DATA SAFETY AND MONITORING PLAN

The purpose of the Data Safety and Monitoring Plan is to maximize the safety and privacy of all study participants and to ensure the integrity, validity, and confidentiality of the data collection and analysis procedures.

I. Study Overview

A. Brief Description of the Purpose of the Study

Aim 1 of this study is a hybrid type 1 effectiveness-implementation trial to test the effectiveness and implementation of a brief skills-based prevention program. This program is aimed at reducing symptoms of depression and anxiety and reducing substance use among pregnant mothers and primary caregivers of children ages 0-2. We aim to recruit *N* = XXXX participants through three diverse tribal communities on [Reservation]. Data collection involves self-administered assessments done by participants at three time points and visit check-in forms at each intervention visit. The intervention involves a series of one-on-one sessions between a home visitor and a participant, typically lasting about 60 minutes, for generally 5-6 sessions. The exact dosage of the intervention is dependent on the participant and guided through a supervision process. The participants in the control group will receive 5-6 evidence-based nutrition focused lessons delivered in the same format as the intervention group.

Aim 2 of this study will estimate the costs, cost-effectiveness, and budget impacts of the intervention. Data will be collected using surveys administered to each study participant described above at each time point. Additional data will be collected through combination of budgetary analysis, time-and-motion study, detailed project record reviews, and feedback from project staff. Aim 3 of the study will identify implementation strategies to promote the scale-up of [Intervention Curriculum]. Data will be collected through in-depth interviews with ~ 10 intervention participants, ~6 home visitors, and ~14 implementation partners in addition to two workshops for home visitors and implementation partners.

B. Overview of the Potential Risks

The proposed trial carries minimal risk for participants. The study will monitor participant safety under the guidance of the Johns Hopkins University IRB, [Tribe] Human Research Review Board (HRRB) and a Data Safety and Monitoring Board (DSMB). In previous work with the sites, they have indicated that the JHU IRB would be sufficient for their local approvals (see letters of support). The research team will work closely with these entities to monitor participant safety, evaluate the progress of the study, and review procedures for maintaining the confidentiality of data, the quality of data collection, management, and analyses.

II. Appointment of a Data Safety and Monitoring Board (DSMB) and Principal Investigators

The Data and Safety Monitoring Board (DSMB) will be comprised of a group of independent experts and will include at a minimum, one mental health expert, one tribal nations expert, and one biostatistician. The DSMB will meet at least twice yearly via phone conference calls for the duration of the study and assist the study in monitoring adverse events. The DSMB will elect a Chair to moderate the meetings. At the initial meeting the DSMB will review and approve all study protocols before study initiation to ensure participant safety. Protocols will include 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. At subsequent meetings the DSMB will be provided with summary study progress reports and adverse events. The DSMB will provide a summary report following each meeting. The DSMB will conduct interim analyses of data prior to end of study to closely monitor effectiveness, and any possibility of harms associated with the programs.

The Principal Investigators (MPIs) will be primarily responsible for oversight of all the proposed research activities, including the development of the protocol, training all study team members on the protocol and the ethical conduct of research, and overseeing all IRB matters. MPIs will work with the Co-Investigators to implement the study, including data collection, data analysis, and dissemination of results. The PIs will be responsible for reporting all adverse events (AEs) to the IRBs and NIH according to their guidelines.

III. Adverse Events

A. Surveillance and Reporting Procedures

Active surveillance for severe adverse events (SAEs) and other adverse events (AEs) will occur using standardized forms timed with data collection throughout the intervention and follow-up. In addition to these fixed time points, participants may report events in other settings, such as at reminder phone calls and intervention contacts with research staff. Any reported events will be referred to study staff who will gather relevant information and complete the standardized adverse event questionnaire. The study MPIs will review the completed form, classify the event according to several dimensions (type, severity, and attribution) and take appropriate action. Safety-related events will be reported in the time interval as proposed and required by the DSMB, Johns Hopkins IRB, [Tribe] HHRB, and NIH. The MPIs and will be responsible for ensuring participants' safety on a daily basis and for reporting SAEs and unanticipated problems to the appropriates channels, i.e., IRB, DSMB and NIH.

B. Definitions

An adverse event (AE) is any untoward medical occurrence in a subject during participation in the clinical study. An adverse finding can include a sign, symptom, abnormal assessment (e.g., vital signs), or any combination of these. A serious adverse event (SAE) is any adverse event that results in one or more of the following outcomes:

- Death;
- Life-threatening event (immediate risk of death);
- Inpatient hospitalization or prolongation of existing hospitalization;
- Persistent or significant disability or incapacity;
- A congenital anomaly or birth defect;
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home.

C. Classification of AE Severity

AEs will be labeled according to severity, which is based on their impact on the patient. An AE will be termed "mild" if it does not have a major impact on the patient, "moderate" if it causes the patient some minor inconvenience, and "severe" if it causes a substantial disruption to the patient's well-being.

D. AE Attribution Scale

AEs will be categorized according to the likelihood that they are related to the study intervention. Specifically, they will be labeled: definitely unrelated, unlikely, possibly related, probably related, or definitely related to the study intervention.

E. Anticipated Risks

This study does not involve any major risks to study individuals screened for this study or participants. All participants will be informed about all known potential risks during the informed consent process. The main potential risks are: i) discomfort during completion of study procedures; ii) breach of confidentiality; iii) the need to report to tribal/state authorities for dangerousness to self or others, or if there is suspected child abuse; iv) other risks not known at this time that may occur during study participation.

Risk Management: The following procedures will be followed to minimize/protect participants against these risks:

i) Discomfort during completion of study procedures: To prevent discomfort or embarrassment during any data collection activities, project staff will undergo intensive training in the administration of all study procedures. Participants are informed prior to the procedures that they may choose to skip any questions they do not want to answer or that make them uncomfortable. If any individual becomes distressed during the study procedures, a break will be provided or the procedures will be stopped, and the project staff will work with the participant to reduce the participant's distress. If the participant's distress is not able to be addressed by these approaches, the staff person will ask if the participant wishes to address the distress in another manner and will facilitate the participant's request when possible.

ii) *Breach of confidentiality:* Participant confidentiality could be breached through inadequate safeguards of the collected data and a direct breach of confidentiality by program personnel. The consent form will describe in detail the methods used to protect participants' confidentiality and those individuals and entities (i.e., Johns Hopkins IRB, NIH) that have access to the data.

- *Data Safeguards*: All participants will be assigned a confidential participant identification number, which will be used on all files and data collection tools. The master list of participants' names and ID numbers will be kept in locked files with restricted access. Only those directly involved in data management will have access to the database, under the close supervision of the PI. All data will be secured on HIPAA compliant servers and all analysis done through HIPAA compliant interfaces such as SAFEDesktop. The information gathered will be used only for scientific, educational or instructional purposes. No information about the identities of participants will be published or presented at conferences. The computers are password protected and maintained in locked buildings that are only accessible to Johns Hopkins personnel.

- *Direct Breach of Confidentiality*: All project staff will be trained and certified in the ethical conduct of human subjects research, including confidentiality safeguards, before beginning work on the study. This involves an on-line training and testing program that focuses on the principles from the Belmont Report. During the study, ongoing review of the needs for participant confidentiality and specific training will occur at regular intervals both formally (i.e., on site trainings by the PIs) and informally (i.e., weekly conference calls). All staff are aware that a breach of confidentiality is cause for termination of employment and subject to both criminal and civil penalties.

iii) *Procedures for Implementing Mandatory Reporting:* Participants are informed in the consent form that study staff must report to the authorities: i) if the participant is an imminent danger to herself or others; and ii) if there is confirmed or suspected child abuse observed in the household. Staff will do whatever is necessary to ensure the safety of the participant, and in acute situations will act immediately to involve appropriate authorities (i.e., call the police), as well as the Staff Supervisor and the PIs in managing the acute crisis. If study staff learn of child abuse, they will follow state/Tribal policies. All study staff will be trained in these policies prior to study initiation.

iv) *Possible Risks of Study Participation Not Known at the Current Time:* It is possible that there are risks to study participants from participation that are not known at this time. The protocol has strategies to provide referrals for all participants who may encounter problems. In the event that participants experience any adverse or untoward effects, regardless of their relationship to the program, every step will be taken to provide the appropriate assistance to the participant.

IV. Safety Review Plan and Monitoring

A. Sample Size Justification

Our study will be powered on differences in the level of depressive symptoms as measured by the CESDR-10 across the three-time points. To calculate our study sample size, we based our effect size estimate on previous [Intervention Other] and [Intervention Curriculum] studies. While [Intervention Other] effect sizes have generally been large, we limit our consideration of effect size estimates to those that parallel the most recent iterations of shorter versions of [Intervention Other] and that have been delivered to sub-clinical populations. In a recent study, a 5-session version of [Intervention Other] showed a medium effect of d = 0.55 on depression symptoms compared to a wait-list control. In a similar trial as to the proposed [Intervention] effectiveness study, adults living with HIV who had severe unhealthy alcohol use that compared CETA plus a brief substance use intervention to the brief intervention alone, the effect size for depression symptoms was d = 0.50. In a recently completed study (unpublished) comparing a prevention-focused version of CETA to basic psychological first aid, the effect size was small but significant (d = 0.20). Given this information, and that we have an active, but unrelated control condition, we use an estimated effect size of d = 0.4 as indicating realistic and meaningful change. [19] compared to a wait-list control. In a similar trial as to the proposed [Intervention Curriculum] effectiveness study, adults living with HIV who had severe unhealthy alcohol use that compared [Intervention Other] plus a brief substance use intervention to the brief intervention alone, the effect size for depression symptoms was d = 0.50. In a recently completed study (unpublished) comparing a prevention-focused version of [Other Intervention] to basic

psychological first aid, the effect size was small but significant (d = 0.20). Given this information, and that we have an active, but unrelated control condition, we use an estimated effect size of d = 0.4 as indicating realistic and meaningful change.

To calculate power we use the approach recommended by Hox[90] and Hedges.[91] Specifically, there are three steps: **(1)** Estimate power for a single-level regression model as the *targeted* sample size. In this case, setting our type I error rate to 0.05 and power at 80%, we would need to enroll n = XXXX participants to detect an effect size of 0.46 between experimental conditions on depressive symptoms in the past two weeks at the 6-month follow-up time point. This n = XXXX is our *targeted* sample size. The next step is to **(2)** compute the *actual* sample size for the proposed study. With n = XXXX participants and 3 measurement time points, there are 375 (non-independent) observations. Finally, in step (3) we penalize the actual sample size for the nesting effect using the design effect formula (i.e., $n_{eff} = n / [1+\{n_{clus} - 1\}\rho]$). This provides the *effective* sample size. If the resulting *effective* sample size is greater than or equivalent to the *targeted* sample size, there is sufficient power for the effect of interest. Assuming a conservative nesting effect of ρ=0.25, our 375 non-independent observations provide the statistical power of 300 independent observations. This is more than the *targeted* sample size (i.e. more than n = XXXX). To account for attrition, we adjusted our targeted sample size by a conservative 20% based on data from previous [Intervention Curriculum] trials (e.g., loss to follow up: [Intervention Curriculum] trial - 17%[13], [Control] trial - < 10%[56]). **The final estimated sample size needed for Aim 1 is N = XXXX**. This sample size would enable detection of a small-medium effect (***d* = 0.32**) or larger for our continuous outcome measures (i.e., symptoms of depression and anxiety, and substance misuse). Showing a small to medium effect or larger compared to an active control condition that mirrors the mechanisms of home visiting (i.e., social support provided through repeated visits), will enhance our understanding of the added benefit of [Intervention Curriculum] compared to what might be expected from home visiting alone.

B. Safety and Study Progress Reviews Reporting to the DSMB
The MPIs will assume the responsibility of monitoring participants' safety, including reporting any breaches of confidentiality and serious and unexpected AEs. All reportable events will be reported to the IRBs and NIH according to their guidelines.

1. Adverse Events forms for surveillance
For our other trials, we have designed and tested adverse events forms to meet the goals of this study. The MPIs review safety reports, which will be sent to the DSMB. The project coordinator will be responsible for assembling the data and producing these reports, as well as assuring that all parties obtain copies of these reports. In addition to real- time surveillance of the study, the MPI's will be informed of SAEs as soon as they occur by the study staff (within 24 hours) and will notify the DSMB within 48 hours of becoming aware of the event (see Table below). The MPIs will report the SAEs and Unanticipated Problems to the IRB within 10 business days of becoming aware of the event and also notify NIH within 2 weeks of IRB notification. In addition, all other adverse events will be summarized in the annual progress report to NIH. Specific triggers for an ad hoc review or initiation of the process of an ad hoc review will occur if an unanticipated problem involving risk to the subject or others and if a death, regardless of the cause, occurs.

2. Content of Data Safety and Monitoring Report
The study MPIs will prepare reports for the DSMB every 6 months that will include the following elements:

- Enrollment and participation status updates.
- Data tables that summarize demographic and baseline clinical characteristics.
- Data quality tables that capture missing study visits and missing case report forms.
- Safety assessments of aggregate tables of adverse events and serious adverse events.
- Listings of any adverse events, including serious adverse events, unanticipated problems and protocol deviations/violations.

3. Stopping Rules
We have pre-planned two interim analyses for early stopping of the trial. The first would be done after 50% of participants completed the post-intervention assessment. This would primarily be done to ensure the intervention does not result in unintended harms. At this analysis, we would examine average changes in depression symptoms (primary outcome as measured by the CESDR-10). If there is any indication that the group assigned to the active control was significantly ($p<0.05$) better off than the treatment conditions, we would stop the trial.

The second interim analysis would be completed when all participants completed the post measurement assessment. If participants who received the intervention showed a statistically significant ($p<0.05$) and moderately clinically meaningful ($D>0.5$) reduction in depression symptoms compared to the control condition, the intervention be offered to all participants. Participants who received [Intervention Curriculum] would continue to be followed, but we would not conduct any comparisons of treatment vs. control at the final time point on outcomes. If these thresholds are not met, the trial will continue as planned with a 6-month follow-up assessment conducted amongst all participants.
As outlined, we will monitor adverse event rates in all participants. The DSMB, together with the study MPIs, will alert the IRB and the NIH if a larger than reasonably expected event rate should occur in the intervention group. Other issues relating to stopping rules for this trial include:

New Information: It is exceedingly unlikely that any new information will become available during this trial that would necessitate stopping the trial.

Limits of Assumptions. It is possible that baseline differences between the groups, excessive study dropouts and/or missing data by the interim measurement time point will limit the value of data analysis of measurements. With a dropout rate of 20% we expect to retain an effective sample size of **150** participants for our primary outcome (by randomizing N=188 participants) with **75** participants in each arm.

Limits of Rules. We acknowledge that there are other situations that could occur that might warrant stopping the trial and have a section on the safety report entitled 'Other situations that have occurred since the last safety report that warrant discussion' to allow for communication of concerns to the MPI's, and the DSMB.

V. Informed Consent
Given ongoing COVID-19 precautions in some of our participating sites, we will have 2 options for informed consent, which we have been utilizing in our other protocols: 1) "Phone-facilitated electronic (online) informed consent" process involves a phone conversation with trained study staff member to go over the consent form, accompanied by a REDCap version of the bulleted version of the consent form with a short series of questions to assess comprehension of the study's risks and benefits (called the "consent quiz") followed by a signature page; 2) In-person written informed consent will also be an option. Study personnel including any home visiting staff employed outside of JHU, and regardless of their exact role in the study, will be certified in the ethical conduct of human research and receive specific training on completing informed consent.

In consenting individuals to participate in the study, the following procedures will be used whether the consent is in-person or phone/electronic: 1) All procedures involved in the study will be fully explained to participants; 2) Participants will be afforded time to read, review the consent form, and ask questions of study staff; 3) Participants will complete a brief "quiz" of their comprehension of the study in the form of several short, clear questions, demonstrating that they understand the risks and benefits of study participation and clearly consent, before consent is accepted. Any wrong answers are corrected and additional information given to clarify, until a person can easily answer all items successfully or they indicate they do not wish to continue; 4) Those agreeing to participate will sign the consent form. The signature confirms that the consent is based on information that has been understood. Each subject's signed informed consent form will be kept on file by the investigators for possible inspection by regulatory authorities, and each participant will receive a mailed copy.

VI. Data quality and management
For data collection and storage, we will use the Johns Hopkins maintained REDCap (Research Electronic Data Capture) platform. REDCap is a secure, web-based application designed to comply with HIPAA regulations. It supports data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Data are collected on password protected and encrypted laptops/tablets and labeled with a unique identification number. The electronic data is accessible only by logging into the REDCap system using a unique username and password, with two-step verification. For in-depth interviews and workshops, participants will be instructed not to use names during data collection. If any transcripts contain names, the names will be redacted.

All data will be stored and analyzed using SAFEdesktop or OneDrive servers which provide a HIPAA compliant workspace and storage system. Computers used for analyzing data are encrypted and password protected. Access to these data is strictly controlled. Such data will not be used by those not connected with the project during its course, or in the future, unless identifiers are first removed.

VII. Confidentiality

Policies are in place to protect the confidentiality of all study participants. Participants will be informed that their confidentiality will be maintained throughout the study. The identity of participants will not be revealed in the presentation or publication of any results from the project. De-identified data will be used for coding and analysis. All personnel have completed training and testing in the ethical conduct of research. Ongoing supervision will assure continued strict adherence to research ethics including respecting participants' rights to confidentiality. Other protections to confidentiality include:

- During this study, all materials collected are for research purposes only, and data will be kept in strict
- confidence.
- No information will be given to anyone without permission from the subject.
- The consent form includes the informed consent statement required by Johns Hopkins University IRB.
- Confidentiality will be ensured by use of identification codes.
- AE reports and annual summaries will not include subject (PHI/PII)- or group-identifiable material. Each report will only include the participant’s study identification code.

VIII. Participant Discontinuation: Events that would preclude a participant from continuing with the trial include death, serious injury, or adverse reactions due to any cause. Moving away from the community, including being incarcerated, could also cause a participant to withdraw from the study. The participant may always choose to discontinue participation without consequence.