PROTECTION OF HUMAN SUBJECTS

1. Risks to Human Subjects

The proposed study will fall under the purview of the Johns Hopkins University and [Tribe] ethical review committees. In previous work with the sites, they have indicated that the JHU IRB would be sufficient for their local approvals (see letters of support). Every effort will be made to assure that the principles of ethical research—beneficence, justice, and respect for persons—are maintained. All study staff have obtained (or will obtain prior to the study in the case of new hires) their institution's required certification to conduct ethical research. In addition to the numerous safeguards that are in place to protect enrolled participants, we will obtain a Certificate of Confidentiality. With this Certificate, researchers cannot be forced to disclose, even by court subpoena, information that may identify our participants in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings.

All study personnel will participate in education in the protection of human research participants. They will be certified through their completion of the Collaborative Institutional Training Initiative (CITI) for Basic Human Subjects Research and Conflict of Interest Training. In addition, study team members will complete training in the Health Insurance Portability and Accountability Act (HIPAA). These are web-based training courses offered by JHU and required for IRB approval.

1.1. Human Subjects Involvement, Characteristics and Design

This application proposes data collection from human subjects for: 1) A hybrid 1 effectiveness-implementation randomized controlled trial of [Intervention Curriculum] in pregnant and postpartum women receiving care at one of the participating study sites; and 2) in-depth interviews with program recipients, home visitors and [Intervention Curriculum] implementing partners. The semi-structured interviews and focus groups do not solicit personal information and focus only on the implementation considerations of [Intervention Curriculum]. As such these activities are considered exempt from IRB oversight per 45 CFR Part 46.

Human subjects characteristics and eligibility criteria

Participants will meet all of the following eligibility criteria: 1) pregnant or be a primary caregiver of a child that is 2 years old or younger; 2) 14 years or older (at time of conception if pregnant); 3) report a family history of substance misuse, and 4) have elevated symptoms of depression or anxiety or risk of substance use disorder; and 5) be part of the service population of one of the participating sites. Key eligibility criteria are listed below:

Inclusion Criteria:

- Pregnant or had a child within the past 24 months
- 14 years or older
- Report a family history of substance misuse
- Have elevated symptoms of depression or anxiety or risk of substance disorder
- Be part of the service population of one of the participating sites

Exclusion Criteria:

- Profound disability that limits the ability to participate in assessments or interventions
- Unlikely to be residing in or near the research site for the next 6 months

1.2. Study Procedures, Material and Potential Risks

1.2.a. Study Procedures

Participants will be recruited through several sources including in partnership with local obstetrics and gynecology clinics, behavioral health services, and social services (see letters of support). The two sites that have existing [Intervention Curriculum] home visiting programs will also recruit through their established participant outreach and recruitment channels. Referrals will come directly from partner organizations, and we will develop recruitment flyers that can be posted/handed out in these clinics, as well as in the community and through social media. We will also pursue direct Electronic Medical Record access as stipulated in the Memorandum of Understanding between Johns Hopkins Center for American Indian Health and Indian Health Services. These strategies have been proven successful through previous studies.

Study staff will recruit participants either over the phone or in person. Consent will be completed either through a telephone assisted verbal process or in person through written consent. Copies of consent forms will be e-mailed or postal mailed to participants if needed.

Following consent, participants will complete an initial screening process and if eligible will proceed to the baseline data collection. Assessments will be completed through REDcap. After baseline is completed, the person will be randomized in REDcap using stratified random sampling to either the [Intervention Curriculum] group or the beneficial control group. Additional assessment batteries will be administered immediately post intervention completion and 6 months after their baseline assessment. Participants will receive a $25 gift card incentive at each time points, resulting in a total of $75 for participants who remain active in the study.

1.2.b. Sources of Study Materials

All data will be collected through HIPAA-compliant REDCap surveys. Data collection will consist of online or tablet-based surveys at 3 timepoints during the study: baseline/enrollment, post-intervention and 6 months follow-up. Additionally, participants will complete a participant check-in form at the start of each intervention session (intervention group only) that allows the home visitor to assess mental health needs and to monitor their client's progress. This assessment also includes safety screening in order to identify participants in need of referral to a higher level of care, beyond the scope of [Intervention Curriculum], such as active suicide ideation or domestic violence.

Data collection methods are detailed below and in the Research Strategy section. All assessment measures, their scoring and timepoints when administered are included in Table 1.

Table 1. Participant assessment measures & timepoints

Domain	Measure	Score indicating sub-clinical distress	Timepoints			
			Base	Post	6 mons	Every visit
Demographics	Previous JHCIH studies		X			
Depression	CESDR-10	8	X	X	X	
Substance Misuse	ASSIST	11 for alcohol; 4 for other substances	X	X	X	
Anxiety	PROMIS-SF 8a	16	X	X	X	
Coping Strategies	Brief Cope	N/A	X	X	X	
Self-efficacy	New General Self-Efficacy Scale	N/A	X	X	X	
Cultural efficacy	Adapted from the Native Wellness Assessment	N/A	X	X	X	
Connectedness	Awareness of Connectedness Scale (ACS)	N/A	X	X	X	
Help-seeking	Help-seeking Index	N/A	X	X	X	
Therapeutic alliance	Working Alliance Inventory	N/A		X	X	

Screening for PTSD	Adapted PTSD Checklist (PCL)	14 indicates the need for referral	X			
Participant Costs	Internally developed questionnaire	N/A	X	X	X	
Health Related Quality of Life (Aim 2 only)	EuroQol five dimensions questionnaire (EQ-5D-3L)	N/A	X	X	X	
Monitoring of symptoms	[Intervention Curriculum] participant check-in form					X

1.2.c Potential Risks
We anticipate minimal risk associated with this study. The main potential risks are: a) the possibility of discomfort in completing the assessments; b) breach of confidentiality including sensitive data regarding substance use; c) the need to report to tribal/state authorities for dangerousness to self or others or if child abuse is suspected; and d) other risks not known at this time that may occur during study participation. In addition, respondents may reveal suicidal intent during the course of the screening, baseline/follow-up questionnaires or intervention. Although this is not a direct risk of participation in this study it is important to have a plan in place. Our team has worked with each of the participating sites to inform how to respond to disclosure of suicide risk in conjunction with local protocols. We also have several clinical psychologists on the study team, including those providing supervision to the [Intervention Curriculum] providers, who can assist with response using the [Intervention Curriculum] safety protocol across groups as needed.

2. Adequacy of Protection Against Risks

2.1.a. 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.

2.2.b. Data Security.
We have described processes to ensure Data Security in the **Data Safety and Monitoring Plan**.

Overview
Data will be collected directly from study participants and used specifically for research purposes. We will communicate any findings of elevated Mental Health scores to the participant as part of referral processes for outside services. In accordance with HIPAA and IRB policies, access to individually identified data will be limited to study investigators and staff with a legitimate need to know this information, primarily those involved directly with the subjects. All data will be contained into a password protected database by study identification number

only. Although most of our participant information will not be on paper, any paper forms will be kept in locked cabinets.

For data management we will used REDCap, a web-based tool for building and managing data entry and databases. REDCap data is housed on secure servers at the Johns Hopkins Biostatistics Center under firewall protection with offsite access through secure VPN. The database will contain embedded checks for internal consistency and data completeness. Missing and illogical data will be followed up and corrected, and double data entry will be performed for outcome data. Database access is password protected and restricted to authorized personnel only (e.g., data collectors cannot see intervention data), and REDCap provides audit trails for tracking data manipulation and user activity. Data will be exported from REDCap for analysis. All exported 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.

2.2.c. Safety Protocols

The safety approach will be implemented similarly to the investigators' other trials. See the Data Safety and Monitoring Plan for details. We will use standardized materials including a manual of procedures and forms.
The Principal Investigators (MPIs) will be primarily responsible for oversight of all the proposed research activities, including the development of the research 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.

In addition, if suicide risk is disclosed, our team has experience developing site specific response plans that are congruent with local protocols and service systems. These generally include doing a brief risk assessment, conducting a safety plan, and elevating to immediate referrals and/or emergency responses as needed. Suicide risk safety protocols will be developed with each team and submitted to the IRBs for approvals.

2.2.d. Additional specific protection again 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: a) the possibility of discomfort in completing the assessments; b) breach of confidentiality including sensitive data regarding substance use; and c) the need to report to tribal/state authorities for dangerousness to self or others or if child abuse is suspected; and d) 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.

3. Potential Benefits of the Proposed Research to Human Subjects and Others

Participants in the [Intervention Curriculum] will receive an intervention designed to reduce symptoms of Depression, Anxiety, and risk for substance misuse. Based on prior literature and experience of similar programs, we anticipate that this will have beneficial effects on the participants with potentially long-term reductions in morbidity and mortality from these problems. Participants in the control condition will receive an evidence-based nutrition intervention, [Control Curriculum]. Research evidence for [Control Curriculum] has shown it is an effective strategy for promoting healthy infant growth and development in the first year of life.

4. Importance of the Knowledge to be Gained

There is an urgent need to address the high burden of mental health challenges, substance misuse, and premature mortality among AI/AN primary caregivers and families. The proposed research addresses gaps in the understanding of these challenges by testing the effectiveness of a skills-based secondary prevention program that can be integrated into existing evidence-based home visiting programs and designed specifically for and by Indigenous communities to reach AI/AN primary caregivers in mental and behavioral health crisis, with broad capacity for scaling and sustainability.

5. In-Depth Interviews and Focus Group Discussions

5.a. Human subjects involvement and characteristics

In order to identify a menu of strategies that target perceived contextual (including community and cultural) barriers to and facilitators of [Intervention Curriculum] implementation and scale-up, we will conduct in-depth interviews and focus group discussions with approximately XXXX participants in [Intervention Curriculum], 6 [Intervention Curriculum] home visitors, and 14 [Intervention Curriculum] implementing partners. All participants will be consented for participation but given that they will be asked about their perceptions of the program, rather than their personal information, this information will be exempt from IRB oversight.

5.b. Sources of materials

Needs and assets assessment will be guided by the Consolidated Framework for Implementation Research (CFIR). The CFIR helps to identify factors that predict effective implementation and to develop strategies to achieve successful health service delivery. It synthesizes the spectrum of terminologies, definitions, and constructs related to implementation into a practical framework of 39 constructs sorted under 5 domains: intervention characteristics, outer setting, inner setting, characteristics of individuals, and process. Interviews will be conducted over phone or Zoom and audio recorded. Recordings will be transcribed and analyzed.

5.c. Potential risks

Risk of loss of confidentiality is the main risk. We expect this risk to be very low. Plans to minimize these risks are described below.

5.d. Adequacy of protection against risks

1. Recruitment and informed consent. Procedures for recruitment, consent, intervention, data collection and analysis will be reviewed and approved by the Johns Hopkins IRB and [Tribe] Human Subjects Review Board. We will invite individuals to participate in interviews and focus groups by e-mailed letters and personal invitations. We will obtain either oral or written informed consent for these interviews.
2. Protection against risk: All information will be considered confidential. This confidentiality will be assured through several mechanisms. Data collectors will be instructed not to use names of participant during the recordings. Transcripts of interviews and focus groups will have any remaining names removed. Audio files will be destroyed after transcription and data analysis. No participants will be identified by name in any publications. All audio files and transcripts will be secured on HIPAA compliant servers and all analysis done through HIPAA compliant interfaces such as SAFEDesktop or OneDrive.

5.e. Potential benefits of the proposed research to the subjects and others

There are no direct individual benefits. Potential benefits to others include the possibility that the research will lead to the understanding of factors that may be important for implementation and scale-up of [Intervention Curriculum].

5.f. Importance of knowledge to be gained

It is critical to know how to implement and scale-up [Intervention Curriculum].