Technology-Based Intervention for Reducing Sexually Transmitted Infections and Substance Use During Pregnancy

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1.0. Research Strategy: Significance

Statement of the Problem: *Sexually transmitted infection (STIs), alcohol, and drug use are common and critical interrelated factors that are associated with negative consequences for the mother and fetus. There are virtually no empirically supported interventions that are tailored to specifically address these growing public health concerns together during pregnancy. Based upon our encouraging R21 findings, we now propose to test a brief computer-based intervention to fill this critical healthcare gap for a vulnerable, high-risk population.*

1.1. STIs are an urgent public health concern for childbearing women STIs are at a record high in the United States, and STI risk is an increasingly critical and costly health problem for American women, especially for pregnant women who can transmit the infections to their babies. STIs among women are associated with significant morbidity and mortality, including premature death. The American Congress of Obstetricians and Gynecologists (ACOG) and Centers for Disease Control and Prevention (CDC) reported that over the past decade, childbearing women have comprised one of the most rapidly expanding group infected by STIs, including HIV, in the U.S., and this epidemic is "accelerating in young women" Nearly 25% of pregnant women are infected with one of four STIs. Among those who had been treated for an STI in the past 6 months, 30% tested positive for a current STI during their pregnancy. Critical to this trend is the intersection of STIs and alcohol/drug use – both highly prevalent among women.

1.2. STIs and alcohol/drug use during pregnancy lead to significant biomedical risks to woman and fetus A pregnant woman carries a risk of transmitting an STI to her infant during pregnancy, delivery, or breast-feeding, especially if untreated. STIs such as chlamydia and gonorrhea can be transmitted from the mother to her infant during the delivery, what the CDC laments as a "tragic systems failure." Adverse effects of prenatal STIs can include miscarriage, ectopic pregnancy, stillbirth, low birth weight, neurological damage, and neonatal sepsis. Illicit drug use also has major health consequences for the pregnant women that can in turn negatively affect fetal development, rates of STIs, depression, intimate partner violence, as well as significant prenatal and neonatal complications (e.g., neurobehavioral and congenital abnormalities). Recent reviews suggest infants whose mothers used marijuana during pregnancy, compared to those who did not, were more likely to have lower birth rates and require neonatal intensive care. Prenatal alcohol exposure can lead to a wide range of adverse effects, known as Fetal Alcohol Spectrum Disorders (FASD) with an estimated 12,000 infants born with FAS each year, and up to three times as many have alcohol-related problems.

1.3. The intersection of STI and substance use disorders in the lives of pregnant women The Healthy People 2020 objectives include increasing abstinence from alcohol/illicit drug use among pregnant women. Past year prevalence of all illicit drug use was 5.4% for pregnant women. There has been a dramatic national five-fold increase in opiate use during pregnancy, leading to a surge in the incidence of neonatal abstinence syndrome (NAS) of 383% over the past decade. NAS is a postnatal drug withdrawal syndrome and includes central nervous system irritability. Marijuana use during pregnancy is also on the rise, increasing by 62% over the past decade. Nearly 12% of pregnant women reported using marijuana in the past year, in part due to an increased perception of the safety of marijuana use during pregnancy Regarding alcohol use, 19% of women in their first trimester of pregnancy report using alcohol, and 3% report binge drinking (4 or more drinks in a row. Since underreporting during pregnancy can be substantial, the actual proportion of women drinking during pregnancy is even higher. The co-occurrence of alcohol and substance use and sexual risk taking contribute significantly to STI acquisition, particularly in high-risk and vulnerable populations. Regardless of partner status, monogamous pregnant women who use alcohol or substances are more likely to engage in sexual risk behaviors than their non-pregnant counterparts, and they are five times less likely to use condoms than their non-pregnant counterparts. The use of alcohol/drugs increases the probability for sex risk behavior through disinhibition and impairment of judgment, making the case for addressing these behavior risks together.

1.4 Critical need to address these risks together during pregnancy Despite the escalating rates of substance use during pregnancy, and that co-occurrence with sex risk behavior contributes significantly to STI acquisition, **there are currently no brief interventions that target both of these risks simultaneously during pregnancy.** The extant literature includes computer-

based interventions with a single focus either on improving sexual health, or reducing alcohol/drug use, and very few of these have targeted pregnant women exclusively. A recent brief intervention study identified alcohol use as a critical factor in reducing sex risk behaviors, suggesting the importance of implementing this target in STI preventive interventions, however, it excluded pregnant women.[9] A review by the U.S. Preventive Services Task Force concluded that "methodologically rigorous trial evidence" is lacking for pregnant women. Ondersma and colleagues are currently testing a brief computer-delivered intervention targeting marijuana use during pregnancy; however, it does not address sex behavior risk. Existing computer-delivered brief motivational interventions for multi-risks (e.g., alcohol/drug use, dating violence, and/or HIV risk behavior) have primarily targeted students and male and female patients presenting to the emergency department, excluding pregnant women. Recent meta-analysis has indicated the superiority of targeting multiple health behaviors rather than just focusing on one behavior. The advantage of fewer sessions, if efficacious, increases the potential feasibility of implementation in a wide variety of settings – and the overall impact is greater when accessible and disseminable to larger populations.

1.5. Pregnancy and postpartum period: a critical time to intervene Given the highly unique set of concerns for this subset of women, including 1) a dramatic national increase in the number of women misusing opioids during pregnancy, leading to a surge in the incidence of neonatal abstinence syndrome (NAS) of 383% over the past decade), 2) marijuana use is on the rise during pregnancy, increasing by 62% over the past decade (and low awareness of the associated health risks for the developing fetus), 3) low rates of condom use during pregnancy; STIs at record high for childbearing women, 4) tremendous health risks and adverse consequences to woman, fetus, and newborn, 5) lack of access to child care services, and 6) the challenges of social stigma, shame and guilt that can be significant for pregnant women who struggle with their substance use, there is a clear need for an intervention tailored to these unique needs of pregnant women. Because the majority (97%) of pregnant women receive at least some prenatal care, the CDC and ACOG have identified the perinatal period as an urgent time for STI prevention and subsequent behavior change, including substance use, to reduce risk for acquiring infection. Further, postpartum women are vulnerable to
increased risk of STIs associated with high-risk sexual behaviors including inconsistent condom use and prevalence of alcohol use – with national data suggesting prevalence rates as high as 30-49% -- and drug use prevalence in the range of 4-9%. Recently, the NIH issued a strong recommendation for physicians to advise pregnant women to avoid marijuana use, with growing concerns of its use by women to treat nausea during pregnancy. To optimize postpartum care, the ACOG has recommended proactively addressing both risky health behaviors during pregnancy given that as many as 46% of women in the U.S. do not receive postpartum care, and only 21% receive routine STI screening. There is thus a tremendous opportunity and a clear need to advance clinical care in this important area, especially during the antenatal period.

1.6. Use of a computer-based, brief motivational intervention is ideally suited for target population

A computer-delivered brief intervention is a self-directed, low cost intervention that has several notable strengths for working with women in the perinatal period. The use of computer-assisted self-interview in disclosure of STI/HIV risk has been empirically supported in terms of encouraging the disclosure of sexual risk-taking and additional STI testing without increasing the rate of STI diagnosis, and very few studies have assessed computer-based STI prevention interventions exclusively in women. In computer-delivered intervention trials using the software we propose here, perinatal participants and participants in general have found receiving the MI intervention acceptable and highly likeable, suggesting that a high proportion will engage with the intervention and return for follow up assessments. Over the past decade, interactive technology for alcohol and other substance use disorders have been available and supported by clinical trials. In the extant literature, technology-based interventions for substance use demonstrate that while the effect of these interventions are again mild-moderate in size, there are positive aggregate effects in meta-analyses that can have meaningful public health impact given their overall low cost and potential reach. Further the reach and impact is magnified, as there is potential to aid both the participant and the fetus.

1.7. Role of economic data to inform clinical and policy decisions on resource allocation

Economic data plays a key role in understanding the relative value of costs and benefits associated with a new health intervention and is critical for future dissemination and implementation. Many preventive interventions do not save money, but require a net investment in health resources to yield additional benefits. Implementation decisions will typically consider disease burden, intervention safety and efficacy, resource use, cost-effectiveness, as well as related factors such as feasibility. The pace of health spending has continued to increase as health reform efforts are aimed at slowing the growth in health expenditures. It is critical that data be available to evaluate the costs and benefits of any new interventions such as the proposed HCEM, Health Check-up for Expectant Moms, an innovative computer-delivered screening and brief intervention (SBI) program tailored for high-risk, non-treatment seeking pregnant women. Economic evaluations can provide information to clinical and policy decision makers on prioritization. Evaluation of resource utilization and costs can also inform feasibility and scale-up considerations for the implementation of HCEM.

Summary of scientific premise: In summary, there are several converging lines of data that support the scientific premise of this proposal. STIs as well as alcohol and drug use are common and critical interrelated factors that are associated with negative consequences for the mother, fetus, and infant. Despite the clear risks of STIs among pregnant adult women, very few STI-focused interventions have specifically targeted this group of women and there are currently no brief interventions that target both of these risks simultaneously to address the unique needs of pregnant women, including health risks to their unborn children. The proposed project will test an innovative, high-reach, easily implementable, low-cost computer-delivered intervention, *HCEM*, which is theoretically driven and will address known barriers in early intervention with at-risk women throughout pregnancy and will extend to the postpartum period. A fully powered trial of the HCEM optimized to extend impact to the postpartum period is necessary to determine efficacy. Given that these risks peak during childbearing years and extend into postpartum period, if this promising intervention of high public health significance is found efficacious, it can be readily integrated into prenatal health care settings and thus reduce the risk for adverse outcomes for very large numbers of vulnerable women and infants.

Importance of the Knowledge to be Gained

STI risk and alcohol/drug use are highly prevalent problems in the lives of pregnant women, in particular. Both are associated with physical, psychological and emotional impairment for the woman, serious negative consequences for the developing fetus, and have been shown to increase the cost of health care during pregnancy. Despite the serious morbidity associated with these health concerns, few women are being screened for both STIs and alcohol/drug use during pregnancy: only one third of women are assessed for alcohol use during prenatal care visits. Further, there are few interventions that address either of these critical issues during pregnancy, and virtually none that target both STI risk and alcohol/drug use during pregnancy simultaneously. The information gained through this research will help us to develop and empirically evaluate the efficacy of an intervention for this population. If our intervention proves to be efficacious, this would enable professionals in primary and prenatal care or other settings to have a meaningful impact on STI risk and alcohol/drug use within their setting. Further, there is promising evidence that the application of brief interventions to women in the prenatal period offers substantial benefits to both the woman and her unborn child. The paucity of research targeting both of these health risks together during pregnancy, and the potential success of implementing a computer-based brief intervention in this population invites the proposed research investigation.

2.0. Innovation The theoretical, methodological and clinical innovation of HCEM improves upon current literature in significant ways, specifically: 1) HCEM is innovative because we are targeting the unique needs of pregnant women early in pregnancy who endorse **both** risk for unsafe sex and alcohol/drug use – common, problematic, dual concern for pregnant women that has not typically been addressed concurrently; 2) HCEM is brief and it includes booster sessions that are specifically designed for a high-risk study population who are likely to benefit from additional contact as the literature suggests increases in efficacy and promotion of gains with behavioral interventions when boosters are provided, 3) HCEM targets STI risk reduction for the postpartum period as well as during pregnancy, extending and sustaining the impact of intervention; and, 4) we include assessment of key birth outcomes that are affected by STIs and alcohol/drug use.

3.0. Specific Aims

Sexually transmitted infections (STIs) are at a record high in the United States, and STI risk is an increasingly critical and costly public health concern for American childbearing women. STIs and alcohol/drug use are interrelated and common morbidities that have significant direct and indirect relationships with health and functioning over the longer term for mother and fetus. Undetected and untreated STIs can lead to serious long-term consequences for childbearing women including infertility; for pregnant women, STIs can lead to a number of serious health risks including premature birth, low birth weight, increased need for neonatal care, and fetal death. Similarly, there has been a dramatic national increase in substance use during pregnancy, particularly opiate and marijuana use, leading to complications during pregnancy and poorer birth outcomes. Nearly one quarter of pregnant women are infected with an STI, and over 15% report some form of risky alcohol or drug use. Women who abuse substances are disproportionately more likely to engage in risky sexual behaviors that can result in STIs. Because of this intersection between substance use and STIs and because both are clearly associated with poor health outcomes, the ACOG and CDC strongly recommend targeting both risks during pregnancy.

Many challenges prevent the implementation of behavioral treatment programs in prenatal settings, and many women fail to engage in treatment even when it is readily available. These same women, however, may be willing to engage with brief, technology-delivered interventions that are tailored to their unique needs, and these approaches may be more applicable to be disseminated within overwhelmed prenatal care practices. Our team has successfully tested an innovative computer-delivered screening and brief intervention (SBI) program tailored for high-risk, non-treatment seeking pregnant women. Our preliminary results (n = 50) indicate that the Health Check-up for Expectant Moms (HCEM) is acceptable and feasible, and is associated with significant reduction in the key outcomes of alcohol or drug use (OR = 0.15, $p = 0.015$), with a trend toward significance in the reduction of unprotected sex (OR = 0.17, $p = 0.12$) during pregnancy.

The objective of this proposed study is to build upon these promising R21 findings by testing whether HCEM, a computer-delivered SBI that simultaneously targets STI risk and alcohol/drug use during pregnancy, reduces antenatal and postpartum risk more than an attention, time, and information matched control condition among pregnant women seeking prenatal care. To meet this objective, we propose a two-group, randomized controlled trial in which a racially diverse sample of 250 pregnant women at risk for STIs and alcohol/drug use are recruited from high-volume prenatal care clinics or through telephone and online methods, and are assigned to either (a) a computer-delivered, single-session brief intervention plus two booster sessions; HCEM); or (b) a computer-delivered control condition. Computer and/or phone-delivered follow-up assessments will occur at 2 and 6 months, and extending to 6-weeks postpartum. Our biometric objective measures include STI incidence (e.g., chlamydia, gonorrhea) and birth outcomes. We propose the following Specific Aims:

Aim 1 (Primary outcomes): To test the hypothesis that HCEM, compared to an attention, time and information matched control condition, will reduce risk of STIs and alcohol/drug use among at-risk pregnant women during pregnancy at 2 and 6-months follow-up.

(a) HCEM, as compared to control, will result in fewer unprotected sexual occasions;

(b) HCEM, as compared to control, will result in lower alcohol use and illicit drug use, and fewer heavy episodic drinking days.

Aim 2 (Secondary outcomes): To test the hypothesis that HCEM will be associated with key secondary outcomes:

(a) HCEM, as compared to control, will result in fewer STIs (re-infection and/or new infections) during pregnancy and at 6-weeks postpartum;

(b) HCEM, as compared to control, will result in fewer unprotected sexual occasions and lower alcohol use and illicit drug use at 6-weeks postpartum;

(c) HCEM, as compared to control, will result in better birth outcomes (e.g., low birth weight);

(d) To collect and measure resource utilization and costs of HCEM to provide preliminary data to assess feasibility for future implementation and dissemination and to inform practice guidelines.

Aim 3 (Mediation): To explore direct and indirect effects in the above hypotheses:

(a) To explore the effect of HCEM on the intermediate outcomes of pregnancy-specific knowledge and risk perceptions, autonomous motivation and self-efficacy during pregnancy;

(b) To test these theory-based mediators of HCEM primary effects hypothesized above.

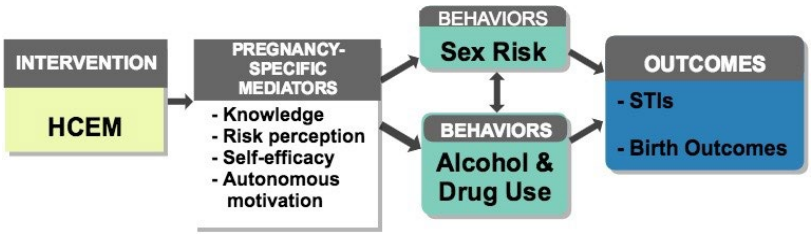
Impact: This project will fill a critical gap and provide much-needed data on the efficacy and utility of a practical computer-delivered, brief motivational intervention tailored to reach high-risk women during pregnancy and extending impact to postpartum. If this promising intervention is found efficacious, it can be readily integrated into prenatal health care settings and thus reduce the risk for adverse outcomes for very large numbers of vulnerable women and infants.

4.0. Approach

The proposed study is a two-group, randomized, controlled design with an initial session (conducted close to the first prenatal visit), plus two booster sessions within one month later (at 2 and 4 weeks). There will be follow up assessments at 8 and 24 weeks, and at 6 weeks postpartum, conducted by computer and delivered by RA either at the clinic, or remotely over the telephone, or at participants' home. Birth outcome data will be available by postpartum medical records. We will focus on testing the efficacy and utility of the theoretically driven HCEM to target STI risk during pregnancy and postpartum, integrating alcohol and drug use given the well-supported relationship between these risks. The proposed study will use a sophisticated intervention development tool, the Computerized Intervention Authoring Software (CIAS). A technology-delivered intervention approach promotes scientific rigor and greatly facilitates replicability in the community.

4.1. The Health Check-up for Expectant Moms (HCEM) is a brief intervention (one session plus two booster sessions) that is theory-driven and derived from empirical support (see Figure 2, below). Motivational interviewing (MI) has been found to be effective for STI/HIV risk reduction. MI is an intervention approach with wide dissemination and demonstrated efficacy. Consistent with the Self Determination Theory (SDT), MI is a client-centered counseling style that facilitates internal motivation to change through alignment of behavior change with deeply held beliefs, values, and goals. MI utilizes evolving readiness and self-efficacy to change. Moreover, the MI model appears to be generalizable to different populations, including low-income urban women. The components of the STI and alcohol/drug use risk reduction to be used in HCEM are formulated to be highly specific to the perinatal setting and entail increasing knowledge and targeting risk perceptions about STI transmission and prevention during pregnancy (which includes education about alcohol/drug use, for example the health risks associated with marijuana use on the developing fetus), increasing intrinsic motivation to act during pregnancy based on that knowledge, and ensuring sufficient behavioral skills (self-efficacy) to change behavior (e.g., increase in condom use, decrease in substance use) during pregnancy, as self-efficacy can be a strong predictor of condom use in women. In previous studies, MI has led to greater changes in the perception of risks of substance use, suggesting it may be an important mediator. In their comprehensive review of the literature evaluating HIV risk reduction interventions, Fisher et al. concluded that effective risk reduction involves separate factors. First, risk reduction entails increasing one's knowledge about STI/HIV transmission and prevention. Second, one's motivation to reduce risk must be enhanced. Third, effective risk reduction requires adequate behavioral skills. In their Information-Motivation-Behavior (IMB) model, the authors argue that information and motivation activate one's behavioral skills, which in turn lead to risk reduction. In the area of STI/HIV risk reduction, the IMB model is a well-established model, and the intervention, HIV-RBI based on this model has garnered strong empirical support, especially among low-income urban women. In general, motivationally-enhanced interventions yielded larger effect sizes (*d* = 0.56) than traditional skills-based interventions (*ds* = 0.32 to 0.43). These IMB components were selected as mediators of HCEM on both theoretical and empirical grounds and tailored for the pregnancy setting. For example, knowledge and risk perception are pregnancy-specific. The other two mediator measures are specifically worded to direct women to respond only about the duration of their pregnancy. Each mediator is either modifiable or could form a basis for tailoring, which will inform future interventions. Such an MI-based, STI risk reduction intervention, may be of particular value for pregnant women at risk for alcohol/drug use in reducing STI risk, because MI identifies these women' strengths and builds upon their successes

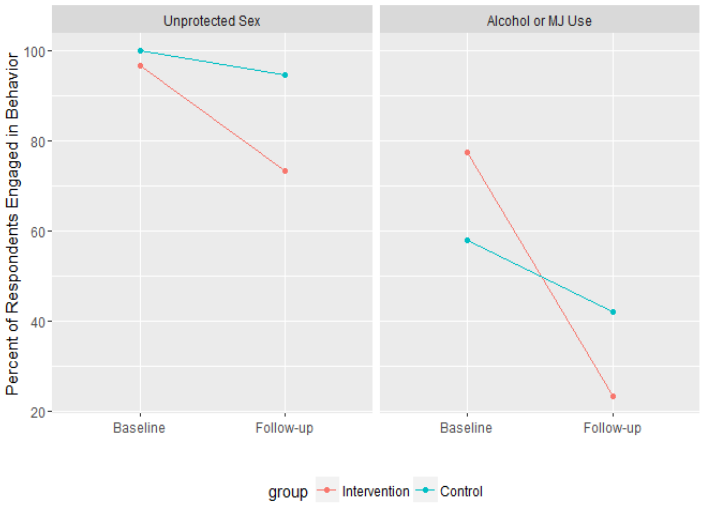
Figure 1. Conceptual Model of HCEM Effects and Mechanisms



(i.e., other changes they have made during pregnancy), thereby countering experiences and perceptions that may make them vulnerable for substance use. Additionally, MI with its collaborative and non-confrontational approach and its emphasis on increasing awareness to successful steps towards their well-being is consistent with recommendations for brief interventions in substance use, including increasing self-efficacy and relapse prevention skill sets to extend into postpartum.

4.2. Preliminary data from R21 Along with two members of this research team, the PI conducted a RCT pilot study of 50 high-risk pregnant women attending prenatal care in a large urban clinic in Providence, RI, with comparable patient demographics to the clinical sites proposed in the current study. The intervention received very high mean ratings of satisfaction (6.3 out of 7), and the computer software was rated highly by both control and the intervention participants (4.6 out of 5). Feedback from the exit interview was positive with participants consistently reporting that they found the intervention educational, interesting, and realistic. The RCT was feasible in terms of recruitment and enrollment of participants. A total of 401 women were screened over the course of nine months, with 34% meeting eligibility criteria. Overall, of the 50 women enrolled for the randomized trial, all 50 completed the intervention session. Forty-nine women (98%) completed the booster session and assessment 4 months later, demonstrating feasibility and uptake of these sessions. Participants in the HCEM condition demonstrated a significantly larger reduction in any self-reported marijuana or alcohol use compared to control condition (time-by-group interaction p = 0.015). There was a higher reduction of unprotected sex at follow-up in the intervention arm than control (27% vs. 5%); the direction and magnitude of this effect was very promising and would be of clinical significance, however, was not significant with this small sample size ((OR = 0.17, p = 0.12); see Fig 3, right). These encouraging findings strongly support the current application. The lack of significance regarding unprotected sex reduction may also indicate that additional contact may be needed for our high-risk group of pregnant women, supporting a second booster session in the proposed trial.

Figure 2. Reductions in Main Outcomes of R21 Study



Evidence of high acceptability of computerized intervention The HCEM is MI-consistent, incorporating the general principles, including expression of empathy and support of client's self-efficacy (Miller & Moyers). Results from our pilot testing found that 100% (50 out of 50) of the women reported feeling respected, and not judged, by HCEM. Further, previous studies using CIAS-based SBIRT packages with thousands of perinatal women have consistently yielded extremely high ratings for acceptability and ease of use.[11,53,83]

Incomplete mediation by alcohol factors supports need for multiple-targeting. Our recent mediation analysis of a computer-delivered brief intervention to reduce alcohol and sexual risk behavior among 372 patients in the ER determined that only 23% of the intervention effect on condomless sex was mediated by reduced heavy drinking This suggests that meaningful reductions in sex risk likely require active promotion of safer sexual behaviors such as condom use skills, in addition to focusing upon alcohol use per se.

4.3. Research Team Our study team is experienced and capable of conducting the proposed study and includes a strong team of investigators with long experience in designing and conducting computer-based brief motivational interventions to address high-risk behaviors among vulnerable women. We have tremendous experience in the recruitment and retention of high-risk samples, including perinatal women in these clinical settings as evidenced by a number of successful NIH trials. The PI and Mmeje (Co-I) are affiliated with the proposed clinic sites, which will facilitate conducting the study (see Letters of Support).

Drs. Tzilos (PI), Zlotnick (Co-I) have conducted a number of brief motivational intervention trials using the same CIAS-based software to be used in the proposed study. The PI adapted and tailored a brief, computer-based intervention for pregnant women at risk for alcohol use. She screened 490 pregnant women from an urban prenatal clinic and randomized 50 women at-risk for alcohol use during pregnancy to complete either a single-session, computer-based brief intervention or a time and attention-matched control condition; both groups completed a one-month follow up assessment. Dr. Zlotnick is a Professor in the Departments of Psychiatry and Human Behavior, and Obstetrics and Gynecology at Brown University. She has extensive experience in testing interventions to meet the unique needs of challenging high-risk perinatal populations within clinical settings (e.g., perinatal women with intimate partner violence, low-income women at risk for postpartum depression) and other high-risk women (e.g., incarcerated women with interpersonal violence and HIV/STI risk behaviors), with very high retention rates. Further, she, the PI, adapted a computer-based SBIRT approach for pregnant women at risk for STIs/HIV primarily, integrating alcohol/drug use given the relationship between these risks during pregnancy (R21 HD075658).

Dr. Ngo (Co-I) is the Research Director at the Hazelden Betty Ford Foundation. She is a fully-licensed Clinical Psychologist with expertise in substance use, violence and trauma, contemplative practice, and technology-assisted psychological interventions. Dr. Kuo (Co-I) is an Assistant Research Scientist in the Department of Internal Medicine at Michigan Medicine. His area of expertise includes clinical economics and decision analysis. Dr. Sen (Co-I) is Professor in the Departments of Family Medicine and Biostatistics at the University of Michigan. He has considerable experience as biostatistician on large clinical trials involving behavioral interventions and his primary role on this study will be supervisory. Dongru Chen, a statistician in the department, will work directly under his supervision and will assist him with statistical analysis, report generation and manuscript preparation. Dr. Sen and the PI have collaborated on the R21 study. Dr. Mmeje is a staff physician at the Von Voigtlander OB clinic and an Assistant Professor in the Department of Obstetrics and Gynecology. Her area of expertise is reproductive infections diseases and HIV/STI risk among pregnant women. Dr. Katherine Gold (Co-I) is a family physician, obstetrics and mental health researcher, and an associate professor in the University of Michigan Departments of Family Medicine and Obstetrics & Gynecology. Our team has demonstrated excellent retention rates with high-risk perinatal samples ranging from 87% for up to one-year postpartum and 94% for a 9 months follow-up period.

In summary, our research team and preliminary studies demonstrate strong support that we can successfully: 1) recruit and retain the target population 2) optimize and deliver the planned technology-delivered intervention, and 3) demonstrate significant behavior change.

5.0. Research Design and Methods

Program and procedure modifications: We will optimize the intervention program based on results of the R21 study, including updates to the tailored content of the intervention and the addition of a second booster session. We will include an additional booster session because 1) our sample will be a high-risk group and likely to benefit from additional contact, 2) boosters will target the prevention or reduction of the behavioral risks during postpartum, and 3) the literature suggests increases in efficacy and promotion of gains with behavioral interventions when boosters are provided. Our proposed Michigan clinical sites are comparable to the Rhode Island clinic site where we conducted the pilot study, with respect to patient volume, clinic setup and flow, and serving pregnant women on public assistance. These procedures will enhance study feasibility by ensuring that procedures are in place to interview participants on schedule, that recruitment procedures are culturally sensitive, that our assessments do not place undue burden on participants, measures are feasible and acceptable, and that dropout rates are minimized. HCEM is specifically tailored, innovative and relevant to diverse pregnant women in a number of ways. First, the images/content will be culturally sensitive and appropriate for a racially/ethnically diverse group of women (e.g., including pictures and video testimonials of women from racially/ethnically diverse backgrounds). Second, we will carefully coordinate appointments with prenatal visits to facilitate travel and increase likelihood of greater follow up rates. The software is highly interactive and individualized, has been found in previous research including our own to be well-understood and liked by low-income, pregnant and postpartum women, relies heavily on realistic interactions with a narrator to mimic the conversational, empathic nature of person-delivered brief interventions. Our team has the expertise and well-established programmer training methods to

work with research staff to complete the programming of the HCEM and assessment materials in a timely manner. We have successfully adapted five previous trials without any delays.

Overview: The 60-minute intervention is focused on reducing STI risk behaviors including alcohol/drug use during pregnancy. It will begin with an introduction to the intervention structure and will provide a tutorial guided by the narrator, which interacts in a collaborative, MI-consistent style with the ability to use emotionally expressive statements and empathic reflection. The Information component, which is consistent with the FRAMES approach and will follow recommended guidelines for brief interventions, will be delivered using the MI-consistent *elicit-provide-elicit* framework, including open-ended questions and reflections in providing facts about STI transmission and prevention; testing and behaviors that can be utilized to reduce risk during pregnancy; associated risks of alcohol and drug use for both woman and fetus and will highlight the bidirectional relationships among these risk factors, especially how alcohol/drug use increases risk for STIs. In order to facilitate condom desensitization and skills, information about various forms of condoms, lubricants and dental dams, as well as their application, will be delivered by the software in video format, to increase interest and engagement. Moreover, HCEM includes short video testimonials of women who share their challenges/successes with respect to changes in their alcohol/drug use during pregnancy, as well as women who had an STI, how it affected them during pregnancy, and how they sought support. In our pilot study, participants rated these components of HCEM as highly acceptable, "interesting and real" and found them to be relevant to their own relationships.

Motivational strategies such as collaborative, reflective listening, exploring goals and values are utilized to elicit change talk and enhance participants' autonomous motivation. The narrator will elicit behavior change by asking open-ended questions, reviewing change rulers (importance, readiness, and confidence rulers (1 to 10)) to support participants' self-efficacy and autonomous motivation (e.g., "On a scale of 1-10, how important is it to you to change your marijuana use during pregnancy?"). The intervention will encourage participants to explore and resolve ambivalence. For example, the narrator will ask for the good things about changing/not changing their selected substance and provide a checklist in which they endorse as many pros as they would like (e.g., marijuana use helps my nausea). The narrator will reflect back to them the specific reasons that they selected, and will note that feeling two ways about one's marijuana use is quite normal. The intervention is designed to explicitly and directly target and enhance autonomous motivation to change STI risk behaviors, including alcohol/drug use (while marijuana use was the primary drug endorsed in the pilot study, the participant will have the option to choose which specific drug(s) she would like to focus on for the duration of the intervention), and provides opportunity for the participant to select and practice behavioral skills necessary to reduce risk (e.g., negotiating communication of their intentions to their partners) during pregnancy. The software tailors the intervention content to include key MI components regarding STI risk (e.g. personalized feedback on STI risk, and optional goal-setting addressing STI risk behaviors). After summarizing personal concerns as identified by the participant (e.g., "I want to cut down on my alcohol use"), the software elicits from participants steps that can be taken to reduce STI risk. In order to enhance behavioral skills and utilization of resources for STI risk reduction, participants are taught male and female condom application with anatomical models as well as strategies to negotiate condom use to respond more assertively within a sexual context during pregnancy. The literature suggests that skill-building interventions improve self-efficacy in condom use among high-risk females.[96] In our pilot testing, participants found these skills as educational and helpful, and several women reported a general lack of knowledge about how to use female condoms and expressed interest to use them. Supporting participants' efficacy for behavior change is a key concept of MI.

The software includes an optional personalized plan which is designed to increase awareness of risk factors for STI and alcohol/drug use in the woman's life, including partner substance use - which may increase these risks for the woman during pregnancy - and offers personalized advice for decision-making that maximizes the woman's sexual safety. The narrator will elicit participants' willingness to change and an emphasis is placed on eliciting change talk. For example, the narrator will ask if she would like to set a change goal during her pregnancy. If she does not wish to do so, the narrator reflects, in a non-judgmental manner, her lack of readiness at this time and elicits information regarding what signs would tell the participant that she did need to change. If the participant wishes to set a change goal, the program will guide her through a brief change plan process. Participants will be provided a menu of choices for when, why, and how she would like to make a change/setting a goal (e.g., a commitment to use

condoms every time she has sex for the remainder of her pregnancy). The plan will extend decision-making to the postpartum period, including change goals that address alcohol/drug use and condom use after her baby is born, and will be reinforced in the booster sessions.

Web-based booster sessions: Within one month of completing the intervention, participants in both conditions will complete two, 15-20-minute booster sessions delivered remotely. For participants in the control condition, the booster content will be similar to the baseline content. For participants in the HCEM condition, the booster sessions will review their own personalized plan and identifying any challenges or barriers to increasing safety behaviors (i.e., intention to increase condom use and/or reduction of the substance that they selected). Review of change plan will include: reduction in STI risk behavior, including alcohol/drug use, identification of triggers for unsafe sex. Booster sessions explicitly target the prevention or reduction of STI risk behaviors including alcohol/drug use during the postpartum period, when prevalence of these risk behaviors increase, and address health risks associated with postpartum substance use (e.g., risks of substance use while breastfeeding). Sessions will emphasize principles of MI (e.g., fostering autonomous motivation), reviewing and reinforcing aspects of their change plan that are also relevant to the postpartum period (e.g., generating options and goal-setting), and accessible at home for ease of completion using a computer or mobile device – an improvement to the R21 study (see Fig 3, above; study homepage). Recent research demonstrates that low-income childbearing women, including women of color and perinatal women, frequently use and show strong interest in technology in general and for acquiring health information. Research of low-income single childbearing women found 78% had a smartphone. Our own research with high-risk perinatal women found that all participants had smartphones and were active users. The booster sessions reinforce and sustain the effects of the brief intervention. The addition of a second booster bolsters the preventive effects for the postpartum period.

5.1. Inclusion/exclusion criteria: Participants will be 250 pregnant women (as close as possible to first prenatal visit), age 18 or older, and will follow similar recruitment to the R21 study given feasibility and acceptability rates. Specifically, the study will include pregnant women who endorse: 1) at least one unprotected vaginal (or anal) sex occasion (USO) in the past 30 days (supported by the literature for our “high risk” sample, identified as such based on childbearing age, urban, ethnically diverse, and reporting co-morbid recent history of substance use), and 2) having more than one male partner in the last 6 months and/or having uncertainty about current sexual partner’s monogamy, and 3) current alcohol/drug use risk, 4) currently resides in the state of Michigan. Exclusion criteria include: 1) inability to provide informed consent (e.g., clear cognitive impairment), or 2) inability to understand English.

5.2. Recruitment: We successfully completed the R21 study in a prenatal clinic in Providence, Rhode Island. We will implement similar methods to recruit for the proposed study. Past year public health data reports increases in STI cases reported in Washtenaw County (Michigan). Recruitment will take place in a number of ways, including in-person at clinical sites within Michigan Medicine, other Michigan based clinics, or remotely. Remote recruitment for Michigan Medicine patients will happen by a member of the research team conducting a chart review (MiChart) and contacting prenatal patients over the phone, via physical mail, or through email messages. The research team will also recruit online by advertising on the University of Michigan Health Research website (https://umhealthresearch.org) or through social media platforms (e.g. Facebook, Instagram). Online/remote recruitment will not be limited to Michigan Medicine patients, however; pregnant women residing in the state of Michigan who are patients of outside

institutions (including, but not limited to The Luke Clinic) will also be eligible to participate if they meet the study inclusion criteria. We chose Michigan Medicine clinics and clinics in the state of Michigan because of the high-volume access to a socioeconomically, racial/ethnically, culturally diverse pregnant population relative to the prenatal clinic in Rhode Island (there are higher rates of African American women, who, compared to white women, are disproportionately affected by STIs). Also, Washtenaw County is in the top third of counties in the U.S. for Chlamydia rate. Further, the CDC reports that STI rates in Michigan surpass those in Rhode Island, where the R21 study was completed, further supporting the clinic selection for the proposed study.[1] Overall, these rates and supporting data reflect a high-risk sample of pregnant women at these two clinics.

In sum, based on these reasons and the prevailing literature (see above sections), we anticipate conservatively that 80% of the women who will meet inclusion criteria for alcohol or drug use (20% of those screened) will also meet criteria for STI risk in the past year, yielding an overall inclusion rate of 16%. Based on the feasibility data of the R21 study, we anticipate that to enroll approximately 250 women (see Power Analysis section, below), we anticipate screening 1,540 women, which will take roughly 48 months (a rate of approximately 32 participants/month). Based on rates determined in the pilot study, as well as estimates of rates for risk behaviors at Michigan Medicine clinic sites (generated from past-year medical records data and supplemented with data reported at the county level as well as the CDC for STI risks in specific counties), we expect that rates of eligibility and enrollment will yield a rate of 5-6 participants completing baseline per month between the clinic sites, yielding a total of 250 participants over the course of Yrs. 1 – 4. Follow up assessments for all 250 participants will be completed by the 5th month of Year 5. The research team has had high follow-up rates (6-14% attrition) in intervention trials involving high-risk pregnant women in prenatal sites,[104-106] and with other challenging populations, including women using substances.[107,108] Moreover, we have had high retention rates (85%) in intervention trials including adults endorsing risky alcohol use who receive care in the proposed (Michigan Medicine) health system.[41]

Recruitment for the implementation phase: research staff will contact each clinic and provide the study information. The clinic director, clinic manager, or responsible party will direct us as to the best method for dispersing the information to the clinic staff (e.g., sending an email with additional information). Interested staff members will then contact the research team to schedule an interview. We anticipate interviews will take anywhere from 30-45 minutes. In addition to recruitment of clinic staff, we plan to recruit and enroll 5-30 participants who have already completed the study to tell us about their thoughts and opinions around the HCEM program. We will use a 2-page addendum as the consent form to enroll these participants since they have already completed the study. These will be participants who agreed to be contacted by us for future research. We will contact these participants via email, phone, and text to see if they are interested in completing the interview which will be conducted virtually (through Zoom). We anticipate these interviews will last 30 minutes or less and participants will receive a $50 Amazon gift card or check.

Recruitment site: The clinical trial recruitment will be conducted at Michigan Medicine clinics, and with non-Michigan Medicine OB clinics. We chose these clinics because they provide access to socioeconomically, racial/ethnically, culturally diverse pregnant patient population. Due to the COVID-19 pandemic, recruitment from these clinics will also take place remotely over the telephone, via physical mail, or through email messages. The research team will also recruit online by advertising on the University of Michigan Health Research website (https://umhealthresearch.org) or through social media platforms (e.g. Facebook, Instagram). The Michigan Medicine team will also work in partnership with the Luke Clinic sites in Detroit and Flint in order to recruit from their patient population.

5.3. Recruitment and Informed Consent

Women from Michigan Medicine will be recruited in one of several ways, including: being approached in the waiting room, being approached by the research assistant or a member of the health care team while waiting for their physician in the examination room (with permission given to introduce the study); through their physician giving them a study flyer or verbally telling them about the study, through a member of the research team conducting a chart review (MiChart) and contacting prenatal patients over the telephone (and text message), via physical mail, or through

email messages; or through study flyers posted in Michigan Medicine clinics/hospitals and throughout the University of Michigan Campus. Non-Michigan Medicine patients will be recruited in one of several ways: through flyers posted in non-Michigan Medicine clinics/hospitals and in offices at the Michigan Department of Health and Human Services, through flyers posted in community/public spaces such as bus stations, libraries, churches, childcare centers, local pre-k through 12 schools, food pantries/grocery stores, laundromats, and similar spaces; through social media (i.e. Facebook, Instagram); through the UM Health Research website, and similar recruitment strategies. Patients from Luke Clinic will be recruited in one of two ways: 1) they will be informed of the study by clinic staff and will complete a contact information sheet if they are interested in being contacted by a member of the study team (remote screening), or 2) they will be approached by study staff in-person and asked if they would like to complete the eligibility screener on a study iPad. In addition to the $5 gift card for completing the screener, patients who fill out the contact sheet or take the screener in-person will receive a small gift bag (containing lip balm, hand lotion, etc.) to show our appreciation for their time. For patients that screen eligible, steps will be taken for enrollment and permission to access their Luke Clinic's Electronic Medical Record system, allowing for patient contact and data access.

In a Michigan Medicine clinic setting, those who express tentative interest in the screening survey will be directed to speak with the study RA to complete the short (10-15 minutes) computer-delivered health survey including questions to determine eligibility. Before completing the screening survey, they are given a copy of the screener consent, to which they must verbally agree to before proceeding. The computerized screening will use software delivered on an easy to use iPad iOS. The research team has used this procedure successfully to recruit this target population. In a remote setting, potential participants will complete the same screener online using their home computer, tablet or smart phone. The screener will include well-validated and recommended measures for this population. Women who score eligible on the screener in a clinic setting, will be informed by the RA about the clinical trial, and interested women will fill out a contact sheet and make an appointment for the baseline session. Before conducting the baseline session, the RA will explain the informed consent process as well as the study procedures, and ask comprehension questions before obtaining consent. Both the informed consent process and the baseline session will be conducted in a private room in the clinic (or a private room at the Department of Family Medicine office), providing a confidential and comfortable environment for the participant.

In a remote setting, the screener consent will be directly before the screener (on Qualtrics) questions. A woman hitting the "next" button and continuing on to the screener questions means that they agree to the consent. This is similar to how the screener consent works in-person, as we provide women with a paper consent and they verbally agree to take the screener. Women who take the screener online will automatically be informed of their eligibility upon completion. If they screen eligible, we will either call them directly to give them more information about the study and to collect additional contact information, or we will send a secure REDCap (or Qualtrics) survey link, where they can enter in their contact information. We employ these methods to allow the screening survey to remain anonymous should a woman decide not to participate in the larger study. For women recruited from social media, they will first see an ad for the study, and if interested, click on it for more information. This will bring them to a brief pre-screener survey on Qualtrics, which will ask them to confirm that they are pregnant and plan on delivering in the state of Michigan. If they are found eligible on the pre-screener survey, they are invited to enter their name and phone number so that the research team can contact them to answer some additional pregnancy related questions. If the participant is able to answer these pregnancy questions, then the RA will invite them to take the screening survey and ask for their email address (screening survey is sent via email). The reason we employ a pre-screener and telephone call is to avoid the possible fraud that can occur with social media recruitment (i.e. participant misrepresentation of their pregnancy status, spammers, and internet bots). Furthermore, if the participant passes the pre-screener survey and phone call and goes on to take the study screener but answers that they are not pregnant or indicate a different gestational age, then we will assume it's a fraudulent screener and we will not pay out the $5 gift card. The pre-screener survey and phone call will not be necessary for Michigan Medicine recruits as we can verify their pregnancy status on MiChart.

Participants' contact information (e.g. phone number) and the contact information of up to three other individuals (e.g., family/friends) will be collected after screening eligible for the study, for the purposes of scheduling the baseline and follow-up assessments; this information will also be stored on the HIPAA-compliant database REDCap, which is administered and managed

through the Michigan Institute for Clinical and Health Research (MICHR) at the University of Michigan. This database will only be accessible by the Study Coordinator and research staff. Any information about a participant will never be released to outsiders without their explicit consent, except in the event of abuse of children/elderly/handicapped (report to the Michigan State) or a medical emergency, when pertinent medical information will be given to the medical personnel caring for the individual. Participants will also be informed about the risk of loss of confidentiality due to STI testing and drug screens.

To obtain study consent remotely, potential participants will be emailed the study consent document and asked to read it before a scheduled phone call with the RA. During this call, the RA will review all sections of the consent document with the woman, answer any questions she may have, and then ask comprehension questions just as is done during in-person informed consent. If the woman agrees to be part of the study, she will give her consent verbally over the phone, rather than signing a paper copy. The remote baseline session itself will be conducted both over the phone and online, using the CIAS study software.

5.4. Methods: We will implement the same study procedures as in our previous studies with pregnant women (see above). Women who express tentative interest in the screening survey will be directed to speak with the study RA to complete the short (10-15 minutes) computer-delivered health survey including questions to determine eligibility. In a remote setting, women will take the screening survey online, and if eligible, provide their contact information for the RA to follow-up with them. The computerized screening will use the CIAS software delivered on an easy to use iPad iOS (in-person), or on the participant's own Internet connected device (remote). The screener will include well-validated and recommended measures for this population. The research team has used this procedure successfully to recruit this target population.

Women who score eligible on the screener will be informed by the RA about the clinical trial and will explain the informed consent process as well as the study procedures (see Fig 4, below). For in-person study visits, the baseline session will be conducted in a private room in the clinic (Michigan Medicine), providing a confidential and comfortable environment for the participant. Given the current COVID-19 pandemic and associated research restrictions, the baseline session will be conducted remotely (August 2020 to present time, February 2023), both over the phone and online, using the CIAS software. Upon completion of the baseline session (whether it is conducted in-person or remotely), and following previous studies with similar design, women in both conditions will receive appropriate referrals for: (1) testing and treatment for STIs, and (2) brochures specifically designed to facilitate reductions in drinking and drug use during pregnancy (note: we will use publications from the National Institutes of Health and/or the Centers for Disease Control and Prevention). Women in both conditions will also receive a comprehensive list of local (Washtenaw County) and online resources for relevant topics such as substance use help, mental health counseling, STI testing centers, food pantries, etc. Additionally, all participants in this study will receive care as usual from their medical team; no screening, referral, or counseling will be withheld in any way at any time. Such a design—involving a treatment as usual control, supplemented by additional referrals and materials—is typical of clinical trials of behavioral interventions for substance abuse and STI/HIV risk interventions. Participants randomized to the intervention arm are offered a "safe sex kit," which includes male and female condoms, dental dams, and lubrication. If the participant is completing the intervention remotely, the research team will obtain permission for this kit to be mailed to their place of residence.

Booster sessions can be completed by the participant in their home and accessed through our secure, HIPAA-compliant study website using either a computer or mobile device (see Fig. 3, above). The use of computer technology for gathering self-report data further enhances overall protection. This software utilizes SSL technology for encrypting of communications between remote computers and the server itself, is HIPAA-compliant, and is currently used in a number of major NIH-funded research studies, including those of the PI. Data will be encrypted in transit between user and server. Importantly, no identifying information will be entered into the CIAS software. Given the sensitive nature of this research, the computer software will simply generate a code number for each participant. Additionally, all forms with participant information will be marked with a code number and not with the participants' name. The link between the participant code number and name will be securely stored on the HIPAA-compliant database REDCap. This database will only be accessible by the Study Coordinator and Research Assistants.

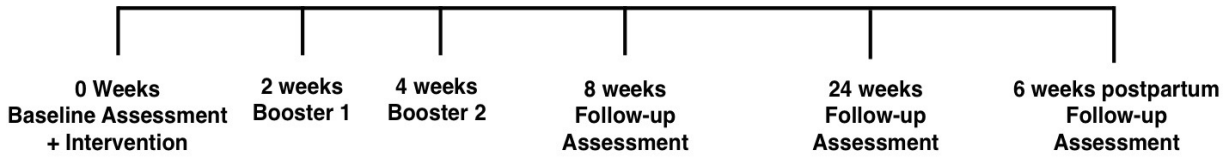
In-person follow-up assessments will be completed at the clinic (Michigan Medicine) and scheduled with prenatal visits when possible. Given the current COVID-19 pandemic and

associated research restrictions, the follow-up assessments will be conducted remotely (August 2020 to present time, February 2023), both over the phone and online, using the CIAS software. The postpartum assessment will be conducted by the RA at a private and confidential location convenient to the participant (e.g., clinic, home, or remotely), coordinated with the timing of the postpartum medical visit, maximizing likelihood of completion.

For the assessment timepoints that require urine sample collection for STI testing, Michigan Medicine participants have the option to complete STI testing at any Michigan Medicine lab site. For both Michigan Medicine and non-Michigan Medicine participants, they have the option to receive an at-home STI testing kit. The study team will be responsible for mailing the kit to the study participant and covering the cost of returning the kit. Drug testing will no longer be required for study participants (as of November 2022). Instead, the study team will collect the results of already existing drug tests in the patient's chart completed during the duration of their study participation. This will include patients at Luke Clinic, for whom the research team will have guest access to the clinic's Electronic Health Record System, allowing for the collection of patient medical information.

Should an already enrolled participant choose to leave the study or not follow through with appointments for some reason, we will ask them for their feedback through an anonymous and voluntary survey that asks what the research team can do to more easily facilitate women's participation in the study.

Figure 4. Study Timeline



Information-matched control condition: We will use the same, well-validated, attention, time and information-matched control used successfully in our five previous studies with pregnant women, including in the pilot R21 (ratings of acceptability were equally high among intervention and control group participants). The content will consist of a series of questions regarding television show preferences and viewing a brief series of videos of popular entertainers/shows, with subsequent requests for ratings of subjective preference, and will also help to limit inadvertent therapeutic effects that plague control groups in brief intervention research. We will include facts about alcohol/drug use and risky sex during pregnancy, along with informational brochures from NIAAA/CDC that provide face validity.

5.5. Measures: Participants meeting inclusion criteria will complete an assessment session on the iPad iOS. The battery is designed to minimize assessment with the control group in order to take in to account growing concerns regarding the motivational properties of assessment, leading to substantial Type II error in brief alcohol intervention studies. All of the self-report measures included in this study have good psychometric properties (see Table 1, below).

Screener items (embedded with general health questions):

1. *Questions for history of STI sexual risk* (i.e., number of occasions of condomless vaginal (and anal) sex in the past 30 days);
2. *T-ACE* (four questions) is a screen for risk drinking developed for use in OB/GYN settings;
3. *Substance Use Risk-Profile Pregnancy Scale (SURP-P)* (three questions) this screening is specifically designed to quickly identify obstetrical patients at risk for alcohol or illicit drug use.

Table 1. Study Measures		Antenatal		Postpartum
Self-report measures	**Baseline**	**19-28 weeks**	**36-39 weeks**	**6 weeks**
Demographic Information	X			
Marlowe-Crowne Social Desirability – Short Form	X			

Timeline Follow-back, sex, alcohol, drug use	X	X	X	X
Condom Use Self-Efficacy	X	X	X	X
Treatment Self-Regulation Questionnaire	X	X	X	X
HIV/STI Knowledge Questionnaire	X	X	X	X
Risk Perceptions Items (STI)	X	X	X	X
Importance, Readiness, and Confidence Rulers	X	X	X	X
Condom Attitude Scale	X	X	X	X
Perceived Competence Scale	X	X	X	X
COVID-19 Family Stress Screener	X	X	X	X
Objective biometric measures				
Urine or Vaginal Swab Collection: STI Testing	X*	X	X	X
Birth Outcomes				X
Hair Sample Testing (suspended 11/2022)	X**		X**	
Economic and implementation measures				
Costs Analysis	X	X	X	X
Clinic staff surveys	X			

*In-person, Michigan Medicine visits only.
**A urine sample may be collected in place of a hair sample in the event that a hair sample cannot be collected.

The following assessment measures will be administered at the baseline assessment:
1. *Demographic information*, including age, race, ethnicity, marital/partner status, parity, employment, socioeconomic status.
2. *Marlowe-Crowne Social Desirability Scale-Short*,[114] includes 13 items sensitive to social desirability bias.

5.5.2 Primary Outcome Measure:

1. *Unprotected sexual occasions (USOs*) at the 8-week follow-up assessment.

   USOs will be obtained from the *Timeline Follow-Back (TLFB)* to assess sex-risk behaviors at baseline and follow up assessments. The TLFB is a calendar assisted structured interview that provides a way to cue memory so that accurate recall is enhanced for event-level data; it has been used to assess sexual risk-taking. USOs will be assessed in the 90 days prior to the baseline, as well as the 8-week follow-up assessments.

5.5.3 Secondary Outcome Measures:

1. *Alcohol use and Illicit drug use:* Self-reported days of alcohol and illicit drug use at 8-week assessment.

   The TLFB will be used to measure alcohol use by using the variable of percent days abstinent. Illicit drug use will also be collected from the TLFB, and measured by using the "yes/no" variable for each day. Both variables will be assessed in the 90 days prior to the baseline, as well as the 8-week follow-up assessments.

Other Outcomes:

A. Alcohol use: In addition to the percent days abstinent variable, the TLFB will be used to measure drinks per drinking day and heavy episodic drinking episodes.

B. Illicit drug use: While not a primary outcome measure, the study has collected objective hair measures at various points through the duration of the research study (1.5-inch samples) providing up to a 90-day window (by Psychemedics, Inc.) to corroborate self-reported drug use at follow-up assessments (see *Data Analysis* section, below), as well as urinalysis. Our team has experience from our pilot study with feasibility of obtaining hair samples from pregnant women; we

improved upon our ability to collect hair samples as the study progressed (e.g., reducing refusal rates by 45% and obtaining samples from 85% of participants). In the case that a hair sample was not obtained, the team attempted to collect a urine sample instead. The urine samples were collected by a trained RA, which corroborated the self-report of drug use in the prior 30 days. Results were read by the RA after 5 minutes, and then the sample discarded. Results, reported by study ID, will be transferred by secure, encrypted electronic file and downloaded to a secure Michigan Medicine server. The study team has discontinued this measure (participants enrolled in November 2022 and on), as collecting hair samples has become increasingly difficult due to the COVID-19 pandemic and the expanding locations of our participant population. These challenges have made meeting participants in-person for sample collection challenging.

C. STI Testing: STI testing for Michigan Medicine patients will be handled in one of two ways: onsite at the Michigan Medicine clinic laboratories (MLabs) by providing a urine sample, or through at-home STI test kits (vaginal swab). Specific infections assessed will include three STIs most common among sexually active childbearing women: 1) Trichomoniasis; 2) Chlamydia trachomatis; 3) Neisseria gonorrhea. For patients outside of Michigan Medicine, no urine sample will be collected, instead, the at-home STI testing kit (testing for the aforementioned STIs) will be mailed to them free of charge. After self-swab collection, participants will mail this kit (with pre-paid postage) directly to the Johns Hopkins University School of Medicine laboratory for analysis (see more detailed information in section 12.1 below). Sensitive nucleic acid amplification tests make it possible to accurately diagnose STIs from urine samples. Vaginal swab tests are run on the Hologic Panther using the Aptima Combo 2 Assay to accurately detect STIs. Clinical outcomes include any incident STI and recurrent STI. These three specific diseases were selected as microbiologic outcomes because they encompass the most common infections seen in sexually active childbearing women that can result in adverse reproductive outcomes, can be unequivocally measured, and are immediately treatable. Women who test positive at any time during the study will be linked to comprehensive STI care at Michigan Medicine. Dr. Mmeje (Co-I), study physician, will facilitate treatment or will refer patients to another Michigan Medicine physician (for Michigan Medicine patients) who will provide treatment and counseling free-of-charge to the participant. For non-Michigan Medicine participants who test positive, Dr. Mmeje will write a prescription for the appropriate treatment which will be available at a Michigan Medicine Pharmacy. Should they prefer to seek treatment elsewhere, research staff will do their best to help facilitate this process, and any cost of treatment outside of Michigan Medicine will be the responsibility of the participant. Research staff will also follow-up with non-Michigan Medicine participants to confirm that treatment was received and/or to help identify any obstacles to treatment (e.g., if patient needs additional treatment referrals, etc.). If the STI is reportable, it will be reported to the Health Department as required by law. It will be outlined in the consent form that if participants are noted to be STI positive, their health care provider will be notified to coordinate care and management. When baseline and follow-up assessments are delivered remotely, we will delay the collection of all biological specimens (urine screens at lab) for STI testing until they have a prenatal visit at the clinic. In this case, the study team will resume (pre-pandemic) study procedures of ordering an STI urine screening on MiChart and direct the participant to go to the clinic lab after their prenatal visit with their provider, which will require no research staff contact. Regardless of this testing, we still plan to obtain consent to access STI results from the participant's prenatal visits with their provider, by checking their medical chart on MiChart. These results will correspond with the participant's prenatal/postpartum medical visits where testing occurred.

D. Birth and maternal health outcomes: Will be collected electronically by the PI and study team through mother and baby's hospital medical records (Von Voigtlander Hospital is the home to the majority of births in Washtenaw County, where participants from all Michigan Medicine study clinic sites give birth). Birth outcomes of interest will include: birth weight, head circumference, preterm birth, NICU admission and length, gestational age, APGAR scores (at 1-minute, 5-minutes, 10-minutes), birth length, fetal distress, neonatal withdrawal (neonatal abstinence syndrome), meconium testing results, vaginal or cesarean birth, and breastfeeding at discharge. We will also be collecting maternal health outcomes. These include antepartum outcomes that are associated with substance use and/or high-risk pregnancies, including: diagnosis of chorioamnionitis and/or endometritis, admission for preterm labor, shortened cervix, vaginal or IM progesterone administration, antenatal steroid therapy, intrauterine growth restriction. We will also review the

participant's medical chart for any provider STI testing, diagnosis, and treatment completed during the pregnancy and postpartum period. If a participant delivers outside of the Michigan Medicine healthcare system, we will ask them to sign a request for outside records authorization form, so that we can request these birth and maternal health outcomes be sent to us from the delivering institution/birth center. Our study team will also have access to Luke Clinic's Electronic Health Record System, allowing for the collection of patient medical information directly by the study team.

E. Unprotected sexual occasions (USOs): A partner-by-partner assessment of sexual behaviors and condom use will be made for each of the participant's sexual partners. USOs will be measured, as will partner type (casual, main).

F. Pregnancy-Specific Intermediate Outcomes and Mediators

Importance, confidence, and readiness rulers modified for the pregnancy context: Questions to determine readiness to change, importance for change (e.g., "How important is it that women quit marijuana use while pregnant?"), and confidence in ability to change substance use during pregnancy.

1. *Condom Use Self-Efficacy (CUSES)* questionnaire. We will administer the subscale including items about individual's perceived ability to use condoms during pregnancy.
2. *HIV/STI Knowledge Questionnaire*: Measure of HIV/STI related knowledge adapted for pregnancy.
3. *Risk Perception*. We will include items previously tested in pregnant samples to assess perception of risk of alcohol, marijuana, and sexual risks during pregnancy (e.g., "To what extent do you see your marijuana use as a problem?").
4. *Treatment Self-Regulation Questionnaire (TSRQ; adapted version*): Based on previous validated research, we will assess subscales of autonomous and controlled motivation for condom use, alcohol and drug use using adapted items from the TSRQ (e.g., "I want to make a change in my drinking because": I personally believe it is the best thing for my health (autonomous) vs. Others would be upset with me if I drank (controlled)).

G. Intervention Costs

This study will be to measure the total costs of HCEM from both the provider and the participant perspectives. Unmeasured time costs for either staff or for participants can be a key barrier to the implementation and long-term viability of a new preventive intervention since preventive and screening recommendations can compete for implementation time from staff. We will address this potential barrier by measuring all relevant costs associated with the study interventions through primary data collection. We will derive estimates of resource requirements for the two study arms (HCEM, control) from process data collected during the RCT, including measuring material costs of hardware (tablet computers, maintenance to computers), expenses of CIAS software, materials costs (e.g., condoms, etc.), as well as managerial time required for screening participants. Costs for personnel will be based on salaries of program staff. In the cost analyses, we will calculate the costs of implementing HCEM. All costs will be adjusted to US 2015 dollars using the Gross Domestic Product Price Index. Control costs will be adjusted to reflect the proportion of time study participants reported spending on the STI-related material, not including the assigned general TV viewing time. Questions on time allocation across activities will be included in the follow-up assessment. Net costs (savings) will be calculated by subtracting mean costs per participant in the control condition from mean costs per participant for HCEM condition. Change in treatment gains will be measured as the difference in STI incidence compared to the control condition. The outcome for the cost analysis will be expressed in dollars per STI averted. Given typical skewness, we will report means, medians, standard errors, minimum, maximum, and quantiles to provide information on cost distribution. Tests will be employed to assess distributions of the cost and identify appropriate methods for generating confidence intervals, such as non-parametric bootstrapping.

H. COVID-19 Family Stress Screener

The current coronavirus (COVID-19) outbreak is causing extra stress for many people, including families with children of all ages. We would like to know how this outbreak is impacting their health, safety and security. The COVID-19 Family Stress Screener will be embedded into CIAS and completed as a part of the baseline and each follow-up visit.

6.0. Retention: The research team has had retention rates (an average of 90%) in large treatment trials involving high-risk, low-income pregnant and postpartum populations. The current study will employ several approaches that we have found helpful in achieving these low attrition rates, including study staff's strong relationships with participants, efforts to value and appreciate the women's participation in the study, and frequent personal contact with the women for the duration of the study. Booster sessions will be web-based and accessible for participants to complete at home. RAs call women to remind them of their assessment appointments and maintain a list of two other people who will always know where the participant resides. Transport and childcare are provided as deemed necessary to complete assessments, particularly during the postpartum assessment. Compensation for participants' time helps facilitate retention.

A. Special circumstances affecting study retention

Because study eligibility includes being pregnant, and the HCEM is specifically tailored for pregnant women, in the event that an enrolled participant experiences a miscarriage, they will no longer be eligible for the study per the study research protocol. If study staff learns of miscarriage, study staff will call (or email if that is the preferred method of contact for the participant) the participant to follow up and offer Michigan Medicine resources for pregnancy loss, as well as notifying them of their new eligibility status.

7.0. Data Analysis: Descriptive statistics will be calculated to summarize baseline characteristics for the full cohort and by intervention arm. Quality inspection will be carried out periodically to screen for missing-ness and data anomalies, and entry error. T-tests and chi-square-tests will be used to compare study arms with respect to demographic characteristics and baseline measures of unprotected sex and alcohol/drug use. Any identified confounders with $p \leq 0.10$ will be included in all subsequent analyses. Using the TLFB, we estimate the frequency of number of days in the 90-day period that the participant is engaged in a risky behavior. This will be carried out separately for each of the outcomes, namely, unprotected sex, illicit drug use and alcohol use, and heavy episodic drinking days (Hypothesis 1 and 2). The outcomes will be analyzed under a clustered count regression framework (Poisson or Negative Binomial) with frequency as outcome, and time (baseline, 2 months, 6 months), group (HCEM, control) and time-by-group interaction as the primary covariates. A generalized linear mixed models (GLIMMIX) approach will be adopted assigning a random subject intercept to account for the clustering within each participant. The regression model will be further controlled for potential confounders such as demographic characteristics, social desirability, and other variables that are identified to be significantly associated with outcome in the univariate analyses. We will adjust analyses for baseline pregnancy stage and assessment timing, as well as delivery status (delivered/not delivered) at follow up assessments in our data analysis, and pregnancy loss during course of study (e.g., miscarriage or stillbirth). Changes over time within each group will be estimated post-hoc by sliced effects derived from the regression model. In additional analysis, reduction in proportion of participants engaged in the risky behavior on ≥ 1 days within the 90-day period will be analyzed using a clustered logistic regression with a dichotomous outcome at the subject level indicating the status of the engagement, and with time (baseline, 2 months, 6 months), group (HCEM, control), time-by-group interaction as the primary factors. As before, a random subject intercept will account for the clustering and the model will be controlled for the same ensemble of covariates as in the case of the count regression models. Similar analyses will be conducted in the secondary aims for the outcomes that will be measured postpartum. To test hypothesis 3a and 3b, we will use structural equation modeling (SEM) approach. These include pregnancy-specific measures of autonomous motivation, self-efficacy, knowledge and risk perceptions (see Table 1). These measures are all continuous and will be measured at all three time points. All relevant direct and indirect effects will be evaluated. Significance of the indirect effect of the mediators will be tested using bootstrap method which appears to have good power in small samples. Birth outcome data will be available to the team by accessing patient medical records postpartum (Hypothesis 2c).

7.1. Procedures for Handling Discordance Between Self-Report and Hair Sample: We will conduct sensitivity analysis to assess hair sample testing and to evaluate the concordance between hair sample results and self-reported drug use on the TLFB at follow up assessments. In the case of discordance between self-report data and hair sample, following standards in the literature supporting the use of hair sample as a secondary measure in clinical trials, we will use hair testing in combination with self-report to confirm reported abstinence (e.g., we will change self-report abstinence to non-abstinence if objective data indicates illicit drug use). Because of the difficulties in collecting samples for drug testing due to COVID-19, we suspended all collection of biological samples for drug testing for participants enrolled November 2022 and on.

7.2. Costs: Summary statistics for total HCEM-specific costs will be reported. Additional component cost outcomes will be reported including implementation time, and patient time. Net costs (savings) will be calculated by subtracting mean costs per participant in the control arm from mean costs per participant for HCEM. Change in treatment gains will be measured as the difference in STI status for HCEM compared to the control arm. The outcome for the cost analysis will be expressed in dollars per STI positive event averted (Hypothesis 2d).

7.3. Missing Data: The missing values at the subject-level will be imputed using multiple imputation (MI) methods. This will use the chained equation method that allows both categorical and continuous variables to be imputed together without making any multivariate joint distributional assumption. We will combine the results from 10 imputed datasets using Rubin's formula.[131] The MI approach is valid for `Missing at Random' scenario, i.e in cases, where the missing-ness mechanism is independent of the outcome after adjusting for covariates. Refusal to provide hair sample is perhaps one variable for which such an assumption may not be appropriate. Thus, for the models we use the information on hair sample, we will equate refusal with substance use. Based on our improved methodology for hair collection in the R21, we expect to yield ≤15% refusal. Given that refusal is likely to be low, impact on results is likely to be small. If refusal exceeds 15%, we will conduct imputation strategies that make various assumptions about missingness and the odds that it represents. Our inability to collect hair and urine samples at remote visits for drug testing (during the COVID-19 pandemic, which began in March 2020 and is currently ongoing as of February, 2023) will result in increased missing data. Because of the difficulties in collecting samples for drug testing due to COVID-19, we suspended all collection of biological samples for drug testing for participants enrolled November 2022 and on.

7.4. Power: We estimated power based on our R21 study and calculated it using extensive simulation. For the count outcomes, power was obtained under a Poisson regression framework with time, group, and time-by-group interaction as covariates. Data was simulated 1000 times from models characterized by time and group specific means as well as the variance of the random effects estimated from the pilot data. Power was assessed for the interaction term as well as the main effects empirically by the proportion of times the corresponding coefficient was deemed statistically significant at 5% level.

For all the outcomes, our proposed sample of 250 should be adequate for detecting small to moderate effect sizes. Even assuming the worst-case scenario of up to 20% drop-out in both arms, we plan to recruit 125 participants per arm. In our data, we observed reduction in risky behavior in both study arms; however, the reduction in the intervention arm was significantly larger. For example, for unprotected sex, the baseline average number of days of unprotected sex was 36 based on the pilot data. Assuming that the average number of days of unprotected sex drops to 32 and 29 in the control and HCEM groups, respectively, (similar to that obtained in the pilot data) at any of the follow up points, using 100 subjects per arm the difference in the reduction in the groups will be deemed as statistically significant with more than 90% power. We assume a difference of 10 days between the intervention and the control groups in the change from baseline to be clinically significant. The differences for alcohol use and drug use were more prominent in our R21 data and we anticipate to be well powered for these aims. Similar effects were obtained when the dichotomous counter-parts were simulated using a clustered logistic regression model. In our data, more than 95% of the participants at baseline were engaged in risky sexual behavior. In the proposed study, we estimate a drop by 50% in the HCEM arm, which would be statistically significant using the above sample size. Outcomes of binary alcohol/drug use also yield power above 80% for scenarios similar to those obtained in the pilot data.

8.0. Factors Affecting Implementation: We will explore factors that affect integration of HCEM into primary care. We will interview up to 30 staff stakeholders (e.g., clinical staff will be some combination of physicians, nurses, social worker, MA's, PA's, etc.) across each site including Michigan Medicine sites where we recruited for the study (West Ann Arbor, East Ann Arbor, Ypsilanti Health Center, etc.) and clinics outside Michigan Medicine, including Packard Health, to assess perceived barriers and facilitators, workflow impact, and fit with patient and site needs. In-depth interviews will be conducted remotely using Zoom. We will ask specific questions (see Interview Guide) relevant to implementation of the HCEM. Additionally, we will include quantitative measurement via a Likert Scale (1-5), for example, providers will be asked questions about the feasibility and clinical utility of HCEM (e.g., "Will HCEM improve the overall quality of perinatal care? "What is the likelihood of incorporating HCEM into your prenatal program?"). We will also include open-ended questions about how HCEM could be improved to be of greater clinical utility to the health care provider and their patients. In addition to interviewing clinic staff, we will also recruit a subset of our study participants (approximately up to 10) to assess patients' recommendations for HCEM modification (e.g. length of HCEM, readability). Additionally, we will be able to describe the program costs that would be needed to implement in a new setting. The interviews over Zoom will be recorded with the permission of the participants and the recordings will be stored on secure password protected computers and will only be accessible by the Study Coordinator and research staff. Recordings will either be transcribed using Zoom, or a third-party company like Lingperfect (audio files only), a HIPAA compliant transcription service.

9.0. Design Considerations to Enhance Rigor, Reproducibility and Impact: A number of our methodological design decisions were determined by our pilot R21 findings. A limitation of many studies on STI risk reduction interventions for women is the imbalance in intensity of sessions between the experimental intervention and control group, which makes it difficult to determine if intervention differences are attributable to differences in attention between the conditions or to the "active ingredients" of the intervention. Our control condition will be matched for time, attention, and information, and will provide a rigorous test of the effect of HCEM. Follow-up assessments will be administered by RAs who are blinded to treatment assignment (and not by the same RAs who administers the intervention). Our study sites reflect considerable socioeconomic and ethnic/racial diversity, and higher rates of STIs and substance use, which will allow for generalizability of the results beyond one study site.

10.0. Limitations and Countermeasures: Limitations of the current study include: potential issues related to disclosure of sensitive information, the use of self-report, assessment reactivity and effect on measured outcomes, the inclusion of only English-speaking participants, and generalizability of study results to other populations. To address these study limitations: 1) We will use technology to minimize socially desirable responses, particularly with stigmatizing behaviors, 2) we will directly assess and adjust for social desirability bias, 3) the baseline computerized assessment will occur prior to randomization to minimize bias; 4) loss to follow-up will be limited by computer-based assessment and home visits during postpartum assessment, and by our experience with long-term follow-up of high risk, vulnerable samples of women; 5) the information-matched control condition has been found acceptable and engaging in at least 4 behavioral studies that we know of including our own previous trials, and 6) based on data available at the clinic sites, there is only a small percent of women who are Spanish-speaking only. While participants will be recruited as close to first prenatal visit as possible, we will also include eligible high-risk women who are at later stages of pregnancy; we will adjust analyses for baseline pregnancy stage and assessment timing, as well as delivery status (delivered/not delivered) at follow up assessments in our data analysis, and pregnancy loss during course of study (e.g., miscarriage or stillbirth). We include monogamous pregnant women because STI risk is significantly elevated when substance abuse is present, regardless of partner status. Moreover, in our R21 study, 86% of the sample was monogamous, and yet intervention reduced condomless sex and substance abuse. We decided not to include genital herpes as an STI outcome as this is not in the clinical guidelines for STI screening set forth by the CDC. Dr. Mmeje will determine on a case-by-case basis for consideration of serological testing of genital herpes based on clinical presentation (e.g., active lesion) or partner history.

11.0. Project Timeline: We include a timeline detailing the proposed study activities (see Table 2, below).

11.1. Table 2. Planned Study Timeline

	Year 1				Year 2				Year 3				Year 4				Year 5			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
HCEM Refinement, IRB, Hiring/Training Staff																				
Recruitment																				
Baseline / Follow-ups, Barriers Assessment																				
Data Analysis/Publications																				

12.0. PROTECTION OF HUMAN SUBJECTS

This Human Subjects Research meets the definition of Clinical Research and of a Phase I clinical trial. It also meets the criteria of the OHRP for permitted research involving pregnant women (45 CRF, Subpart B, Part 46.204).

12.1. Risks to the Human Subjects

Human Subjects Involvement and Characteristics

Participants will include a total of 250 women in the prenatal period and their infants (details in proceeding section). Participants will be recruited from either Michigan Medicine or non-Michigan Medicine clinics. The inclusion criteria will be pregnant women (as contemporaneous as possible to first prenatal visit), age 18 or older, and will follow similar recruitment to the R21 study given feasibility and acceptability rates. Specifically, the study will include pregnant women who endorse 1) at least one unprotected vaginal (or anal) sex occasion (USO) in the past 30 days (supported by the literature for our "high risk" sample, identified as such based on childbearing age, urban, ethnically diverse, and reporting co-morbid recent history of substance use), and 2) having more than one male partner in the last 6 months and/or having uncertainty about current sexual partner's monogamy, and 3) current alcohol/drug use risk, and 4) is receiving medical care in the state of Michigan. Exclusion criteria include: 1) inability to provide informed consent (e.g., clear cognitive impairment), or 2) inability to understand English (understand the consent form when read aloud and assessments that are narrated by computer). No women will be excluded from recruitment on the basis of race or handicap. The inability to understand English will be determined by the inclusion of a subject comprehension assessment that will consist of a brief (five-question) true/false 'quiz' at the end of the consent form. These questions will relate back to key issues covered in the consent (e.g., "I can quit the study once I have started?" True_ False_) and will be modeled after the recommendations made by the NIH/U.S. Department of Health and Human Services. Incorrect answers will be reviewed with the participant and determination will be made regarding ability to understand English. For clinic-based or remote-based assessments, the women will receive cash, check, and/or gift cards (total equivalent to $270) for their participation ($5 gift card for taking the eligibility screener, $60 for baseline session, $20 for the first booster session, $20 for the second booster session, $15 for the first STI test, $30 for completing the first follow-up assessment, $15 dollars for the second STI test, $30 for completing the second follow-up assessment, $60 for completing the final follow-up assessment, and $15 for the final STI test during postpartum). For remote-based assessments, the women will receive the same compensation amount for each session, but payments will be delivered in the form of electronic gift cards or check. Women in the prenatal period were selected for two primary reasons: (a) interventions at this juncture may take advantage of a particularly salient point in a woman's life, in which she may be more open to considering behavior change; and (b) any positive change made has the possibility of a dual impact, on the woman's life as well as that of her infant. Of these 250 women, 125 women will be randomized to an intervention condition (Health Check-up for Expectant Moms, a brief motivational computer-delivered intervention) and 125 to a time, attention and information-matched control condition.

Because pregnant women are a special population, we will have a DSMB (see below). During baseline and follow-up assessments, urine samples or at-home vaginal swabs will be collected so sensitive nucleic acid amplification tests can be conducted to diagnose STIs of interest (i.e., chlamydia trachomatis, neisseria gonorrhea). When baseline and follow-up assessments are delivered remotely, the study team will direct Michigan Medicine participants to go to the clinic lab when they have scheduled prenatal visits with their provider, which requires no

physical contact with research staff. Regardless of this testing, we still plan to obtain consent to access STI results from the participant's prenatal and postpartum visits with their provider, by checking their medical chart on MiChart. The at-home STI testing kits are provided and analyzed by The Center for Innovative Diagnostics for Infectious Diseases at the Johns Hopkins University School of Medicine. They run an online outreach screening program for sexually transmitted infections (STIs) that was initiated in 2004. A kit is mailed to participants' homes with the materials needed to collect urogenital (vaginal) specimens for STI testing. Each kit includes the dry swabs needed for specimen collection, sample collection instructions, a biohazard bag for returning the specimens, a contact form, and a cardboard mailer for the specimen return (with prepaid postage). Upon return of the specimens by participants, JHU personnel log in the returned specimens, prepare them for testing, conduct the laboratory tests, verify results, and report results to the contracting organization (our research group) or directly to participants as requested. All samples obtained in the study will be used for research purposes only and will be discarded immediately upon completion of data entry and quality control procedures. While this STI testing will be performed primarily for research purposes, all results will be provided to study participants. Participants who test positive for any of the three STIs or with a recurrent STI will be referred for comprehensive STI care to their treating physician or health care provider at Michigan Medicine (if participant is a Michigan Medicine patient) to receive treatment to ensure cure. For Michigan Medicine patients, Dr. Mmeje (Co-I), study physician, will facilitate treatment or will refer patient to another Michigan Medicine physician who will provide treatment and counseling free-of-charge to the participant. For participants who test positive and are not Michigan Medicine patients, Dr. Mmeje will write a prescription for the appropriate treatment which will be available at a Michigan Medicine Pharmacy. Should they prefer to seek treatment elsewhere, research staff will do their best to help facilitate this process, and any cost of treatment outside of Michigan Medicine will be the responsibility of the participant. At the participants request, research staff will also confidentially communicate STI results to the participant's health care physician, asking the participant to sign a medical release of information for this purpose. Research staff will also follow-up with non-Michigan Medicine participants to confirm that treatment was receive and/or to help identify any obstacles to treatment (e.g., if patient needs additional treatment referrals, etc.). Because both chlamydia and gonorrhea are reportable to the Michigan Health Department, they will be reported to the Health Department as required by law. We will not include genital herpes as this is not standard of care and not in the clinical guidelines for STI screening set forth by the Centers for Disease Control and Prevention (CDC). Dr. Mmeje will determine on a case-by-case basis for consideration of HSV serologic tests based on clinical presentation (e.g., active lesion) or partner history.

Hair samples will also be obtained at specific follow-up assessments (see Table 1). In the case that a hair sample cannot be collected, we will attempt to collect a urine sample for drug testing in its place. The hair samples will be obtained by a trained RA and will corroborate self-report of drug use in the prior 3 months. The samples will be collected from cosmetically undetectable areas on the scalp. Samples will be labeled with the study ID only, sealed, and stored into a locked cabinet in the locked research offices. They will be sent monthly by tracked mail to the Psychemedics laboratory in Culver City, CA for analysis. Urine samples are collected by a trained RA at specific study visits, and will corroborate self-report of drug use in the prior 30 days. Results are read by the RA after 5 minutes, and then the sample is discarded. Results, reported by study ID, will be transferred by secure, encrypted electronic file and downloaded to a secure Michigan Medicine server. Participants enrolled after August 2022 will no longer submit hair samples.

Participants in this study are pregnant women; as such, are a federally protected population in research studies. Since the goal of this research is to develop effective interventions for pregnant women who use are at risk for STIs and substance use during pregnancy, research with pregnant women is necessary. This research meets all conditions for research involving pregnant women (45 CFR, Subpart B, Part 46.204).

Sources of Research Materials

Research materials obtained from the participants in this study will include self-report measures gathered by use of the iPad iOS (or online for remote visits), STI and hair sample testing.

12.2. Potential Risks

There is the potential for low risks to participants associated with this research project:

12.2.1.Breach of confidentiality: Assessment procedures could reveal sensitive information about participants' medical history and history of alcohol/drug use. Risk of breach of confidentiality is possible, though highly unlikely. Specifically, if a participant tells research staff that she is planning to harm herself or her children, the research staff will report this information to the appropriate agency, as required by law. Other than the need to report those incidents that are regulated by mandatory reporting laws (the reportable STIs in Michigan are Chlamydia and Gonorrhea), we feel that there is minimal risk to participants with regard to other breaches in their confidentiality.

12.2.2 Coercion: Coercion occurs when potential participants feel compelled to participate in research for reasons such as perceived demand or the availability of large sums of reimbursement. This can be particularly true when there is little benefit to the individual for their participant (not an issue in this study). In the present study, the inclusion of a protected population and protection from coercion is of the utmost importance.

12.2.3 Discomfort: Participation in the study may lead to psychological distress due to the sensitive nature of questions regarding disclosure of STI and/or alcohol/drug use during pregnancy the related negative social and psychological consequences. There are no physical risks conferred by urine testing for the sensitive nucleic acid amplification tests to be conducted to diagnose the STIs of interest. However, testing for any sexually transmitted disease can involve the psychological burden of finding out one has an infection that needs treatment or having a false positive test result.

Adequacy of Protection Against Risks

At each point of contact in the study, participants will be reminded of the alternative of not participating in the study (or once enrolled, to discontinue participation), and will be informed that their care at Michigan Medicine clinics, or any care within Michigan Medicine and in any other follow-up medical care at the clinics and/or Michigan Medicine will in no way be affected by their decision to participate or not to participate in the study. Moreover, we will provide referral information to all participants at each point of contact. Further procedures to minimize each of these risks are described below.

12.3. Protection Against Risk

We will take the following steps to protect against risks associated with this research project:

We will minimize the risk of breach of confidentiality. A Certificate of Confidentiality will be obtained from the National Institutes of Health prior to the commencement of research. The purpose of this certificate is to protect the identity of research subjects participating in studies that collect sensitive information. Potential participants will be informed that a Certificate of Confidentiality has been obtained for this project and that this certificate will protect the investigators from being forced to release any research data in which participants can be identified, even under court order or subpoena, although this protection is not absolute. Potential participants will be informed of the situations in which they may not be protected under the Certificate of Confidentiality. No information about participants will be released without their permission or where required by law. This approach has been successfully carried out by Drs. Tzilos Wernette and Zlotnick in previous studies involving women in the perinatal period.

Risk of social or legal consequences as a result of disclosure of STIs and/or alcohol/drug use during pregnancy will be dealt with in several ways. We will minimize the potential risks due to loss of confidentiality by strictly adhering to the guidelines for research outlined by the University of Michigan IRB, Michigan state law and the DHHS Federal Policy for the Protection of Human Subjects (45 CFR Part 46 Subpart D). As described in the previous section, there will be full informed consent prior to participation in the study (a two-part consent process). Participant data will be encrypted in transit between user and server. No identifying information will be entered into the CIAS software; the software will designate a unique participant code for each participant. Additionally, all forms with participant information will be marked with a code number and not with the participant's name. The link between the participant code number and name will be securely stored on the HIPAA-compliant database REDCap, which is administered and managed through the Michigan Institute for Clinical Research (MICHR) at the University of Michigan. This database will only be accessible by the Study Coordinator and study staff. Lastly, potential participants will

be informed of the situations in which they may not be protected under the Certificate of Confidentiality. Participants will also be informed about the risk of loss of confidentiality due to the STIs screens. No information about participants will be released without their permission or where required by law. Further, we have confirmed with Child Protective Services (CPS) of the Michigan Department of Health and Human Services, that they do not respond to reports of substance use during pregnancy unless the report is of a newborn infant with alcohol/drug in its system. Further, per the Michigan Department of Health and Human Services guidelines, there is no mandatory reporting of the disclosure of alcohol or drug use during the postpartum assessments.

Possible distress due to sensitive items will be noted clearly in the informed consent information sheet (for screening) and in the written informed consent form (for participants). All participants will be told that they can skip any question, test, or quit at any time if they become uncomfortable. To further address possible distress due to sensitive items, participants will be asked by the computer program if anything the computer has asked or done is making them feel upset right now. The computer program will notify the research team at completion of study if any participant answers yes to this question, in addition to notifying the research team if the participant has endorsed any items indicative of possible need/desire for further assistance. (Note that the computer program will not provide details regarding any answers, only that there is a need to follow-up with the participant verbally to evaluate the need for assistance). At a minimum, all participants indicating some distress will be given a list of referral options that will include information on how to contact a Michigan Medicine social worker. We will minimize the psychological burden associated with STI tests (i.e., trichomoniasis, chlamydia trachomatis, and neisseria gonorrhea).

Participants face the risk of increased psychological distress due to the research procedure of STI testing and distress due to a positive test for one of the selected STIs or having a false positive test result. All women will be informed that they do not need to be tested for the selected STIs, if it poses too much distress for them. They will be reminded that they can discontinue participation at any time. Moreover, as mentioned in the section above, clinical backup will be provided during all assessments and during the intervention phase of the study by a licensed clinician to help facilitate the stabilization and referral process for participants who decompensate during assessment procedures.

At any phase of the study (i.e., during the follow up assessments), participants who test positive for any of the three STIs or with a recurrent STI will be referred for comprehensive STI care to their treating physician or health care provider at Michigan Medicine (if participant is a Michigan Medicine patient). For Michigan Medicine patients, Dr. Mmeje (Co-I), study physician, will facilitate treatment according to the 2015 CDC STD Treatment Guidelines or will refer patient to another physician who will provide treatment and counseling free-of-charge to the participant. If the STI is reportable, it will be reported to the Health Department as required by law. Results of STI testing and any subsequent treatment or referrals will also be confidentially communicated to the participant's health care physician, if the participant requests this transfer of information. Participants will be asked to sign a medical release of information for this purpose. The study will arrange and cover transport costs for participants without transport who need these follow–up appointments for STI treatment. Research staff will assist participants in addressing any barriers to accessing treatment and will follow-up with participants to confirm that treatment was received. For participants who test positive and are not Michigan Medicine patients, Dr. Mmeje will write a prescription for the appropriate treatment which will be available at a Michigan Medicine Pharmacy. Should they prefer to seek treatment elsewhere, research staff will do their best to help facilitate this process, and any cost of treatment outside of Michigan Medicine will be the responsibility of the participant. At the participants request, research staff will also confidentially communicate STI results to the participant's health care physician, asking the participant to sign a medical release of information for this purpose. Research staff will also follow-up with non-Michigan Medicine participants to confirm that treatment was received and/or to help identify any obstacles to treatment (e.g., if patient needs additional treatment referrals, etc.).

12.4. Potential Benefits of the Proposed Research to the Subjects and Others

The potential risks associated with participation in this study appear to be mild to moderate. Although there is a risk for distress, the procedures proposed for monitoring distress should ensure that participants who require a higher level of care receive it. The potential benefits of study participation are great, and include STI testing and referral for treatment for STIs. Other benefits to women participating in this study include close monitoring of participants' STI risk,

alcohol/drug use, as well as participants' increased awareness of resources for STI and treatment providers for women with alcohol/drug difficulties. We will follow standard clinical practice as declared in the state of Michigan, and **all** women in both conditions will receive (1) a brochure specifically designed to facilitate reductions in drinking/drug use during pregnancy, and (2) a list of referrals, including sites for free STI testing and treatment as well as treatment for alcohol and drug use. Half of the participants will receive a brief intervention designed to increase the likelihood of self-change and/or obtaining resources for STI and alcohol/drug use. Moreover, participants are helping other childbearing women with STI risk through providing information that will improve STI risk prevention interventions for this population of women. Such an intervention, then, could potentially be presented to unprecedented numbers of persons (within primary care or other settings) in a way that is financially and logistically feasible, potentially leading to beneficial effects for large numbers of women as well as their infants. Thus, the potential benefits outweigh the potential risks of the study.