. Will it be encrypted? Yes ☒ No ☐

7. Will you be backing up your data? Yes ☒ No ☐

c. **Audio Recording**: Yes ☒ No ☐

If yes, please answer the following:

1. Will you store the audio recording securely in a locked cabinet/room until transcription is complete?
   Yes ☒ No ☐

2. Will you use a transcription service?
   Yes ☐ No ☒
   If yes, if the PII comes from JHH/JHHS, you must use an approved vendor; otherwise, be aware of the data security protections that the transcription service provides.

3. Will the audio recording be destroyed after transcription? Yes ☒ No ☐

   If no, why not?

- **Photograph/Video**: Yes ☐ No ☒

If yes, please answer the following:

1. Will the photographs/videos be stored securely in a locked cabinet or room? Yes ☐ No ☐

2. Will the photograph/video be destroyed? Yes ☐ No ☐

   If yes, when?

d. PII De-Identification of Data Used for this Study:

1. When will you destroy the PII and/or the code linking the PII with the study ID? PII will be destroyed immediately following the end of the participant's participation in the study (i.e., following the last study visit with the participant when their contact information will no longer be needed)

2. What is the method you will use to de-identify the data? All PII will be stripped from datasets. Only a unique ID number will be included in de-identified data.

3. Is your research data governed by HIPAA (U.S. clinical data remaining within the covered entity)?
   Yes ☐ No ☒
   1. If yes, who is doing the de-identification?
   2. If yes, what level of de-identification will you achieve (Limited data set? De-identified?)

e. Data Storage and Analysis:

One of the keys to protecting PII is the proper use of tools to share and conduct your analysis. JH and JHSPH offers several options for you to consider. Please select the system that you plan to use to protect your study data by clicking the box. Consult JHSPH IT for assistance if needed.

☐ **JH Virtual Desktop**: The Hopkins Institute for Clinical and Translational Research (ICTR) provides a virtual Windows desktop (SAFE Desktop). It includes productivity software such as Microsoft Word and Excel, as well as statistical software, including SAS, Stata, R, R Studio, and Python. 100 GB of storage space is provided.

☐ **JHSPH SharePoint and File Shares**: These systems provide a managed and secure platform for your research project. They also provide a built-in encrypted backup solution.

☐ **JHSPH RedCAP**: These are departmentally managed applications. RedCAP is an application designed for collaborative research projects.

☐ **JHSPH HPCC:** High Performance Computing Cluster (HPCC: https://jhpce.jhu.edu/) can provide the high capacity computing required for very large data sets.

☐ **JHBox**: Johns Hopkins Box (JHBox) is a secure cloud-based file sharing service which enables people to collaborate and share information and may be accessed through any device: desktop, laptop, phone, or tablet with appropriate permissions. JHSPH IT recommends that investigators not use JHBox as a primary storage location, but use it instead for initial data collection, sharing results, and other collaborative information with the research team.

☐ **Independent Departmental Servers and Systems**: These servers are typically managed by departmental or research team IT staff. Because these servers are not centrally managed by JHSPH IT, all documentation regarding data security protections will need to be provided by the owner/administrator of the server. This responsibility may fall to the data owners (PI).

☒ **Other**: Please provide details regarding any other systems being utilized. Examples may include servers and applications located at another university participating in your study or a 3rd party web-based application. Data will be securely stored on CIDRZ DHIS-2 server, which is used for all of their HIV clinical programming. Access to the server is restricted to only essential personnel. Data are encrypted. Only the data manager at CIDRZ and Dr. Kane will have access to data for this project. Dr. Kane will have secure access to the server remotely through a VPN.

f. **Other Data Security Measures:**

In addition to the details regarding data collection, please review the following questions. This additional information will be utilized to assist in the development of a comprehensive Data Security plan. This would include the systems used to analyze the data, data security contacts and additional requirements.

a. During the analysis phase, do you plan to use computer systems that are not managed by JHSPH or JH? Yes ☐ No ☒

If yes, please explain:

b. Do you have a designated person on your research team other than the PI who is the technical contact for a Data Security plan? Yes ☐ No ☒

If yes, please provide a contact name:

1. Does your sponsor have other specific data security requirements for the study data? Yes ☐ No ☒
   If possible, please explain:

c. Please add any other information that you believe is relevant to data security.

g. Certificate of Confidentiality:

All NIH studies include Certificate of Confidentiality protections with the grant; the consent form must include the C of C language provided in our template. Other funders may obtain C of C protections through NIH. (https://humansubjects.nih.gov/coc/index)

Does the study have Certificate of Confidentiality protections?

Yes ☒ No ☐

h. **JHM Clinical Records:**

Will you use clinical data of 500 records or more from Johns Hopkins Hospital and its affiliates?
Yes ☐ No ☒

If yes, please complete the JHM Data Security Checklist available on the JHSPH IRB website: www.jhsph.edu/irb and upload a copy of the checklist to the "Miscellaneous" section.

VII. Risks of the Study:

- Describe the risks, discomforts, and inconveniences associated with the study and its procedures, including physical, psychological, emotional, social, legal, or economic risks, and the risk of a breach of confidentiality. These risks should be described in the consent documents.

  Risk associated with the study include:
  - Emotional distress, resulting from assessment measures or therapy sessions
  - Risk of breach of confidentiality, including stigmatizing conditions such as HIV and alcohol use disorder

- Describe the anticipated frequency and severity of the harms associated with the risks identified above; for example, if you are performing "x" test/assessment, or dispensing "y" drug, how often do you expect an "anticipated" adverse reaction to occur in a study participant, and how severe do you expect that reaction to be?

  Based on previous studies by our team in Zambia with similar study populations and trial designs, we expect the frequency of harms to be low and the severity to be minor.

- Describe steps to be taken to minimize risks. Include a description of your efforts to arrange for care or referral for participants who may need it.

  Study staff and peer educators will be trained in responding to distress and multiple levels of back-up support have been developed. Assessors and study staff are encouraged to contact the clinical supervisors and/or Ms. Skavenski van Wyk who are extensively trained in clinical matters such as identifying levels of distress, local referral options and processes, and clinical interviewing on sensitive topics. We will also have a safety protocol that has been developed in collaboration with the University of Zambia, University Teaching Hospital, CIDRZ, and the Ministry of Health which includes: a) immediately contacting a clinical supervisor, b) the supervisor guiding them through additional questions and help make a decision if the participants needs to be brought to see a specialist, if they need to do an immediate home visit, or if a 1-day safety contract may be completed, c) Ms. Skavenski van Wyk and Dr. Paul will be contacted immediately by the supervisor to further assess and give

recommendations, and d) MPIs Drs. Kane and Vinikoor and Dr. Murray (clinical co-I lead) and will be contacted within 24 hours and notified of the situation.

i. Emotional distress

Assessments and Intervention: Participants will receive questions each week during the intervention phase to assess suicide and homicide risk (in person for CETA participants during their session; via phone for BI participants). A primary outcome of the proposed study is retention in CETA. Therefore, we want to minimize research contacts with participants as much as possible. We must balance that research aim, however, with the need to clinically monitor our study participants for safety. If a participant in the pilot RCT indicates high risk, their counselor will immediately follow the locally developed safety protocol above. In the BI control arm, if the participant does not respond within 24 hours to the phone contact, a counselor will do a home visit to assure response to safety questions. All assessors will be trained in how to recognize and respond to distress that may occur during the intervention, and will call their supervisor if they are unsure. At least one member of the clinical study team (Skavenski van Wyk, Paul, Murray, Zambian clinical supervisors) will be on-call at all times to address any urgent cases.

ii. Disclosure of HIV or other confidential information

Subjects will be protected against the risk and repercussions of accidental disclosure of HIV status in several ways. Confidentiality of study data is a priority and we will take many precautions to protect against the possibility of a breach of confidentiality. All research staff are aware of the importance of maintaining strict confidentiality and we have extensive experience dealing with sensitive mental health/alcohol use/HIV information. The following precautions will protect the privacy of participants and maintain confidentiality of research data: 1) All study staff will be well trained and will receive ongoing supervision in confidentiality and data security procedures, specifically in ethical conduct, confidentiality protection, mandated reporting, and other topics of human participant protection. 2) Privacy will be maintained by conducting all data collection activities in closed and private clinic rooms at CIDRZ/MoH clinics, in CIDRZ offices, and in MoH offices. Data will be transported daily in secure study vehicles from study sites to CIDRZ Headquarters where it will be uploaded to CIDRDZ secure DHIS-2 server. 3) Each participant will be assigned a unique study ID number, and all data will be coded with ID numbers only and will not contain identifying information. The spreadsheet linking participant names, phone numbers, and addresses with ID numbers will be stored in a separate password protected document on a password-protected computer, to which only essential study staff will have access. Following the end of the study, the link will be destroyed such that all data are completely de-identified. 4) Paper-based data will be securely stored in separate locked file cabinets in locked offices. 5) Biological data (UEtG) will be labeled only with an ID number and destroyed following recording of the test result. 6) Electronic data will be coded (no identifying information will be included) and stored on CIDRZ secure DHIS-2 encrypted server. Access to data storage areas and computers will be restricted. 7) Analysis will occur only on de-identified data and be presented in aggregate. 8) All participants will be encouraged to contact the local study direct, local investigators, or other staff to report any undesirable conduct associated with the study. These reports will be brought to the attention of the study director, local PIs and co-Is and the MPIs, and appropriate steps will be taken to solve the problems, including reporting to relevant ethical review boards.

- Describe the research burden for participants, including time, inconvenience, out of pocket costs, etc.

  Therapy sessions and assessments can be delivered either in the clinic or in a community location to minimize time or inconvenience burden on participants. While most study-related activities will occur during regular HIV care visits, participants may be required to come to the facility more often during the study, which incurs the cost of transportation and time.

- Describe how participant privacy will be protected during data collection if sensitive questions are included in interviews.

Data collection will be conducted in a private location within the HIV clinic where the participant is already receiving care or in a private room within a community location if the participant prefers. Data forms will only contain a study ID number and no personal identifying information of the participant. The only form linking the personal identifying information and the participant's ID number will be stored separately in a locked cabinet at CIDRZ headquarters and will only be accessible to required personnel. An electronic version of this form will be on a password-protected excel file that is also securely stored on CIDRZ DHIS-2 server. Outcomes data will be collected via ACASI, so an interviewer will not know the participant's responses to sensitive questions.

VIII. Direct Personal and Social Benefits:

- Describe any potential direct benefits the study offers to participants ("payment" for participation is not a direct personal benefit).

Through participation in the research, participants will receive assessments that may benefit them by providing information about some of their problems, including alcohol use and mental health. Recipients of CETA will receive an evidence-based intervention that we already know positively impacts mental health problems.

- Describe potential societal benefits likely to derive from the research, including value of knowledge learned.

Capacity building: By training local interviewers in the assessment tools and peer educators in the two interventions, there is local clinical and research skill building. This has enormous benefit for them as individual professionals living in a low-resource country.

Scientific Field: We anticipate that this study will generate substantial indirect benefits to the participants as it will provide urgently needed answers to what may be effective interventions for reducing hazardous alcohol use and comorbid mental health problems.

Policy: A core principle of this research is that key stakeholders, including policymakers such as the Zambian Ministry of Health, will be involved in the study. Policy makers will be invited to the workshops and relevant meetings, and included on relevant communications, to share the research data for improving and integrating mental health services. Their involvement will serve as a compass for the work of this study, and allow real-time policy influence.

IX. Payment:

- Describe the form, amount, and schedule of payment to participants. Reimbursement for travel or other expenses is not "payment," and if the study will reimburse, explain.

We recognize that additional time will be needed to complete study activities; therefore, we will provide reimbursement for travel to all study visits (screening visit, assessments and therapy sessions). The amount of this reimbursement will be 20 Zambian Kwacha, approximately $2, which is the cost of round-trip bus fare (the usual mode of transport for clients to reach the clinics).

- Include the possible total remuneration and any consequences for not completing all phases of the research.

Participants are not being paid to participate in the study. There will be no consequences to the participants for not completing all phases of the research.

X. Study Management:

A. Oversight Plan:

- Describe how the study will be managed.

  A multiple PD/PI (MPI) approach will be used in the proposed study. Drs. Vinikoor (based at CIDRZ/UAB) and Kane (based at JHU) are Early Stage Investigators (ESI) who have complimentary areas of expertise, were both responsible for project conceptualization and development, and will share responsibilities for overall scientific direction and oversight of the project. We are confident based on the extensive JHU-CIDRZ collaborative history working in Zambia and ongoing meetings and joint involvement with the development of the study idea and design, that we will be able to function together as a leadership team and that the benefits of a joint leadership approach will be evidenced through the strength of the study implementation and impact on policy and services. The MPIs will both have ultimate shared oversight for the operation of the research.

  Three senior investigators were deliberately selected as Co-I to support the MPIs: (1) Dr. Laura Murray, a clinical psychologist, developer of CETA, and co-founder of the Applied Mental Health Research Group at JHU; (2) Dr. Geetanjali Chander, an NIAAA-funded HIV clinical epidemiologist specializing in the treatment of alcohol use disorders; and (3) Dr. Anjali Sharma, a Social Scientist with >20 years of experience in design and evaluation of large health programs in Africa and Asia. Each Co-I has vast experience as PIs and are current collaborators with both Drs. Kane and Vinikoor on active projects in Zambia.

  The MPIs will be in constant communication by email (daily), phone (at least weekly; more as needed), and in-person (quarterly trips to Zambia by Dr. Kane funded through this and other projects). MPIs will be in constant communication with the Zambia-based team, including two conference calls per week (one full-team call; one for the data M&E team) to ensure ethical, scientifically sound, and productive implementation of the study.

- What are the qualifications of study personnel managing the project?

  Dr. Vinikoor is an HIV Clinician-Researcher (supported by a K01 grant) who has lived full-time in Zambia and worked at CIDRZ since 2012. He has served as PI or Co-I on multiple NIH/CDC-funded HIV observational and interventional studies in Zambia, including the IeDEA cohort, from which the proposed study will recruit participants. He will take responsibility for the administration of the overall grant in Zambia, including subcontracts with partner institutions (CIDRZ and his home institution, UAB). He will facilitate connections between Zambian organizations, policy makers, and the research team, and will oversee the setup of the trial within the proposed HIV clinical sites, Kanyama and Matero Reference clinics.

  Dr. Kane is a Psychiatric Epidemiologist who specializes in alcohol use disorders. He is the PI of an LRP award from NIAAA, has served as Methodologist and Co-I on three randomized trials in Zambia (PI: Murray), and led related investigations into improving measurement of alcohol among HIV-affected populations. As MP at the primary grantee institution (JHU), Dr. Kane will oversee financial and administrative reporting to NIH/NIAAA with budget support from administrative staff at JHU. Leveraging his 6+ years of clinical trial experience with HIV-affected populations in Zambia, Dr. Kane will take the lead role in the design and appropriate implementation of the pilot RCT, data collection quality assurance/control, adherence to trial protocol, and data analysis.

  Dr. Anjali Sharma (Co-I/Site PI in Zambia) is a social scientist and Senior Research Technical Advisor at the Centre for Infectious Disease Research in Zambia (CIDRZ) with >20 years experience in design and evaluation of large health programs worldwide. Although my scope of research is broad and includes both HIV and non-HIV-infected populations, my career focus has been on marginalized and populations at increased risk for poor health outcomes. She has experience in HIV health systems research and investigated the roots of insufficient organizational and clinical performance at HIV clinics in five sub-Saharan countries including Zambia. She will oversee implementation of the project in Zambia and bring expertise in adaption of interventions to the problem of hazardous alcohol use among HIV-infected Zambia.

In addition to the PI's, investigators include Dr. Murray as well as Ms. Stephanie Skavenski van Wyk, a licensed clinical social worker, who has over a decade of clinical and research experience in Zambia and will lead along with Dr. Murray all CETA trainings and supervision. Finally, the field activities will be monitored by Ms. Flor Melendez who has over a decade of program and research management in Zambia, including as study director of our team's recently completed CETA trial.

- How will personnel involved with the data collection and analysis be trained in human subjects research protections? (Use the JHSPH Ethics Field Training Guide available on the JHSPH IRB website: www.jhsph.edu/irb.)

  All personnel involved in human subjects research will be trained with the JHSPH Ethics Field Training Guide, the NIH human subjects modules. All will be certified before they are allowed to be involved in data collection or human subjects activities.

- If the PI will not personally be on-site throughout the data collection process, provide details about PI site visits, the supervision over consent and data collection, and the communication plan between the PI and study team.

  Dr. Vinikoor will be on-site regularly throughout the data collection process. Dr. Kane will be in contact with the team daily by email and twice weekly by conference call. Dr. Kane will make at least annual trips to Zambia.

B. **Recordkeeping:**

Describe how you plan to ensure that the study team follows the protocol and properly records and stores study data collection forms, IRB regulatory correspondence, and other study documentation. For assistance, contact housecall@jhu.edu.

Recordkeeping will be a core component of the weekly full team teleconferences. The study director based in Zambia will maintain a study spreadsheet to monitor that all study documentation, IRB regulatory correspondence, and other study documentation are organized and up to date.

C. **Safety Monitoring:**

1. Describe how participant safety will be monitored as the study progresses, by whom, and how often. Will there be a medical monitor on site? If yes, who will serve in that role?

   Participant safety is monitored throughout the study by the clinical team, led by Co-I's Dr. Murray, Ms. Skavenski, and Dr. Paul. We will also convene a DSMB.

2. If a Data Safety Monitoring Board (DSMB), or equivalent will be established, describe the following:

   a. The DSMB membership, affiliation and expertise.

      The 3 member *DSMB* will include individuals from CIDRZ, UAB and JHU faculty including an HIV expert, a statistician, an expert in conducting MH research in low-resource settings.

   b. The charge or charter to the DSMB.

The DSMB will assist the study in monitoring adverse events. The DSMB will meet as needed for the duration of the project. We will circulate to all DSMB members study protocols including formal procedures for reporting and tracking all adverse reactions to the NIH and IRBs; tracking progress in the study; and identifying any need for premature termination of the protocol. The DSMB will provide feedback to the PIs on these draft protocols. We will prepare progress reports to the DSMB every six months on concerning enrollment, attrition, and adverse events.

The DSMB will review these progress reports and respond with concerns to the MPIs. Conference calls with the DSMB will be conducted on a schedule determined at the first DSMB meeting . Final reports approved by the DSMB will be generated.

c. Plans for providing DSMB reports to the IRB.

All DSMB reports will be forwarded to the IRB within 30 days of the report being finalized.

d. Describe plans for interim analysis and stopping rules, if any.

There are no plans for interim analyses.

D. **Reporting Unanticipated Problems/Adverse Events (AEs) to the IRB (*all studies must complete this section*)**:

Describe your plan for reporting to the IRB and (if applicable) to the sponsor. Include your plan for government-mandated reporting of abuse or illegal activity.

Reportable Events

Adverse Events. The PI will be responsible for oversight of potential adverse events. An adverse event (AE) is any untoward medical occurrence in a subject during participation in the study. We anticipate two potential types of AEs that could be directly related to study participation. These include distress experienced with regard to research participation and breach of confidentiality and privacy. With regard to both matters, we have protocols in place that include conferring with the PI or a project mental health provider and appropriate safeguards to reduce risk of breach of confidentiality and privacy. Additional potential AEs are not likely, however we anticipate that AEs related to suicidal ideation and/or intent, homicidal ideation and/or intent, clinical worsening necessitating a higher level of care, and neglect/abuse may come to the attention of research staff during the consenting and recording process and during provision of care.

Classification and Documentation of Adverse Events. AEs will be classified by severity (mild, moderate, or severe) depending on the intensity of the event on the patient. An AE will be "mild" if it does not have a major impact on the patient, "moderate" if it causes some minor inconvenience, and "severe" if it causes a substantial disruption to the patient's well-being. A severe AE is distinct from a serious adverse event (SAE), which is any AE that results in death, a life-threatening event, inpatient hospitalization, disability, congenital anomaly or birth defect, and/or an important medical event based upon appropriate medical judgment. AE's and SAE's will also be classified according to the likelihood that they are related to the study intervention. They will be labeled definitely unrelated, definitely related, probably related, or possibly related to the study processes. We will also collect unanticipated problems involving risks to subjects or others (UPIRSOs), protocol violations, and instances of non-compliance.

Timeline for reporting. We will provide bi-annual reports to the DSMB. We will use the following procedures in the event of an AE, SAE, UPIRSO, protocol violation, and instance of non-compliance. In the case of any of these instances, the research team will alert the PIs immediately (same business day). Subsequently, the PIs will submit a report within 10 working days (with one exception) of events that meet the definition of an unanticipated problem involving risks to subjects or others. The exception is if the SAE involved death and indicates that participants or others are at increased risk of harm, the PI will be required to submit a report to the DSMB within 3 days. Reports will be submitted electronically to the DSMB chair. The DSMB representative, when necessary in conjunction with the full DSMB, review reports and decide whether the event meets the definition of an unanticipated problem increasing risks to subjects or others. Events that meet these criteria will be considered unanticipated problems involving risks to participants or others, will be reviewed by the convened

DSMB. We will of also notify the IRB within 3 days of unanticipated AEs related to the study and of any deaths using the adverse event reporting form. All adverse events will also be included in annual reports to the IRB.

NOTE: The IRB does not require PROMPT reporting of all AEs, only those that are **unanticipated, pose risk of harm to participants or others, and are related to the study**. Anticipated AEs may be reported with the Progress Report.

E. **Other IRBs/Ethics Review Boards:**

If other IRBs will review the research, provide the name and contact information for each IRB/ethics review board and its Federal Wide Assurance, if it has one (available on OHRP's website at http://www.hhs.gov/ohrp/assurances).

As in previous studies, the research will be reviewed by a local IRB: University of Zambia Biomedical Research Ethics Committee (UNZA BREC), P.O. Box 32379, Lusaka Zambia, Tel. +260 211 290 258, Fax +260 211 293 937 email drgs@unza.

The UNZA BREC has requested that their informed consent template be used for the study. We have therefore included the informed consent documents with their format but have ensured that they include all content requested by JHSPH.

F. **Collaborations with non-JHSPH Institutions:**

For studies that involve collaboration with non-JHSPH institutions, complete the chart below by describing the collaboration and the roles and responsibilities of each partner, including the JHSPH investigator. This information helps us determine what IRB oversight is required for each party. Complete the chart for all multi-collaborator studies.

Insert Name of Institutions in Partner column(s); add additional columns if necessary.

	JHSPH	Partner 1 CIDRZ	Partner 2
Primary Grant Recipient	x		
Collaborator		x	

For the following, indicate "P" for "Primary", "S" for "Secondary" (as appropriate to role and level of responsibility.) Add additional items if useful.

1.	Human subjects research ethics training for data collectors	P	S	
2.	Day to day management and supervision of data collection	P	S	
3.	Reporting unanticipated problems to the JHSPH IRB/Sponsor	P	S	
4.	Hiring/supervising people obtaining informed consent and/or collecting data		SP	

5.	Execution of plan for data security/protection of participant data confidentiality, as described in the Data Security and Confidentiality Protections section above	P	S	
6.	Biospecimen processing, storage, management, access, and/or making decisions about future use	P	S	

COMPLETE THE FOLLOWING SECTIONS WHEN RELEVANT TO YOUR STUDY:

XI. Secondary Data Analysis of Existing Data:

A. **Study Design:**

1. Describe your study design and methods. The study design must relate to your stated aims/objectives.

2. Provide an estimated sample size and an explanation for that number.

- Provide a brief data analysis plan and a description of variables to be derived.

B. **Participants:**

1. Describe the subjects who provided the original data and the population from which they were drawn.

2. If you are receiving, accessing, or using data from a U.S. health care provider, the need for HIPAA review is likely. If you plan to bring identifiable health information from a foreign country to a U.S. covered entity (e.g., lab at the Hopkins SOM), HIPAA may be triggered. If either of these conditions is met, check "yes" to the HIPAA question in the PHIRST application.

1. If you plan to analyze human specimens or genetic/genomic data, provide details about the source of those specimens and whether they were collected using an informed consent document. If yes, explain whether your proposed use is "consistent with" the scope of the original consent, if it potentially introduces new analyses beyond the scope of the original consent, and/or if it introduces new sensitive topics (HIV/STDs, mental health, addiction) or cultural/community issues that may be controversial.

XII. Oversight Plan for Student-Initiated Studies:

- For student-initiated studies, explain how the PI will monitor the student's adherence to the IRB-approved research plan, such as communication frequency and form, training, reporting requirements, and anticipated time frame for the research. Describe who will have direct oversight of the student for international studies if the PI will not personally be located at the study site, and their qualifications.

- What is the data custody plan for student-initiated research? *(Note: Students may not take identifiable information with them when they leave the institution.)*

XIII. Creation of a Biospecimen Repository:

Explain the source of the biospecimens, if not described above, what kinds of specimens will be retained over time. Clarify whether the specimens will be obtained specifically for repository purposes, or will be obtained as part of the core study and then retained in a repository.

a. Describe where the biospecimens will be stored and who will be responsible for them.

b. Describe how long the biospecimens will be stored, and what will happen at the end of that period.

c. Explain whether the biospecimens will be shared with other investigators, inside and outside of JHU, how the decision to share will be made, and by whom. Include your plans, if any, for commercial use. Also explain how downstream use of the specimen will be managed, and what will happen to left-over specimens.

d. Describe whether future research using the biospecimens will include specimen derivation and processing (cell lines, DNA/RNA, etc.), genomic analyses, or any other work which could increase risk to participants. Explain what additional protections will be provided to participants.

e. If future research could yield unanticipated incidental findings (e.g., an unexpected finding with potential health importance that is not one of the aims of the study) for a participant, do you intend to disclose those findings to the study participant? Please explain your position.

f. Explain whether the specimens will be identifiable, and if so, how they will be coded, who will have access to the code, and whether the biospecimens will be shared in linked (identifiable) form.

g. Explain whether the repository will have Certificate of Confidentiality protections.

h. Explain whether a participant will be able to withdraw consent to use a biospecimen, and how the repository will handle a consent withdrawal request.

i. Describe data and/or specimen use agreements that will be required of users. Provide a copy of any usage agreement that you plan to execute with investigators who obtain biospecimens from you.

XIV. Data Coordinating Center:

Complete if JHSPH serves as the Data Coordinating Center.

4. How will the study procedures be developed?

5. How will the study documents that require IRB approval at each local site be developed? Will there be some sort of steering or equivalent committee that will provide central review and approval of study documents, or will template consent forms, recruitment materials, data collection forms, etc. be developed by and provided to the local sites by the coordinating center without external review?

6. Will each local clinical site have its own IRB with an FWA? State whether the coordinating center will collect IRB approvals and renewals from the clinical centers; if not, explain why.

7. How will the coordinating center provide each local site with the most recent version of the protocol and other study documents? What will be the process for requesting that these updates be approved by local clinical center IRBs?

8. What is the plan for collecting data, managing the data, and protecting the data at the coordinating center?

9. What is the process for reporting and evaluating protocol events and deviations from the local sites? Who has overall responsibility for overseeing subject safety: the investigators at the recruitment site, the Coordinating Center, the Steering Committee, or a Data and Safety Monitoring Board (DSMB)? Is there a DSMB that will evaluate these reports and provide summaries of safety information to all the reviewing IRBs, including the coordinating center IRB? Please note that if there is a DSMB for the overall study, then the coordinating center PI does not have to report to the coordinating center IRB each individual adverse event/problem event that is submitted by the local site PIs.

10. Some FDA regulated studies have different AE reporting criteria than that required by the IRB (IRB Policy No. 103.06). How will you reconcile the different requirements, and who is responsible for this reconciliation?

11. Who is responsible for compliance with the study protocol and procedures and how will the compliance of the local sites be monitored and reviewed? How will issues with compliance be remedied?

XV. Drug Products, Vitamins, Food and Dietary Supplements:

Complete this section if your study involves a drug, botanical, food, dietary supplement or other product that will be applied, inhaled, ingested or otherwise absorbed by the study participants. If you will be administering drugs, please upload the product information.

1. List the name(s) of the study product(s), and the manufacturer/source of each product.

Name of Study Product	Manufacturer/Source

2. List each study product by name and indicate its approved/not approved status.

Approved by the FDA and Commercially Available	Approved by Another Gov't Entity (provide name)	Cleared for Use at Local Study Site

C. If your study product has an Investigational New Drug (IND) application through the U.S. Food and Drug Administration, provide the IND number, the Investigators Brochure and complete and upload into PHIRST the Drug Data Sheet available on the JHSPH IRB website www.jhsph.edu/irb.

1. If your study product is a marketed drug, provide the package inserts or other product information. If the study product WILL NOT be used for its approved indication, dose, population, and route of administration, provide a detailed rationale justifying the off label use of the study product.

2. If the study product does not require FDA approval (e.g., dietary supplements, botanicals, products not subject to the U.S. FDA, etc.), provide safety information (as applicable) and a certificate of analysis.

- Explain who will be responsible for drug management and supply, labeling, dispensing, documentation and recordkeeping.

- What drug monitoring and/or regulatory oversight will be provided as part of the study?

XVI. Medical Devices:

Complete this section if your study will involve an approved or investigational medical device (diagnostic, non-significant risk, significant risk).

1. List the name(s) of the study product(s), the manufacturer/source of each product, and whether or not it is powered (electric, battery). Provide product information. If it is electric, upload documentation of clinical engineering approval or its equivalent from a local authority.

Name of Study Product	Manufacturer/Source	Powered?

2. List each study product by name and indicate its status as approved by a government authority or not approved.

Approved by the FDA and Commercially Available	Approved by Another Gov't Entity (provide name and approval information)	Not Approved

3. If your investigational device is Exempt from the FDA IDE regulations, explain which section of the code applies to your device and why it meets the criteria provided. If it is a diagnostic device, provide pre-clinical information about the sensitivity and specificity of the test and the anticipated failure rate. If you plan to provide the results to participants or their physicians, justify doing so, and explain how those results will validate (or not) against the current "gold standard".

4. If you believe the investigational device is not IDE exempt under 21CFR 812.2(c), but is a "Non-Significant Risk" device considered to have an approved IDE application, provide information from the manufacturer supporting that position.

A. If you are using an investigational device that is a Significant Risk Device, provide the IDE number given by the FDA, or if not under FDA jurisdiction, explain why it is appropriate to use this device in this study. Provide a description of the device, and upload a picture or manufacturing schematics into PHIRST. Provide any other information relevant to a determination of its safety to be used for the purposes outlined in this research plan.