R01AA026596, Ondersma & Yonkers e-SBI for alcohol use in pregnancy trial

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Summary of Changes from Previous Version:

Version	Affected Section(s)	Summary of Revisions Made	Rationale
v.0.178	Not applicable	This is the first version of this protocol	
v.2.0	Investigator Signatures; Sections 1.1, 1.3, 4.1, 5.1, 5.2, 5.3, 5.4, 5.5, 6.3, 6.4, 7.3, 8.1, 8.2, 10.1.1.1, 10.1.1.2, 10.1.3, 10.1.4, 10.1.8, and 10.1.9; miscellaneous formatting corrections and revisions.	Changed from in-person recruitment to online recruitment for phase 1 and phase 2 (using community flyers and social media ads). Corrected number of participants from 336 to 384. Changed the participant age range from 18 and older to 18-35 years. Changed study duration for Phase 1 from 4 weeks to 6 weeks to include timing of fingernail specimen collection. Replaced a measure and updated list of measures and timepoints, replaced a lab specimen type, and moved the postpartum battery of assessments to 34 weeks gestation (eliminating in-person data collection at this time point for all participants), leaving a brief remote follow-up assessment at postpartum. Updated consenting procedures to include electronic consent, limits of anonymous screening for those who choose to participate in the full study, and gathering participant contact	Change to remote recruitment because of COVID-19.

		information. Updated inclusion/exclusion criteria relevant to remote recruitment. Revised compensation for remote data and fingernail specimen collection. Revised lost to follow-up procedures and removed clinic-related content. Revised timing and source of medical records information (now birth certificate/vital statistics data obtained through the state rather than hospital medical records). Updated project coordinator. Updated consenting procedures and use of e-consent and e-signature. Included use of Qualtrics for consent and survey collection, data storage in NIAAA$_{DA}$ (data archive), use of Ripple for data management, collection of state birth data (instead of EMR data), and changed location of linkage data storage. Miscellaneous minor updates to formatting of tables, spacing, and line breaks throughout the document. *(see detailed updates in section 10.4)*	
v.3.0	Title page, 1.3, 4.1, 5.5, 6.4, 7.3, 8.1, 10.1.1.2	Added National Clinical Trial (NCT) number. Revised Table 3b to remove unused measures and updated the overall timeline. Clarified efforts to aid blinding of study staff and updated unit of measure used for EtG detectability. Revised social media recruitment to include ads and posts. Clairfied applicability of reminder schedule for participant completion of study activities and its applicability to retention. Updated the frequency of text messages in Phase 1 (20 participants) from twice a week to once a day for 4 weeks.	Add NCT number to title page. Reduction of participant time burden, correct lab units of measurement, provide clarification where needed for procedures and study staff blinding efforts. Updated online recruitment description to include posts in order to fully describe the different types of study information dissemination on social media platforms. Increase frequency of text messages for feedback group to obtain sufficient feedback on content.
v.4.0	4.1, 5.5, 8.1, 10.1.1.2	Also updated the overall design to indicate additional efforts to reduce fraudulent enrollment (i.e., visible and invisible survey questions). Revised the online recruitment description to more broadly indicate online advertising for via multiple platforms that may appear as banners, text, images, video, and/or URL links to the study website, which further links to the screening survey. Examples of digital platforms include social	Additional fraud detection measures were added to aid early detection and improve data integrity. Advertisement policies and platform popularity change frequently. We have learned from initial online recruitment efforts and expert consultation that, successful online recruitment of difficult to find potential

		media such as Facebook, Instagram, and Twitter; search engines/Google AdWords; digital flyer and ad placement on organization websites such as local health departments and non-profits serving the target population, listservs, message boards, forums, and blog websites.	participants, requires flexible efforts to keep up with rapid changes in the digital world. Ads become "stale" on digital platforms very quickly if they are not updated or the general content becomes too familiar to users.
v.5.0	10.1.1.1, 10.1.1.2, 10.1.3, 10.1.4	Removed language referencing use of HIPAA form (sections 10.1.1.1, 10.1.1.2, 10.1.3), and revised language in section 10.1.3 to indicate that the authorization for the research team to obtain state birth outcome data will be included on the informed consent form. Updated language regarding statistical packages used for data (section 10.1.4).	A covered entity will no longer be used to obtain data for this study, thus HIPAA forms are not needed and reference to them has been removed. Language has also been revised in section 10.1.3 to indicate that authorization to obtain state birth outcome data will be included in the informed consent form. Language about statistical packages used for analysis was also updated to be more general, accounting for different software packages that may be used.
v.6.0	1.1, 1.3, 4.1, 6.1, 6.3, 6.4, 7.2, 8.1, 8.2, 10.1.3, 10.1.9.1	Revised study synopsis graphic to better reflect use of multimedia content in Baseline and Boosters (section 1.1). Revised Table 3b to include the CAT-MH in the baseline assessment (section 1.3). Updated language from "reside" to "planning to give birth" in the target states to more clearly reflect eligibility criteria (section 4.1). Revised language for sending boosters to include email as a possible send method (sections 4.1, 8.1). Revised language referring to testimonials to broaden the description, removing reference to "a mother" (section 6.1). Updated language referring to linking table storage to indicate use of a secure server (section 6.3). Revised delivery of follow-up surveys for data collection to indicate delivery via CIAS rather than Qualtrics (section 6.4). Clarified language regarding participant withdrawals and missed sessions (section 7.2). Added a new example of referral guide content to the safety assessment (section 8.2). Added a description of the CAT-MH technology	Revised study synopsis graphic to reflect changes to multimedia. Added the CAT-MH as a new assessment measure and moved follow-up surveys from Qualtrics to CIAS. Minor updates to language were made to improve consistency with prior protocol revisions (eligibility criteria, use of text and/or email, secure storage), broaden the description of testimonial content so that content is not limited to other mothers, and updated safety assessment section to reflect example of new referral guide resources.

		and access (section 10.1.3). Updated the description of computer security to remove the portion referring to computers being stored in offices (section 10.1.9.1).	
V.7.0	5.5, 10.1.1.2, 10.1.3, 10.1.8	Updated online advertisement strategies with targeted audience advertising and digital tags/code, such as Meta Pixel (section 5.5). Specified use of participant mailing addresses to mail nail collection kits (10.1.1.2 and 10.1.3). Described electronic storage of participant information in Ripple, (section 10.1.8).	Strategies to improve efficiency and accuracy of online recruitment efforts were recommended by advertising consultants. Language in other sections indicated that nail kits would be mailed to participants, but this information was not specified where uses of the mailing addresses were listed. Use of Ripple software for secure electronic study data storage, including the linkage list, will make study operations more efficient given that study staff have remained primarily remote. Participant management and protection is cumbersome without electronic access to this information.
V.8.0	1.1, 1.3, 4.1, 5.1, 5.3, 5.5, 8.1	Revised the description of geographic locations in which recruitment and enrollment will take place to indicate the "United States" (previously just Connecticut, Massachusetts, and Michigan; sections 1.1, 4.1, 5.1). Revised Table 3b and its associated notes to include the Birth Data Self-Report measure in the baseline assessment and clarify that state birth data will not be collected from all states (sections 1.3, 5.3, 8.1). Revised the description of recruitment and use of recruitment materials to include the use of smaller community handouts, plus recruitment assistance from organizations such as Wayturn or Qualtrics; sections 4.1, 5.5, 8.1).	Expanded recruitment geographic locations to the United States to improve recruitment rate. Added the Birth Data Self-Report as a new assessment measure. Expansion of recruitment locations to include the United States in whole makes obtaining state birth data from all states less feasible and adds to cost and paperwork burden. Research literature supports the use of self-report birth data and some state level data will still be gathered for comparison. Additional types of community recruitment resources not previously described (handouts) have been added to provide 'take away' materials, recruitment assistance from organizations that connect researchers and potential participants, as well as assist with

			advertising, is needed to improve recruitment rate.
V.9.0	4.1, 5.5	Revised the study recruitment strategies to include examples of how community flyers may be distributed and by whom (sections 4.1, 5.5).	Clarified activities by those distributing flyers to demonstrate that they are not engaged in human subjects research by distributing the flyers.
V.10.0	4.1, 5.5	Updated recruitment and retention strategies to include the use of Calendly for participant and potential participant self-scheduling as an option (sections 4.1, 5.5).	Added use of Calendly to facilitate appointment scheduling.
V.11.0	1.3, 4.1, 5.3, 6.4, 7.3, 8.1, 10.1.1.2, 10.1.3, 10.1.8, 10.1.9.1	Revised protocol in sections 1.3 (Table 3b notes), 4.1, 5.3, 6.4, 7.3, 10.1.1.2, 10.1.3, and 10.1.9.1 to indicate that biosamples (nail clippings) will no longer be collected and analyzed, per an IRB modification submitted on 9/19/24. Revised protocol in sections 1.3 (Table 3b notes), 5.3, 8.1, 10.1.3, 10.1.8, and 10.1.9.1 to indicate that state birth data will no longer be collected, per the same IRB modification submitted on 9/19/24 . Due to changes in feasibility, nail specimen collection and analysis, as well as state birth data collection have been discontinued, effective with the approval of the IRB modification submitted on 9/19/24. Participants who consented to submit biospecimens (nail clippings) and receive the associated incentive will still be offered the opportunity to submit them and receive the incentive; however, the specimens will not be sent to the external lab (USDTL) for analysis. Added additional language to indicate that ineligible people who wished to be informed of other studies may be provided with basic information such as study contact information and/or study link. Sections 4.1 and 10.1.3 of this protocol were updated for this purpose.	Due to changes in feasibility, nail specimen collection and analysis, as well as state birth data collection have been discontinued, effective upon the approval of the IRB modification submitted on 9/19/24. Per IRB consultation, we needed to indicate that basic information about other studies could be provided to ineligible people indicating that they wished to receive it.

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Statement of Compliance

The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

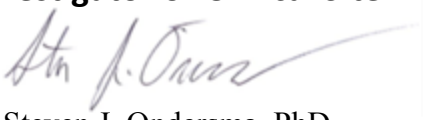
- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

INVESTIGATOR'S SIGNATURE

Principal Investigator or Clinical Site Investigator:

Signed:  Date: 10/15/2020

Name*: Steven J. Ondersma, PhD
Title*: Professor and Study Principal Investigator

Investigator Contact Information:

Affiliation*: Michigan State University
Address: 200 East 1st Street, Flint, MI 48502
Telephone: 313-444-9797
Email: Onders12@msu.edu

For multi-site studies, the protocol should be signed by the clinical site investigator who is responsible for the day to day study implementation at his/her specific clinical site:

Signed:  Date: 10/15/2020

Name: Kimberly A. Yonkers, MD
Title: Study Principal Investigator
Affiliation: Yale University

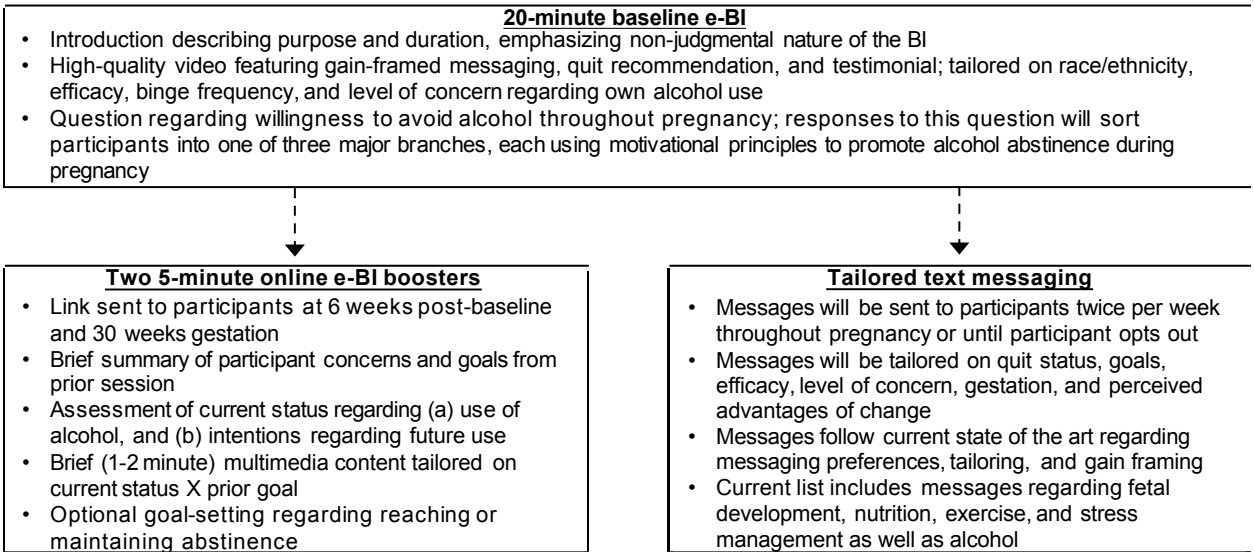
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	R01AA026596, Ondersma & Yonkers e-SBI for alcohol use in pregnancy trial	
Grant Number:	R01AA026596	
Study Description:	The purpose of this research study is to find out if pregnant women screening positive for alcohol risk like the brief alcohol intervention application that we have developed (called the MommyCheckup, which is a technology-delivered SBIRT, or e-SBIRT), and if it helps them to reduce alcohol use. We also wish to test whether e-SBIRT effects can be enhanced by booster sessions and/or tailored text messages.	
Objectives*:	Primary Objective:	To determine whether the MommyCheckup reduces alcohol use among pregnant women who screen positive for alcohol risk.
	Secondary Objectives:	To determine these effects can be enhanced by additional booster sessions via participants' own mobile devices, and/or by tailored text messaging (SMS).
Endpoints*:	Primary Endpoint:	There will be a main effect for MommyCheckup dose (i.e., amount of treatment), such that a single baseline session will result in greater 90-day alcohol abstinence that no brief intervention, and the single baseline session plus boosters will result in greater abstinence than the single session alone.
	Secondary Endpoints:	1)There will be a main effect for tailored SMS on 90-day abstinence; 2)Analyses will reveal an interaction effect, such that participants randomized to e-SBIRT+boosters+tailored text messaging will exhibit significantly greater 90-day alcohol abstinence than those randomized to e-SBIRT plus either supplement alone; and 3). There will be a main effect for -SBIRT on healthy birth outcome (defined as a full-term live birth (>36 weeks + 6 days) of normal birthweight (>2500 grams), with no days in neonatal intensive care).
Study Population:	Women 18-35 years of age who can communicate in English and who screen positive for alcohol risk.	
Phase* or Stage:	We will do a phase 1 feedback/trial preparation component with 20 women and then a phase 2 clinical trial/factorial trial with 384 women	

Description of Sites/Facilities Enrolling Participants: Participants for Phase 1 and Phase 2 of this study will be recruited online, and must be planning to give birth in the United States, but do not need to be associated with a particular site or facility.

Description of Study Intervention/ Experimental Manipulation: *The MommyCheckup baseline e-intervention plus booster sessions & text messages.*



Study Duration*: 52 months

Participant Duration: For the 20 women recruited in Phase 1, participation will last 6 weeks. For the 384 women recruited for Phase 2, participation will last from 0-20 weeks gestation to 4 weeks post-partum (a total of 24 to 44 weeks) (6 to 11 months).

1.2 SCHEMA

Table 2. *Factorial design and description of individual cells.*

	No BI	**Baseline BI**	**Baseline BI + Boosters**
SMS=No	No intervention	Baseline BI only	Baseline BI + Boosters
SMS=Yes	SMS only	Baseline BI + SMS	Baseline BI + Boosters + SMS

Note: N for each cell = 64 (total *N* = 384). Allocation to all cells is random, stratified by state and binge frequency.

1.3 SCHEDULE OF ACTIVITIES

Table 3a. *Measures and follow-up time points - feedback participants*

	Screening (up to 20 weeks gestation)	Baseline (≈ 12 wks gestation, end of 1st trimester)	Week 1 (post-Booster 1)	Week 3 (post-Booster 2)	Week 4	6 weeks post-baseline
Screener (general health)	X					
PROMIS Positive Affect	X					
PROMIS Sleep Satisfaction	X					
T-ACE alcohol screen	X					
Euroqol EQ-5D	X					
Demographics		X				
Preg. Intendedness		X				
Readiness rulers		X				
Satisfaction with Software		X	X	X		
Satisfaction with Text Msgs					X	
Qualitative Feedback					X	
Web analytics (booster & SMS completion)					X	
EtG (nail samples)						X

Table 3b. *Measures and follow-up time points - trial participants*

	Screening (up to 20 weeks gestation)	Baseline (≈ 12 wks gestation, end of 1st trimester)	4 weeks post baseline	27 weeks gestation (end 2nd trimester)	34 weeks gestation (end of 3rd trimester	4 weeks postpartum
Screening (general health)	X					
PROMIS Positive Affect	X					
PROMIS Sleep Satisfaction	X					
T-ACE alcohol screen	X					
Euroqol EQ-5D	X				X	X
AUTI		X	X	X	X	X
RFC		X	X	X	X	X
Demographics		X				
Preg. Intendedness		X				
AASE-12 (alc self-effica.)		X			X	
ASSIST (alc, marijuana, opioids)		X			X	
Alc Use in Social Group		X			X	
CES-D (depression)		X			X	
Prescription drug use		X			X	
Readiness rulers		X			X	
CAT-MH (mental health)		X				
Satisfaction with Software		X				
Satisfaction with Text Msgs					X	
Timeline follow-back					X	
Web analytics (booster & SMS completion)					X	
EtG (nail samples)					X	
Birth certificate data						X
Birth data self-report						X

Table 3a and 3b notes:

- All assessments will be completed remotely
- EtG will be determined using nail specimens, to be requested from participants at 36 weeks gestation (6 weeks post-baseline for Phase 1); note: per an IRB protocol modification submitted 9/19/2024, biospecimen collection and analysis has been discontinued.
- Window for baseline is 20 weeks or less gestation
- Window for follow-up assessments is 10 days around the assessment time-point, except for the 34-week follow-up window, which may be extended through the postpartum hospitalization
- Birth certificate data is available from each state approximately 6 months after the end of the birth year and will be requested in batches throughout the study (state birth data may be requested from one or more states, as determined by the study PI); note: per an IRB protocol modification submitted 9/19/2024, state birth data will no longer be collected.
- Self-report birth data will be collected instead of state birth certificate data

Overall timeline

Task Name	Year 1				Year 2				Year 3				Year 4				Year 5			
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Q17	Q18	Q19	Q20
Hire RA																				
Populate Ripple																				
Finalize Procedures																				
Booster/SMS feedback																				
Booster/SMS revisions																				
COVID-19 Transition																				
Trial recruitment																				
Trial follow-up																				
Data analysis																				
Manuscript write-up																				
Resource / Data sharing																				

2 INTRODUCTION

2.1 STUDY RATIONALE

Nearly 1 in 10 pregnant women in the U.S. report past-month alcohol use. Strong evidence connects prenatal alcohol exposure with a spectrum of conditions known as Fetal Alcohol Spectrum Disorders (FASDs), with consequences including reductions in brain volume, neurochemical and connectivity-related abnormalities, executive functioning deficits, and preterm birth. The burden of these consequences is disproportionately borne by African-Americans. Screening, Brief Intervention, and Referral for Treatment (SBIRT) has been recommended as a key intervention for pregnant women by the American College of Obstetricians & Gynecologists and the National Task Force on Fetal Alcohol Syndrome/Fetal Alcohol Effect. SBIRT has clear advantages, including (a) its proactive and universal approach; and (b) its use of a single motivational session that is brief enough to be acceptable to a high proportion of patients, even among those with little interest in treatment. Unfortunately, provider time, training, and fidelity are tremendous obstacles for SBIRT implementation, and implementation challenges are associated with reductions in effectiveness. Technology delivered SBIRT (e-SBIRT) may address these obstacles. e-SBIRT requires far less time and training on the part of providers, facilitates disclosure, and can be disseminated with perfect fidelity. In the first randomized trial of e-SBIRT with pregnant women, we developed a single-session e-SBIRT that received high satisfaction ratings and yielded odds ratios in the medium range for alcohol abstinence and a positive birth outcome. A subsequent trial with women in a reproductive health setting showed this approach to be equivalent to person delivered SBIRT and superior to enhanced usual care, at far less cost. This exciting potential, however, must be optimized and validated carefully prior to implementation. The proposed study will build upon the pilot trial by testing whether the intervention reduces alcohol use among pregnant women screening positive for alcohol risk. We will also use intervention optimization techniques (Multiphase Optimization Strategy, or MOST) to evaluate the extent to which intervention effects can be enhanced by adding subsequent booster sessions via participants' own mobile devices, and/or tailored text messaging. Specifically, we will (a) finalize booster session and text message content with iterative participant feedback, and (b) randomly assign pregnant women screening positive for alcohol risk (*N* = 384) to a 3 (no brief intervention; one session; or one session plus two boosters) X 2 (SMS present or not present) factorial trial. The primary analysis will test for dose response effects of the e-intervention on alcohol use during pregnancy. Secondary analyses will examine main and interaction effects of tailored text messaging, as well as intervention effects on birth outcomes. Exploratory analyses will examine theory-driven mediators and moderators of intervention efficacy, as well as intervention effects on additional drinking-related outcomes (e.g., days of binge use). If successful, the proposed study would yield an optimized, practical, and readily disseminated method for prevention of FASD.

2.2 BACKGROUND

Software platform. The e-SBIRT app was developed using the Computerized Intervention Authoring System (CIAS), an authoring tool that allows creation or editing of internet-delivered interventions without the need of a programmer. Interventions built using CIAS feature a synthetic text to speech

engine that reads all questions and speaks aloud to the participant (e.g. using headphones); synchronous interactivity, natural language reflections, branching logic, a clean user interface, and the ability to easily incorporate specific images, graphs, figures, text, or videos.

CIAS mobile is cross-platform compatible, meaning that it deploys readily on any device including those running the Android or Apple mobile operating systems. On Android devices, PCs, and Macs, CIAS mobile deploys as an HTML5 mobile web app with responsive design, meaning that it runs through the browser and automatically formats itself to the size of the screen being used. In contrast, because the Apple mobile operating system (iOS) does not allow automatic playing of sound files with each page load, we have developed a native app (available on the Apple app store) that "wraps" the web content in a way that allows the sound files to play automatically. This means that any content developed using CIAS is centralized and immediately available to all users, without relying on users to download each update. It also means that individual packages can be easily disseminated as a simple link (URL). For example, in future applied use, clinic staff can readily prompt patients to access a simple website through which they could complete the MommyCheckup. In the future, this same site could eventually screen for a range of other key risks such as illicit drug use, smoking, depression, partner violence, and others (many of which are already under development). Evidence-based brief interventions can then be provided as needed, allowing a single mobile web app to promote motivation and help-seeking in any number of key areas.

CIAS has been used with thousands of participants, many of whom have little to no prior experience using computers, and has consistently received extremely high satisfaction ratings (e.g., Naar-King et al., 2013; Ondersma et al., 2005, 2007, 2012). In the pilot trial of the baseline *MommyCheckup* e-SBIRT for alcohol use in pregnancy, using a 1 to 5 scale (where 1 = "not at all" and 5 = "very much"), mean scores ranged from 4.7 to 5.0 for ease of use, helpfulness, respectfulness, and whether it might help other moms like them (Ondersma et al., 2015). ***This is a crucial point:*** low SES participants have no difficulty with well-designed intervention software, and in fact are typically quite familiar with mobile app and web-based interfaces. Further, CIAS Mobile is additionally built to leverage powerful trends in technology ownership. The Pew Research Center (2016) reports that rates of smartphone ownership are rising every year, are higher among Blacks than Whites, and vary more with age than with income; for example, current data show that ***92% of adults age 18-34 own a smartphone.*** Further, 96% of Americans age 18-29 and 85% of pregnant minorities report having access to the internet (Gilbert et al., 2015; Perrin & Duggan, 2015). These data are consistent with our findings from a local sample of 185 low-income, African-American mothers receiving WIC nutrition assistance, in which ***85%*** reported owning a smartphone (McGoron, Hohentanner, Montgomery, Bocknek, & Ondersma, under review). ***At present,*** only a minority of even low-income pregnant women do not own a smartphone. Further, this proportion is shrinking constantly; smartphone ownership and internet access will soon be virtually ubiquitous. ***At present***—let alone in the near future—smartphones are an ideal platform for reaching non-treatment seeking women, and can reach far more of this population than alternative methods. The studies below provide evidence for the efficacy of CIAS-based brief interventions in a range of contexts, including during pregnancy.

Computer vs. therapist-delivered SBIRT for women seeking reproductive health care. Dr. Yonkers, along with Dr. Steve Martino, is PI of a recently completed NIDA-funded trial comparing person-delivered to a CIAS-based brief interventions for substance use among women seeking reproductive health services. Dr. Ondersma is a Co-Investigator on this study. Over a six-month follow-up, results of that trial show significant reductions in use of the primary substance for participants assigned to either the therapist-delivered or computer-delivered brief intervention, vs. an enhanced services as usual condition (Martino, Ondersma, Forray, Olmstead, Howell, Gilstad-Hayden, Kershaw, & Yonkers, 2017). Effect sizes were small but more than sufficient to support a public health impact (e.g., .30 at 3 months and .17 at 6 months, vs. .22 and .06, respectively, for the therapist-delivered condition), particularly given the relative ease of implementation and low cost of technology delivered approaches. With respect to cost, the e-intervention dominated both the enhanced usual care and therapist-delivered SBIRT conditions in terms of incremental cost effectiveness ratio.

Computer vs. counselor-delivered SBIRT in a general adult outpatient sample. Schwartz, Gryczynski, Mitchell, Gonzales, Moseley, Peterson, Ondersma, & O'Grady (2014) compared a CIAS-delivered brief intervention to a trained counselor-delivered brief intervention for substance use in a general adult outpatient setting. Schwartz et al. found equivalent results on overall substance use for the CIAS-based intervention at 3 months, but superior results for the software with respect to marijuana and cocaine (the therapist-delivered SBIRT showed no advantages on any specific substances). No overall or substance-specific group differences were detectable at 12 months (Gryczynski et al., 2015).

e-SBIRT for smoking in pregnancy. In this trial, 110 pregnant smokers were randomly assigned to either the CD-5As intervention, a highly modified contingency management intervention (CM-Lite), both interventions, or a control condition. There were significant main effects for the CD-5As intervention, which led to significant increases in abstinence and help-seeking. Participant satisfaction with the CD-5As intervention was high, ranging from 92.9% to 98.2% endorsement of the highest possible satisfaction for ease of use, respectfulness, and interest in using the software again (Ondersma, Svikis, Lam, et al., 2012). Ratings of participant state motivation taken immediately before and after completing CD-5As revealed increases on all items, including likelihood of quitting during pregnancy (d = .55, $p < .001$) and confidence in a successful quit attempt (d = .61, $p < .001$). Note that this study also used a factorial trial design, and although for tobacco rather than alcohol use, provides further evidence that an interactive and lifelike brief e-intervention can motivate behavior change as well as help-seeking among pregnant women.

Multi-site validation of screeners for detecting substance use in pregnancy. This CDC-funded study involves three sites, at New Haven (led by Dr. Yonkers, PI), Detroit (led by Dr. Ondersma), and Boston (led by Dr. Chang). Its goal is to identify best-practice evidence-based screening tools for use among pregnant women. The final sample included 1,198 pregnant women, 38% of whom were African-American and 15.5% of whom were Latina; 35% of participants had a Bachelor's degree or higher. A total of 15.4% of women from the New Haven site, and 23.8% from the Detroit site, reported having had 4 or more drinks at a time in the month before becoming pregnant. For this recent study, Dr. Yonkers

(PI) recruited 554 pregnant women from the proposed site in 14 months; Dr. Ondersma (Co-I) recruited 333 women in 12 months.

MommyCheckup e-SBIRT pilot for alcohol use in pregnancy. In a recently completed pilot trial evaluating a single-session e-SBIRT for alcohol use in pregnancy, Dr. Ondersma and colleagues found that participants rated a single-session mHealth intervention for alcohol use as highly acceptable (Pollick et al., 2013). Although this pilot trial was not powered to detect significant differences (*N* = 48), effect size estimates for abstinence and birth outcomes among this primarily African-American sample were in the medium range. In addition, participant ratings of ease of use, helpfulness, etc. ranged from 4.7 to 5.0 on a 1-5 scale, and 75% of participants said that they were more likely to change their alcohol use/maintain a preexisting quit goal because of the intervention (Ondersma et al., 2015). This pilot trial provides strong support for the present application.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

This study presents minimal risk to participants. Some risk may be present due to potential distress or guilt regarding the negative effects of alcohol use during pregnancy. Second, there is also some risk that a participant's responses might become known against their will. Third, because text messaging takes place via cellular service providers, it is an insecure technology that does not allow for encryption. Further, text messages on a participant's phone can potentially be seen by others with access to that phone.

2.3.2 KNOWN POTENTIAL BENEFITS

Five of six participants in this study (83.3%) will receive some form of intervention for alcohol use in pregnancy. These participants and their infants may benefit from the intervention. The other participants in this study will not receive any form of intervention and are not expected to derive any clear benefit.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

We believe that the risks to participants in this study are minimal, particularly given the positive nature of the intervention and the fact that alcohol is legal. We believe that the minor risks that are present are justified given the tremendous potential of this research to produce: (a) a method of connecting a large proportion of women who are at risk for alcohol use during pregnancy with intervention; and (b) data regarding a replicable, high-reach, and low-cost intervention that is designed specifically for pregnant women. This intervention could potentially be presented to large numbers of pregnant women in a way that is financially and logistically feasible.

This study presents minimal risk to participants. Some risk may be present due to potential distress or guilt regarding the negative effects of alcohol use during pregnancy. Second, there is also some risk that a participant's responses might become known against their will. Third, because text messaging takes

place via cellular service providers, it is an insecure technology that does not allow for encryption. Further, text messages on a participant's phone can potentially be seen by others with access to that phone.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
Primary			
To examine the effectiveness of e-SBIRT and e-SBIRT + boosters on alcohol use in pregnant women	90-day alcohol abstinence	There will be a dose-response association between abstinence and e-SBIRT frequency using a trend test.	
Secondary			
1)To examine the effectiveness of tailored text messaging 2)To examine the combined effectiveness of tailored text messaging + boosters 3)To examine the effectiveness of e-SBIRT on birth outcomes	1) 90-day alcohol abstinence 2) 90-day abstinence 3)healthy birth outcome defined as a full-term live birth (>36 weeks + 6 days) of normal birthweight (>2500 gms) and with no days in neonatal intensive care	1)There will be a main effect for tailored text messaging on 90-day abstinence using mixed-effects logistic regression 2)There will be an interaction effect of tailored text messaging and boosters using a factorial design-based mixed model 3)There will be a main effect of e-SBIRT on birth outcomes using mixed-effects logistic regression	
Tertiary/Exploratory			
To examine whether variables consistent with Self-Determination Theory, as well as subsequent treatment-seeking, mediate the association between intervention and abstinence	Potential moderators include severity, partner drinking, depression, intended pregnancy, and race/ethnicity	Exploratory analyses of moderators will use fixed-effects linear logistic regression models based on a mixed effects model, with each moderator being treated as fixed effect. Main effects will be tested first, and subsequent models will examine the incremental contribution of the treatment-by-moderator interaction.	

4 STUDY DESIGN

4.1 OVERALL DESIGN

There will be 20 participants in phase 1 and 384 participants in phase 2. Participants in both phases will be pregnant women age 18-35 years who score positive on a frequently used and well-validated screening tool for alcohol use risk in pregnancy (the T-ACE). We will also add an additional requirement of either drinking weekly or more in the past month, or having 4 or more drinks at a time at least monthly in the 12 months before becoming pregnant. To be eligible for the study, participants must also report mobile device ownership (e.g., smartphone), willingness to receive study-related text messages and to use their mobile device for study-related assessments and/or booster sessions, and being at 20 weeks gestation or less. Participants will be excluded if they are not planning to carry the pregnancy to term, or are unable to communicate in English. All participants must be planning to give birth in the United States. Completion of the baseline assessment is an enrollment criterion that is also necessary for inclusion.

Participants (Phase 1 and Phase 2) will be recruited via recruitment materials including community flyers and other handouts such as business card-sized mini flyers, as well as by online posts, flyers, and other advertising via multiple digital platforms that may appear as banners, text, images, video, and/or URL links to the study website, which further links to the screening survey. Examples of community locations where participants may be recruited include OB clinics and social service agencies. Staff at these locations may offer approved community flyers and handouts to women. For example, OB staff members may offer a flyer to all new OB intakes with or without a brief statement about it such as, "Michigan State University is conducting a study on pregnancy health. If you're interested, you can scan the QR code or go to the website to complete their brief screening survey." Such interactions would not involve answering questions about the study, screening, data collection, consenting, or acting as representatives of the investigator. Community flyers may also be made available to potential participants via bulletin boards, including electronic bulletin boards, be placed in intake packets (paper and/or electronic), and/or be placed on walls, tables, and countertops. Examples of digital platforms include social media such as Facebook, Instagram, and Twitter; search engines/Google AdWords; organization websites such as local health departments, listservs, message boards, forums, and blog websites likely to be visited by members of the target population. In addition, recruitment assistance may be obtained from organizations that assist with advertising, access to subject pools/panels and registries, and matching researchers to potential participants (e.g., Wayturn, Qualtrics). Advertising material specific to the Women's eHealth Study used by such organizations will be submitted to the Michigan State University IRB for approval before use. Recruitment materials will be targed based on study eligibility criteria and contain basic information, for example indicating that they are for a health-related study for women 18-35 years of age who can communicate in English. Some will indicate pregnancy and drinking eligibility criteria. Interested women meeting these criteria will be provided a website address, QR code, or link to a study website, where they will be provided with additional basic information about the study and link to the screening information sheet and screening survey via their own smartphone or tablet. Clicking on the link will first take them to the screening information sheet in

Qualtrics. Those who click "I agree" at the end of the information sheet, will then be offered the initial computer-directed screening survey. This survey will ask a range of questions so that the study's inclusion and exclusion criteria are not readily apparent (in order to limit fraud). Both the information sheet and screening survey will be accessible via their own smartphone or tablet.

The screening survey will be used to determine whether initial inclusion criteria have been met [(age, state of intended delivery of baby, pregnancy status, and alcohol risk (T-ACE positive and either drinking weekly or more in the past month, or having 4 or more drinks at a time at least monthly in the 12 months before becoming pregnant)]. Study staff will contact interested women who meet study inclusion criteria by phone in order to validate their eligibility (survey completed by a real person, who can communicate in English, has a working smartphone, is willing and able to receive text messages, and understands study requirements). The following strategies will also be implemented to reduce the possibility of fraudulent participation: 1) manual review of IP addresses to screen for duplicates, identify addresses of non-US origin, detect fraudulent completion (e.g., bots), 2) manual review of Qualtrics survey data to detect suspicious response times (e.g., completing the survey too quickly), unusual patterns in responses, respondent names, respondent email addresses, and patterned completion timestamps indicating that one person/bot is completing the survey repeatedly until eligible, 3) inclusion of a required open-ended narrative response to detect fraudulent completion, and 4) inclusion of invisible questions that only a bot could respond to, as well as visible nonsense questions directing the respondent to provide a particular answer. IP addresses will be deleted from the participant's screening survey data when no longer needed for fraudulent participation detection purposes. Only interested women who pass these screens and can be confirmed via the phone call will be enrolled. Ineligible people who have indicated that they wish to be informed of other studies may be provided with basic information, including study contact information and/or study link.

Additionally, to facilitate scheduling appointments with study staff members, Calendly, a scheduling platform, will be used to allow participants and potential participants to self-schedule at times when staff are available. Use of Calendly will not be required and appointments can still be scheduled with a staff member via phone, text, or email. Those who do choose to use Calendly will access it online and will be asked to provide their name and basic contact information (i.e., phone number and/or email) so that a staff member may contact them at the requested time.

The full trial consent will also be presented electronically and will proceed only if participants provide written informed consent via e-signature (using DocuSign, see section 10.1.3 of this protocol for additional information). Participants who meet all eligibility criteria and who provide consent will then be randomly assigned to a study condition during the baseline assessment. The staff member who enrolls the participant will not have access to the assigned condition/content at the time of consent and intial study condition assignment, which will aid in blinding study staff.

This trial includes varying levels of two separate interventions. The interactive and tailored baseline MommyCheckup single-session e-SBIRT was built on principles of Motivational Interviewing and Self-Determination Theory, and is presented to participants directly via their own electronic device (e.g.,

smartphone, tablet), which interacts with them through an animated talking narrator. The e-SBIRT booster sessions will be sent to participants as a text message and/or email that includes a link to the booster content. Participants will be sent these links on two occasions: 6 weeks following the baseline session, and at 30 weeks gestation. Participants assigned to the text messaging intervention will receive a test message at the conclusion of their baseline session, in order to confirm that the software has the correct cellphone number. These participants will then begin receiving text messages twice weekly until after the 34-week assessment, or until they text back "STOP" to end the messages.

Following the baseline session*, participants will be asked to complete follow-up assessments at 4 weeks post-baseline, at 27 weeks gestation, 34 weeks gestation, and at 4 weeks postpartum. In addition, all participants will be mailed a nail specimen collection kit at 36 weeks gestation asking them to provide nail clippings that will be analyzed for Ethyl Glucuronide (EtG). Fingernails will be collected at 36 weeks gestation, or toenails may be collected at 38 weeks gestation as an alternative to fingernails. (Nails will be gathered from Phase 1 participants at 6 weeks post-baseline for fingernails, or 8 weeks post-baseline for toenails, in order to assess the effectiveness of the specimen collection procedures). Nail types may not be mixed for a single specimen collection. Specimens from all available fingernails or toenails weighing 50-100 mg gathered at 36 weeks (fingernails) or 38 weeks (toenails) will allow for sufficient nail growth to capture EtG as evidence of alcohol use concentrated in the timeframe of approximately 20-34 weeks gestation, based on typical fingernail and toenail growth rates. Additionally, this timeframe will allow us to avoid detecting post-delivery alcohol use since it takes approximately two weeks for fingernails and four weeks for toenails to grow sufficiently for detectability. Participants will be reminded of the upcoming nail specimen collection at their 27-week and 34-week data collections, plus reminders will be included when the survey links are sent for these data collection timepoints. In the event of preterm birth, nail specimens will be requested immediately. The level of detectability for either nail type will be set at 8 pg/mg, which is the lower level of quantitation used for research (the standard level of detectability used for non-research testing is 20 pg/mg). (*Note: per an IRB protocol modification submitted 9/19/2024, biospecimen collection and analysis has been discontinued.)

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The primary significance of this study lies in the fact that, despite the clear public health threat posed by alcohol use in pregnancy, ***the vast majority of pregnant women with risky drinking neither seek treatment nor receive recommended screening and brief intervention, thus impeding efforts to prevent Fetal Alcohol Spectrum Disorders (FASD).*** This premise rests on extensive and highly rigorous evidence. **(1)** First, the many negative consequences associated with prenatal exposure to alcohol have been clearly demonstrated over the past four decades[1] [2]. **(2)** High-risk drinking among women increased by 57% between 2001-2002 and 2012-2013 [3]; representative national survey data show that **5.2%** of all pregnant women (and **12.8%** of those in the first trimester) report past-month binge drinking (Substance Abuse and Mental Health Services Administration, 2018). **(3)** Despite these clear dangers, most women who drink alcohol during pregnancy do not seek treatment. Nearly 90% of people who need treatment for alcohol use neither receive treatment, nor feel they need it [4]. This is also true of pregnant women: in 2014, a weighted estimate of 153,273 pregnant women needed treatment for

alcohol use, but only 1,087 (less than 1%) felt they needed it [5]. **(4)** This gap between need and service receipt has led to interest in universal screening with proactive brief interventions, which—notably—are not seen as a substitute for more intensive treatments. They are instead an alternative to receiving no help at all for the non-treatment seeking majority. Unfortunately, despite recommendations from the United States Preventive Services Task Force, the CDC, and the American College of Obstetricians & Gynecologists, only 10.6% of Obstetricians report using an evidence-based alcohol screener and only 40.1% refer at-risk women to treatment [6].

The significance of this study also rests on the potential for brief interventions to promote reductions in drinking and improved health outcomes, especially (in the present case) birth outcomes. This premise rests on a more mixed empirical base. SBIRT for alcohol use has repeatedly shown effects that are small but meaningful from a public health perspective [7]. However, SBIRT for alcohol use has not fared as well in implementation trials [8], in part because of implementation obstacles[9] . Further, SBIRT effects do not appear to extend to either treatment involvement or to drinking-related consequences [10](McCambridge & Saitz, 2017). Taking this literature into account, the most recent United States Preventive Services Task Force review[11] recommended use of SBIRT with pregnant women, but with a more cautious "B" rating. Importantly, the implementation challenges noted above are particularly problematic since SBIRT effects appear to be enhanced by provision of more than one brief session [7 12 13 14]). The fact that the majority of studies in this area test only a single brief session may limit our knowledge of SBIRT's true impact.

Finally, the significance of this study is also based on the promise of technology to address the weaknesses noted above. We argue that technology-delivered SBIRT will be far easier to scale up with fidelity; that it is more amenable to careful research that can identify key components or personalize messages based on participant characteristics; that it can facilitate disclosure, thus increasing the proportion of at-risk patients who are identified; and that it can readily support repeat contacts with patients, thus potentially increasing efficacy. Support for this premise is growing. **(1)** Meta-analyses have shown that technology delivered interventions [15 16] and text messaging [17] reduce alcohol use among non-pregnant samples. **(2)** Our randomized preliminary trial of e-SBIRT for alcohol use in pregnancy showed high feasibility and acceptability, with encouraging effect estimates [18]. **(3)** Disclosure appears higher in technology-based screening methods [19]. For example, in the pilot work supporting this application, 37.5% of new Obstetric intakes disclosed at least occasional alcohol use to their intake nurse, but 61.2% disclosed when asked the exact same question via the e-SBIRT app. **(4)** Text messaging may allow extended contact, leading to greater effects than might be seen with a single SBIRT session alone; but such a trial has not yet been conducted. Thus, although person-delivered, single session SBIRT has mixed support in the literature, we believe that technology shows great promise as a way to enhance SBIRT scalability and efficacy. ***The ultimate significance of this study rests on the importance of rigorously testing this premise.***

4.3 JUSTIFICATION FOR INTERVENTION

The proposed study will build upon the pilot trial by testing, in a fully powered multi-site factorial trial, whether the *MommyCheckup* reduces alcohol use among pregnant women screening positive for alcohol risk. We also seek to evaluate whether its effects can be enhanced by additional booster sessions via participants' own mobile devices, and/or by tailored text messaging (SMS). Consistent with the MOST approach [20], we propose a randomized factorial trial with the following aims:

1. **Evaluate e-SBIRT and SMS main effects as well as interactions in a factorial trial.** In this 3 (no brief intervention; one session; or one session plus two boosters) X 2 (SMS present vs. not present) randomized full factorial trial, 384 pregnant women who screen positive for alcohol risk will be randomly assigned to one of six cells representing all possible combinations of the two factors.

    1. ***Hypothesis 1 (primary):*** *There will be a main effect for* MommyCheckup *dose, such that a single baseline session will result in greater 90-day alcohol abstinence than no brief intervention, and the single baseline session plus boosters will result in greater abstinence than the single session alone.*

    2. ***Hypothesis 2 (secondary):*** *There will be a main effect for tailored SMS on 90-day abstinence.*

    3. ***Hypothesis 3 (secondary):*** *Analyses will reveal an interaction effect, such that participants randomized to e-SBIRT + boosters + plus tailored text messaging will exhibit significantly greater 90-day alcohol abstinence than those randomized to e-SBIRT plus either supplement alone.*

    4. ***Hypothesis 4 (secondary):*** *There will be a main effect for e-SBIRT on healthy birth outcome (defined as a full-term (>37 weeks) live birth of normal birthweight, with no days in neonatal intensive care).*

2. **Explore theory-driven mediators and moderators.** We will examine whether variables consistent with Self-Determination Theory, as well as subsequent treatment-seeking, mediate the association between intervention and abstinence. Potential efficacy moderators include severity, partner/friend/family drinking, depression, pregnancy intention, and race (especially in relation to birth outcomes).

Alcohol use in pregnancy is a significant threat to public health. If successful, the proposed study would yield an optimized, practical, and scalable method for prevention of FASD.

4.4 END-OF-STUDY DEFINITION

The end of the study is defined as completion of the 4 weeks postpartum assessment (or provision of the nail samples at 6 weeks post-baseline for feedback participants) as shown in the Schedule of Activities (SoA), **Section 1.3.**

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Inclusion criteria:

- Age 18-35 years
- Pregnant
- Self-report of alcohol risk (those who score positive on the T-ACE screen (Sokol, Martier, & Ager, 1989), and also report either drinking weekly or more in the past month, or having 4 or more drinks at a time at least monthly in the 12 months before becoming pregnant
- 20 weeks or less gestation
- Planning to give birth in the United States
- Owning a mobile device that they are willing to use to receive study-related text reminders and to complete online study activities including assessments/boosters
- Completion of baseline assessment (enrollment criterion)

5.2 EXCLUSION CRITERIA

Exclusion criteria:

- Not planning to carry the baby to term
- Unable to communicate in English

5.3 LIFESTYLE CONSIDERATIONS

During this study, participants are asked to:

- Receive some combination of an electronic brief intervention, two booster sessions, and/or tailored text messages—or no intervention at all—depending on randomization condition.
- Complete online assessments provided via texted link on their mobile device (e.g., smartphone or tablet) (provided via texted link)
- Provide fingernail or toenail clippings for EtG analysis (Note: per an IRB protocol modification submitted 9/19/2024, biospecimen collection and analysis has been discontinued)
- Provide permission for birth data to be collected from relevant state agencies (e.g., Connecticut Department of Public Health, Massachusetts Department of Public Health, Michigan

(Department of Health and Human Services); state birth data will not be collected from all states in which participation occurs and some participants will only be asked for self-report birth data (Note: per an IRB protocol modification submitted 9/19/2024, state birth data will no longer be collected.)

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to be screened but are not subsequently assigned to the study intervention or entered in the study. Rescreening is not allowed.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Participants will be recruited via recruitment materials including community flyers and other handouts such as business card-sized mini flyers, as well as by online posts, flyers, and other advertising via multiple digital platforms that may appear as banners, text, images, video, and/or URL links to the study website, which further links to the screening survey. Examples of community locations where participants may be recruited include OB clinics and social service agencies. Staff at these locations may offer approved community flyers and handouts to women. For example, OB staff members may offer a flyer to all new OB intakes with or without a brief statement about it such as, "Michigan State University is conducting a study on pregnancy health. If you're interested, you can scan the QR code or go to the website to complete their brief screening survey." Such interactions would not involve answering questions about the study, screening, data collection, consenting, or acting as representatives of the investigator. Community flyers may also be made available to potential participants via bulletin boards, including electronic bulletin boards, be placed in intake packets (paper and/or electronic), and/or be placed on walls, tables, and countertops. Examples of digital platforms include social media such as Facebook, Instagram, and Twitter; search engines/Google AdWords; organization websites such as local health departments, listservs, message boards, forums, and blog websites likely to be visited by members of the target population. In addition, recruitment assistance may be obtained from organizations that assist with advertising, access to subject pools/panels and registries, and matching researchers to potential participants (e.g., Wayturn, Qualtrics). Online advertisements and posts will implement well-established best practices following input from consultant Dr. Jaimee Heffner, who has conducted many trials using online recruitment. Strategies will include adequate compensation, clear communication, and phone contact to establish a personal relationship. Our prior studies have also enabled us to develop realistic and appropriate recruitment targets. Additionally, online advertisement strategies will include selective advertising to maximize recruitment of eligible women. Such strategies will include maximizing exposure of ads for target audiences based on tailored interests, demographics, and geographical location when options to do so are available. Advertising may also include use of digital tags/code, such as Meta Pixel, to improve recruitment effectiveness (no strategies tracking identifiable information about potential participants will be used). Finally, we note that our brevity, the user-friendly and private nature of the software, and participant input regarding the form of

compensation will all serve to help participants feel themselves to be valued and involved in a mother and baby-friendly activity.

Retention strategies will focus on regular communication through multiple means, particularly via text messaging (use of which is an inclusion criterion for this study, and which we have found to be greatly preferred by our participants—largely a younger cohort—over any other form of communication). Participants will receive Rewards Genius by Tango Card credit (hereafter "Rewards Genius credit" or "credit") as compensation for their time and inconvenience when completing study activities. They can use the credit to select a gift card from any one of several popular stores, including Amazon, CVS, and Walmart. Participants can also select a debit card that works like cash (but worth approximately $3.00 less than a store gift card, to account for debit card loading fees). We will also emphasize that the compensation credit will be issued once each follow-up assessment is completed. We have found that retention is further maximized by helping participants to feel appreciated for taking part in the voluntary research process, and by framing their participation in terms of the larger scientific endeavor aimed at benefits to their community. Importantly, the online assessments for this study can be completed at a time and place convenient to the participant.

Additionally, to facilitate scheduling appointments with study staff members, Calendly, a scheduling platform, will be used to allow participants and potential participants to self-schedule at times when staff are available. Use of Calendly will not be required and appointments can still be scheduled with a staff member via phone, text, or email. Those who do choose to use Calendly will access it online and will be asked to provide their name and basic contact information (i.e., phone number and/or email) so that a staff member may contact them at the requested time.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

The interactive and tailored baseline *MommyCheckup* single-session e-SBIRT was built on principles of Motivational Interviewing [21] and Self-Determination Theory [22], and seeks to facilitate self-change and/or treatment-seeking through a 20-minute interactive session, using techniques such as (a) education regarding alcohol-related pregnancy risks; (b) helping the participant evaluate the extent to which avoiding alcohol might align with deeply held values or goals; (c) personalized normed feedback regarding drinking frequency and costs; and (d) the option to choose a specific goal regarding drinking in pregnancy, with proactive problem-solving for those who set a goal (problem-solving options including temptations to drink because of cravings, a desire for positive feelings, or escape from negative feelings; and pressure from a partner or others in the participant's social network). Goals are optional driven by participants and so can include no change, abstinence, or reductions in alcohol use. It includes videos featuring physicians providing gain-framed information about alcohol use in pregnancy and testimonials regarding alcohol use during pregnancy.

6.1.2 ADMINISTRATION AND/OR DOSING

After completing the baseline assessments, those assigned to one of the e-SBIRT conditions will subsequently receive the 20-minute brief intervention. Participants assigned to the boosters will be texted a link to the booster session on two occasions: 6 weeks following the baseline session, and at 30 weeks gestation. Participants assigned to the text messaging intervention will receive a test message at the conclusion of their baseline session, in order to confirm that the software has the correct cell phone number. These participants will then begin receiving text messages twice weekly until they give birth, or until they text back "STOP" to end the messages. (As noted, the majority of our participants have unlimited messaging plans. The consent form will clearly state the possibility of charges for those on fee-based plans; costs, if present, will be a small fraction of overall compensation.)

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

N/A

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Participants will be randomized following a plan designed by biostatistician, Ms. Gilstad-Hayden, at baseline, into one of the six cells (1. General information control; 2. General information control + text messaging; 3. Baseline brief intervention; 4. Baseline brief intervention + text messages; 5. Baseline brief

intervention + two boosters; 6. Baseline brief intervention + 2 additional sessions + text messaging). Randomization will be stratified by state and by baseline alcohol frequency, using permuted block randomization to ensure roughly equal cells; stratified randomization will ensure balance of the treatment groups with respect to the combinations of the prognostic variable. In the subsequent statistical analysis we will first test if the stratification variables have a significant association (r>.30) with the primary outcome. If significant, we will include that correlated variable/s in the adjusted analysis of primary outcome in order to preserve power and estimate confounding effect, if any [23].

To enhance rigor and reproducibility, the biostatistician and data analyst will be blinded for all hypothesis-testing analyses by coding experimental condition with a non-identifying number, the table for which will be maintained on a secure server.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

Retention strategies will focus on regular communication through multiple means, particularly via text messaging (use of which is an inclusion criterion for this study, and which we have found to be greatly preferred by our participants—largely a younger cohort—over any other form of communication). Participants will receive Rewards Genius credit as compensation for their time and inconvenience when completing study activities. They can use the credit to select a gift card from any one of several popular stores, including Amazon, CVS, and Walmart. Participants can also select a debit card that works like cash (but worth approximately $3.00 less than a store gift card, to account for debit card loading fees). We will also emphasize that the compensation credit will be issued once each follow-up assessment is completed. We have found that retention is further maximized by helping participants to feel appreciated for taking part in the voluntary research process, and by framing their participation in terms of the larger scientific endeavor aimed at benefits to their community.

Online assessments (including baseline and follow-up assessments), brief intervention (BI), and boosters for this study can be completed at a time and place convenient to the participant. For all participants at all time points, we will send a text message and/or email with a link to the relevant study activity, plus reminders up to six times during a 10-day period surrounding the associated study activity timepoint in order to promote completion and give participants a chance to access public WiFi (such as at their prenatal clinic) if they prefer. These reminder messages will cease once the participant responds by completing the associated study activity or informing study staff that they no longer wish to participate in the study.

For phase 1 and phase 2, participants will receive a Rewards Genius credit of $40 following the completion of the baseline session, which includes a 20-minute interactive session. The total time expected to complete the baseline session (including the interactive session) is 40 minutes. Subsequent follow-ups are described by phase below. Additionally,* all participants in both phases will receive an additional $100 credit for providing nail clippings (plus a $20 bonus credit if clippings are provided within 1 week). Materials for collecting and returning clippings will be sent to participants at 36 weeks

gestation (at 6 weeks post-baseline for feedback participants). (*Note: per an IRB protocol modification submitted 9/19/2024, biospecimen collection and analysis has been discontinued for Phase 2.)

For phase 1, a 10-minute phone interview will be scheduled following 4 weeks of active study participation. Participants will receive a Rewards Genius credit in the amount of $20 following the completion of the phone interview. Additionally, participants will be asked to participate in two 5-minute booster sessions and receive text messages once a day for 4 weeks, which are interventions that are not compensated. The total time commitment for phase 1 study participation from enrollment through postpartum is approximately 1 hour and 45 minutes, including the consenting process.

For phase 2, online follow-ups (at 4 weeks post-baseline, 27 weeks gestation, 34 weeks gestation, and 4 weeks postpartum) will be delivered by text message and/or email with a link to the secure questionnaire (delivered via CIAS). The questionnaires for the first two follow-up timepoints and the postpartum follow-up timepoint are expected to take 5 minutes each to complete. In order to maximize completion, participants will receive a Rewards Genius credit of $20 following completion of the questionnaire sets at each of these three timepoints (maximum credit of $60 for completion of all three). The 34 weeks gestation assessment will be more intensive and is expected to take about 40 minutes to complete. For this crucial follow-up point, participants will receive a credit of $50 in compensation for completing the survey, plus a $20 bonus credit for completing it within 24 hours. Additionally, some participants will be randomized to participate in two 5-minute booster sessions and some will receive text messages twice a week from enrollment to 40 weeks (or the delivery of their baby, whichever is sooner, unless they tell us they want to discontinue receiving messages sooner). The text messages will be in addition to or instead of the booster sessions, depending on randomization. The text messages and boosters are interventions and, therefore, not compensated. The total time commitment for phase 2 study participation from enrollment through postpartum is approximately 2 - 2 ½ hours, depending on study condition randomization and including the consenting process.

6.5 CONCOMITANT THERAPY

For this protocol, participants may have recently participated in, or be actively be participating in, any additional form of pharmacological or behavioral treatment. We will have no restrictions based on treatment seeking either before or during participation in this study.

6.5.1 RESCUE THERAPY

No form of rescue therapy is applicable to this protocol.

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

N/A

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. When a participant discontinues using the e-SBIRT sessions or misses 1 or more sessions, but does not withdraw from the study, remaining study assessments will continue to be sent to the participant to be completed as indicated by the study protocol.

An investigator may discontinue a participant from the study for the following reasons:

- Lost-to-follow up; unable to contact subject (see section 7.3)
- Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation from the study will be recorded in the electronic case report form (eCRF).

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if she fails to complete the 34-week assessment before the end of her postpartum hospitalization and also does not provide nail clippings for EtG testing. (Note: per an IRB protocol modification submitted 9/19/2024, biospecimen collection and analysis has been discontinued.)

The following actions will be taken regarding required study assessments, brief intervention, and/or boosters:

- For all participants at all time points, we will send a text message and/or email with a link to the relevant study activity, plus reminders up to six times during a 10-day period surrounding the associated study activity timepoint in order to promote completion and give participants a chance to access public WiFi (such as at their prenatal clinic) if they prefer; these messages will cease once the participant responds.

- In addition, before a participant is deemed to have missed any given follow-up assessment, the investigator or designee will make every reasonable additional effort to regain contact with the participant including email, text, and telephone contact (depending upon patient preference). If a participant does not respond to email or text, we will attempt up to 3 telephone calls to the participant and any available collateral contacts. If necessary, a certified letter to the participant's last known mailing address or local equivalent methods. If the participant responds but does not respond again, this will reset the attempts to contact unless she has asked us not to contact her. These contact attempts will be documented in the participant's online study file.

- Although we will only continue trying to encourage a participant to complete each scheduled assessment within a 10-day window, we will again send invitations to complete the next regularly scheduled assessment. Participants will only be considered as having withdrawn if they indicate that they wish to do so.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

All assessments will be completed electronically. Participants will complete them using their own electronic device (smartphone or tablet).

Screening Procedures:
Screening participants will be recruited via recruitment materials including community flyers and other handouts such as business card-sized mini flyers, as well as by online posts, flyers, and other advertising via multiple digital platforms, and through organizations that provide recruitment assistance such as advertising, access to subject pools/panels and registries, and matching researchers to potential participants (see sections 4.1 and 5.5 for more detailed information). Those interested in completing screening will be directed to a study website, where they will be presented with a link to the electronic study information sheet and screening survey. Those who click "I agree" at the end of the information sheet, will be invited to complete the initial computer-directed screening survey via a link from the study website to a Qualtrics survey. Screening questionnaires include self-report of alcohol risk using the T-ACE alcohol screener and answering if they have been either: drinking weekly or more in the past month, or having 4 or more drinks at a time at least monthly in the 12 months before becoming pregnant. Additional follow-up screening will be conducted by phone to confirm eligibility before study enrollment.

Screening Assessments: All participants will complete the questionnaires listed in Table 3a and 3b (see Section 1.3).

Phase 1 Procedures (Feedback/Trial Preparation)**:**
A total of 20 eligible, consenting participants will be enrolled in Phase 1 and will complete the assessments listed in Table 3a (See Section 1.3) at the specified timepoints. They will be recruited in two waves of 10 participants each. After the first 10 participants have provided feedback, the PIs and consultants will review it and determine necessary changes to meet standards of acceptability, helpfulness, and ease of use (ratings of 4 and above on a 1 to 5 Likert scale). After changes are made, an additional 10 participants will be recruited if necessary and their feedback will inform any further changes necessary before recruitment for the Phase 2 trial.

During the Phase 1 baseline session, participants will:

- Be asked to answer questions about their health, use of alcohol, and pregnancy.
- Access questions via their own electronic device and also a video designed to help pregnant women reduce the amount of alcohol they drink during their pregnancy.
- Be asked to rate the ease of use, helpfulness, and respectfulness of the material.

Following the baseline session, Phase 1 participants will:

- be sent text messages once a day for the next 4 weeks.
- be texted links to participate in two additional 5 minute online sessions where they will watch an additional video and be asked about their use of alcohol and plans for future use in weeks 1 and 3 post-baseline.
- be asked to rate the ease of use, helpfulness, and respectfulness of the booster materials and text messages.
- be called by a research assistant in week 4 post-baseline, who will ask questions about their experience after completing the second booster session on their phones. This phone call is expected to last about 10 minutes.

Web analytics for the booster and text messages will be run for Phase 1 participants following week 4 of their participation.

We will also request fingernail or toenail specimens at 6 weeks post-baseline and participant contact information to enable follow-up completion will be requested at the time of consent.

Phase 2 Procedures (Clinical Trial / Factorial Trial):
A total of 384 eligible, consenting participants will be enrolled in Phase 2 and will complete the assessments listed in Table 3b (copied below) at the specified timepoints.

All participants, including controls, will get a referral guide to services, which will be sent by email or text link.

Phase 2 participants will be randomized into one of the six specific conditions: 1) General information control; 2) General information control + text messaging; 3) Baseline brief intervention; 4) Baseline brief intervention + text messaging; 5) Baseline brief intervention + two boosters; 6) Baseline brief intervention + 2 additional sessions + text messaging.

Phase 2 participants assigned to one of the e-SBIRT conditions will receive the 20-minute brief intervention during their baseline session. The baseline battery of assessment measures and all procedures are intentionally very brief in order to maximize the proportion who can complete them in one session; the full baseline session will take approximately 20 minutes for those in the two no-BI conditions, and 40 minutes for those in the remaining four cells.

Phase 2 participants assigned to the boosters will be texted and/or emailed a link to the booster session on two occasions: 6 weeks following the baseline session, and at 30 weeks gestation.

Phase 2 participants assigned to the text messaging intervention will receive a test message at the conclusion of their baseline session, in order to confirm that the software has the correct cell phone number. These participants will then begin receiving text messages twice weekly until they give birth, or until they text back "STOP" to end the messages.

Web analytics for the booster and text messages will be run for Phase 2 participants in applicable randomization groups following completion of the 4-weeks postpartum time-point.

Also following the 4-weeks postpartum time-point, birth data* may be requested from the state in which delivery occurred. Permission to gather birth outcomes data will be requested at the time of consent (note: availability of specific data may vary by state and collection date and is typically available 6 months after the end of the birth year). Participants will be asked to provide self-report birth data and this may be gathered in addition to state birth data. (Note: per an IRB protocol modification submitted 9/19/2024, state birth data will no longer be collected.)

8.2 SAFETY ASSESSMENTS

Regardless of condition, participants who report significantly increased alcohol use will be provided with contact information for a national referral service (e.g., United Way 2-1-1, National Maternal Mental Health Hotline) that provides services free or based on ability to pay. Significantly increased alcohol use will be determined by participant self-report. We will ask participants at each follow-up assessment if their alcohol use has significantly increased or if they have experienced any significant problems because of their alcohol use since their last contact with us. Because pregnant women now have priority status at treatment centers, women with uncontrolled use may be eligible for inpatient treatment. The PIs have extensive connections in their respective communities with respect to substance abuse treatment services for pregnant women. Trained study staff will contact at-risk participants by phone to provide this referral (Dr. Ondersma is a licensed clinical psychologist, and Dr. Yonkers is a Board-certified psychiatrist). We will use this same approach for participants showing high levels of depression on our risk screener [e.g., those scoring 12 or higher on the 10-item Centre for Epidemiological Studies Depression Scale (CES-D-10)].

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

This protocol uses the below definition of unanticipated problems that may involve risk to subjects or others (UPIRSO) provided by the Michigan State University (MSU) IRB to identify adverse events.

Researchers must promptly report all unanticipated problems that may involve risk to subjects or others (UPIRSO) to the MSU IRB. Any unanticipated problem that may involve risk to subjects or others that also constitutes an adverse event shall be reported, and will be reviewed. Only a small subset of adverse events occurring in human subjects participating in research will meet the definition of a UPIRSO.

UPIRSO's are incidents, experiences, or outcomes that are:

1. Unexpected (in terms of nature, severity or frequency) given the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB) approved research protocol and informed consent document and the characteristics of the subject population being studied; and
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, social, legal, or economic) than was previously known or recognized.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

An adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

1. Results in death;
2. Is life threatening (places the subject at immediate risk of death from the event as it occurred);
3. Requires inpatient hospitalization or prolongation of existing hospitalization;
4. Results in a persistent or significant disability/incapacity;
5. Results in a congenital anomaly/birth defect; or
6. Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

It should be noted that participants are expected to have a hospital admission for delivery.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

Adverse events will be graded according to the following guidelines:

- **Mild** - Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** - Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

- **Severe** - Events interrupt a participant's usual daily activity and may require systematic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All adverse events (AEs) will have their relationship to study procedures, including the intervention, assessed by an appropriately-trained clinician based on temporal relationship and his/her clinical judgement. The degree of certainty and causality will be graded using the categories below:

- **Related** - The AE is known to occur with the study procedures, there is a possibility that the study procedures caused the AE, or there is a temporal relationship between the study procedures and the event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study procedures and the AE.
- **Not Related** - There is not a reasonable possibility that the study procedures caused the event, there is no temporal relationship between the study procedures and the event onset, or an alternate etiology has been established.

8.3.3.3 EXPECTEDNESS

Given the population of study participants the following AEs are expected and will not recorded as part of the study. Examples of this include hospitalization for preterm labor resulting in delivery or not, or for delivery with or without complications. Both preterm labor and deliveries are expected events and adverse birth complications are not uncommon in this population.

Other common and expected events include delivery of infants who require admission to a neonatal intensive care or step-down unit. Again, this is a common event among women who use substances, including alcohol.

Women may live in poverty or confront violence. Sadly, this is not uncommon in this population so events such as assault, even if it culminates in hospitalization, would not be considered a severe AE related to the study conditions.

Women with at-risk alcohol use commonly have co-morbid problems with conditions such as depression and post-traumatic stress disorder. The presence of these conditions or symptoms of these conditions would not be attributable to this trial given that they are common outside of the trial and nothing in the trial promotes the onset or maintenance of these problems.

An example of an event related to the trial would be that the participant is upset by the questions that are asked of the participant. In this instance, every attempt will be made to discuss this with the patient and provide referral information care and treatment for their distress related to this.

Another example of an event related to the trial would be a breach of confidentiality. Although we will add measures to minimize this risk, should it occur we will take corrective measures with the study team member who is responsible and/or modify systems to decrease the likelihood of a breach.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study assessments and other study-related contacts with a participant, or upon review by a study monitor.

All AEs, not otherwise precluded per the protocol, will be captured on the appropriate electronic case report form (eCRF). Information to be collected includes event description, time of onset, study staff or PI's assessment of severity, relationship to study procedures (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring during the study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical or psychiatric condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

At the qualitative interview timepoint for Phase 1, and at each of the post-baseline follow-up timepoints for Phase 2, the investigator will inquire about the occurrence of AE/SAEs since the last assessment.

8.3.5 ADVERSE EVENT REPORTING

All AEs will be reported to the NIAAA project officer annually in the form of the Data Safety and Monitoring Board (DSMB) report. This DSMB report will include confirmation of adherence to this data and safety monitoring plan, a summary of any data or safety monitoring issues that took place since the last reporting period, a description of any changes to the research protocol or DSM plan that do or could potentially affect risk, and all new and continuing IRB approvals.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

SAEs and unanticipated events that are considered at least possibly related to the study will be reported to the Michigan State University (MSU) IRB (which will serve as the IRB of record for this study) as well as the NIAAA project officer within 48 hours, following the Office of Human Research Protection (OHRP) decision tree for adverse event reporting. Other SAEs and unanticipated events will be reported to the MSU IRB.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

N/A

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

N/A

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEMS REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) according to local policy and to Drs. Ondersma and Yonkers. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number
- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP

To satisfy the requirement for prompt reporting, UPs will be reported to Drs. Ondersma and Yonkers within 24 hours of becoming aware of the event. This will be compiled and provided to the DSMB at regularly scheduled meetings or within 24 hours if they are serious AEs.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

N/A

9 Statistical Considerations

9.1 STATISTICAL HYPOTHESES

Primary Efficacy Endpoint(s):

- There will be a dose-response association between e-SBIRT condition and abstinence, such that a single e-SBIRT session will result in greater 90-day alcohol abstinence than control, and multiple sessions will result in greater abstinence than the single session.

Secondary Efficacy Endpoint(s):

- There will be a main effect for tailored SMS on 90-day abstinence.
- Analyses will reveal an interaction effect, such that participants randomized to e-SBIRT + boosters + tailored SMS will exhibit significantly greater 90-day alcohol abstinence than those randomized to e-SBIRT plus either SMS or boosters alone.
- There will be a main effect for e-SBIRT on healthy birth outcome (full-term live birth of normal birthweight, with no days in NICU).

9.2 SAMPLE SIZE DETERMINATION

Our primary hypothesis predicts a dose-response association between e-SBIRT condition and abstinence, such that a single e-SBIRT session will result in greater 90-day alcohol abstinence than control, and multiple sessions will result in greater abstinence than the single session. As this hypothesis is based on a dose-response association between abstinence (binary) and e-SBIRT frequency, we plan to perform a trend test (a Mantel-extension type test, based on isotonic regression). Transformations will be used when distributional assumptions are not fulfilled for inferential tests. If a baseline variable is not balanced between groups and is correlated with the dependent variable (r >.30), we will include this variable as a covariate in subsequent analyses. This primary outcome analysis will use an alpha level of 0.05, and will be based on the principle of intention to treat [24].

For power analysis purposes we have assumed two dose-response scenarios: (a) a strictly monotonic dose–response relationship, and (b) a 'plateau' scenario in which the baseline session is superior to control, but the boosters do not add additional efficacy. Sample size calculations are based on Monte-Carlo simulation of over 2000 iterations for α=0.05 using the one side formulation of H1, and using Barlow and colleagues' one-sided chi-square test (χ^2) based on isotonic regression and the restricted likelihood ratio statistic. The chi-square statistic is the weighted average of difference between squared order restricted estimators with each of the cell proportions and their standard estimator, with k-degrees of freedom. For sample size, we considered small to medium values of the slope for monotonic

pattern (a) and small to medium values of step for the "plateau" pattern (b). Based on Mantel and χ^2 tests, a total sample of 300 (=3×N) is sufficient for 80% power. Our proposed sample size is 128 (384 total) per dose level, which is slightly increased in order to protect power against dropout of up to 15%, or other unforeseen threats.

9.3 POPULATIONS FOR ANALYSES

Primary analyses will use an intention-to-treat analysis population. If missing data are a significant issue, we will use sensitivity analyses and/or multiple imputation methods, depending upon the nature of the missing data. Datasets for sensitivity analyses include per-protocol, complete cases, missing imputed as positive outcome (e.g. retained in treatment) and/or missing imputed as negative outcome (e.g. not retained in treatment). Multiply imputed data sets will be based upon multiple imputation methods that are appropriate for clustered data and the quantity, type (missing completely at random, missing at random, not missing at random), and pattern (monotone, or non-monotone) of missing data. Our safety analysis data sets will include all enrolled patients.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

We will follow CONSORT guidelines for reporting the trial (www.consort-statement.org)(IR-5). Plans for data analysis will follow the major aims articulated in section 9.1. We will examine the distribution of variables through descriptive statistics and graphical tools to verify that model assumptions are met to assess relationships between variables. Data analyses will use the intent-to-treat principle and we will attempt to follow all participants regardless of their retention to treatment. Dropouts (MD-3) and completers will be compared on baseline characteristics. Missingness (MD-2,4) will be examined for quantity, type (missing completely at random versus missing at random or not missing at random), and pattern (monotone, or non-monotone). If missing data are a significant issue, we will use sensitivity analyses (MD-4) and multiple imputation methods that are appropriate for clustered data to fill in missing values in order to minimize bias, maximize available information and get accurate estimates of uncertainty. The possible impact of missing data on interpretation will be discussed in reports.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

- *There will be a dose-response association between e-SBIRT condition and abstinence, such that a single e-SBIRT session will result in greater 90-day alcohol abstinence than control, and multiple sessions will result in greater abstinence than the single session.* (The primary outcome of abstinence will be defined as no self-report of alcohol use in the past 90 days via Timeline FollowBack, and no evidence of use via EtG.) To establish the dose-response relationship indicating that higher frequency of sessions will result in greater abstinence, we will conduct a trend-test based on isotonic regression. Leurad and Benichou (2001) considered several methods for testing monotonic dose response relationships. We plan to test H_0: $p_1 = p_2 = p_3$ against H_1: $p_1 < p_2 < p_3$ with at least one strict inequality. For power analysis purposes we have

assumed two dose-response scenarios , which are (a) a strictly monotonic dose–response relationship, and (b) a 'plateau' situation with $p_1 < p_2 = p_3$. (Other possibilities exist but are not considered here for brevity.) Sample size is based on Monte-Carlo simulation of over 2000 iterations for α=0.05 using the one side formulation of H_1. Barlow and colleagues (Barlow, Bremner, & Brunk, 1972) developed a one-sided chi-square test ($\bar{\chi}^2$) based on isotonic regression and the restricted likelihood ratio statistic. The chi-square statistic is the weighted average of difference between squared order restricted estimators with each of the cell proportions and their standard estimator, with *k*-degrees of freedom (k=3 here). They suggested using the same statistic for a binary response (abstinence) and applying it to the observed proportions of cases. For sample size, we consider small to medium values of the slope for pattern (a) and small to medium values of step for pattern (b). Based on Mantel and χ^2 tests, a total sample of 330 (=3×N) is sufficient for 80% power. Our proposed sample size is 128 (384 total) per dose level, which is sufficient to protect power against dropout of up to 15% or other unforeseen threats.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

- *There will be a main effect for tailored SMS on 90-day abstinence.* ***H3:*** *Analyses will reveal an interaction effect, such that participants randomized to e-SBIRT + boosters + tailored SMS will exhibit significantly greater 90-day alcohol abstinence than those randomized to e-SBIRT plus either SMS or boosters alone.* Secondary hypotheses H2 and H3 will be analyzed using mixed-effects logistic regression (SAS PROC GLM/NLMIXED). The model will include SMS and e-SBIRT specific main effects and subject-specific random effects. We will also include an interaction term (fixed effect) between SMS and eSBIRT, as well as a site-specific fixed effect. Independent variables will include clinical and unbalanced demographical variables which may act as potential confounders. For H2 the model will be based on all participants (N=384), whereas H3 will be based on a reduced data set (N=224) as we are only interested in testing the interaction between the group e-SBIRT + boosters + tailored text vs. e-SBIRT plus either supplement alone. As is customary with RCTs, this proposal is only powered for the primary hypothesis; powering of other hypotheses would require alpha correction, which would severely inflate the sample size. The secondary hypotheses are intended to help us strengthen future validation studies regarding SMS-specific effects and their interaction with e-SBIRT. However, effect sizes in Table 5 can be applied to secondary hypotheses for information regarding the size effects that could be detected if those analyses were treated in isolation. ***H4:*** *There will be a main effect for e-SBIRT on healthy birth outcome (full-term live birth of normal birthweight, with no days in NICU).* The model for secondary for H4 will be similar to that of previous H2, but testing effects on birth outcome (binary; considered positive if a full-term live birth of normal birthweight, with no days in neonatal intensive care) instead of abstinence. The model will include other main and interaction effects as earlier. However, our primary interest will be to test the main effect due to e-SBIRT. Other Independent Variables will include treatment and the stratification variables (site and demographics), as well as other substance use. This hypothesis is also not powered, but will guide us in developing future studies and could guide design of

subsequent confirmatory trials. Following secondary analyses, exploratory regression analyses will also consider intervention effects on alternate/continuous outcomes such as number of drinks since the baseline randomization session, number of alcohol use days, and days of binge use.

9.4.4 SAFETY ANALYSES

N/A

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Differences between care models in baseline demographic and clinical characteristics will be assessed within matched pairs and overall using chi-square tests for categorical variables and t-tests for continuous variables, or their non-parametric counterparts if the assumption of normality is not met.

9.4.6 PLANNED INTERIM ANALYSES

N/A

9.4.7 SUB-GROUP ANALYSES

Theory-driven moderators will be explored as described in section 9.4.9.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will be listed by measure and timepoint in the dataset but will not be analyzed at the individual level.

9.4.9 EXPLORATORY ANALYSES

Exploration of theory-driven mediators and moderators. Mediator and moderator analysis will be exploratory and will guide design of subsequent confirmatory trials. *We will examine whether variables consistent with Self-Determination Theory, as well as subsequent treatment-seeking, mediate the association between intervention and abstinence (each measured at five time points).* Following [25], we will initially test for simple intervening variable effects using [26] joint significance of α and β test (where α and β refer to the two paths involved in mediation: intervention to mediator, and mediator to abstinence). Additional exploratory analyses will be considered as appropriate (e.g., depending on values of α and β, and on the need for an estimate of the magnitude of mediation). *Potential moderators include severity, partner drinking, depression, intended pregnancy, and race/ethnicity (the latter being of particular interest regarding birth outcomes).* Exploratory analyses of moderators will use fixed-effects linear logistic regression models based on a mixed effects model, with each moderator being treated as fixed effect. Main effects will be tested first, and subsequent models will examine the incremental contribution of the treatment-by-moderator interaction. To demonstrate moderation, there must be a treatment-by-moderator interaction with R^2 [3].05. In addition, treatment effect sizes will be presented for each level of the moderator. These analyses will provide critical data regarding (a) intervention efficacy among racial/ethnic and other subgroups; and (b) the extent to which Self-Determination Theory and/or treatment involvement can explain any behavior change associated with the intervention.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

During recruitment, an electronic screening information sheet will be presented to interested women when they click on an online ad to determine their eligibility for participation. Participants will view the information sheet on their own electronic device (e.g., smartphone, tablet, or computer) and click a button stating "I agree" prior to completing the screening portion of the study, including the follow-up phone call for eligibility verification if initial eligibility is met on the electronic screening survey. They will also be informed on the information sheet that they are agreeing to participate by answering the screening questions.

Eligible women who are interested in participating in the larger study will also be presented with an electronic informed consent form (e-consent) on their own electronic device. They will provide their agreement to participate by providing their e-signature on the consent document. E-consents and e-signatures will follow OHRP guidance and will comply with applicable state and institutional IRB regulations. A study staff member will review e-consents with participants by phone and will email a copy of the signed consent to the participant after the e-signatures are obtained.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Potential participants will access a study website directly by typing the study website address into their browser address bar, scanning a QR code, or by clicking on a link, which will direct them to a study website where they will be able to click a link to review an electronic screening information sheet. Those who click "I agree" after being presented with the information sheet will be presented with a brief electronic screener that includes general health questions, T-ACE, and questions about drinking during the 12 months prior to pregnancy as well as in the past month.

At the conclusion of the screening survey, those who meet study inclusion criteria will be asked if they wish to have a study staff member contact them to proceed with additional eligibility verification. Those who express interest will be asked to provide their name and contact information (phone number and email). A study staff member will manually review the screening data to check for fraudulent participation by: 1) manual review of IP addresses to screen for duplicates, identify addresses of non-US origin, detect fraudulent completion (e.g., bots), 2) manual review of Qualtrics survey data to detect suspicious response times (e.g., completing the survey too quickly), unusual patterns in responses, respondent names, respondent email addresses, and patterned completion timestamps indicating that

one person/bot is completing the survey repeatedly until eligible, 3) inclusion of a required open-ended narrative response to detect fraudulent completion, and 4) inclusion of invisible questions that only a bot could respond to, as well as visible nonsense questions directing the respondent to provide a particular answer. IP addresses will be deleted from the participant's screening survey data when no longer needed for fraudulent participation detection purposes. Those not flagged for fraudulent enrollment will be contacted by telephone to validate their eligibility (e.g., survey completed by a real person, who can communicate in English, has a working smartphone, is able to receive text messages, and understands study requirements). Only those who meet the final inclusion criteria based on the screening (T-ACE positive and either drinking weekly or more in the past month, or having 4 or more drinks at a time at least monthly in the 12 months before becoming pregnant) and validation procedures will be invited to participate the full trial (or Phase 1 feedback for the first 20 participants), and complete a separate written consent for that portion of the study. The entire screening process will take approximately 10 minutes.

Those interested in participating will be asked to complete an e-consent on their own electronic device. Procedures used will be compliant with OHRP guidance on electronic informed consent. Two-factor authentication will be required for the participant to access the consent form. This validation step has been included to ensure that the electronic signature on the consent is legally valid. Next, the study staff member will review the e-consent form with the potential participant by phone. Participants will be asked to provide overt, active consent by providing e-signatures to complete the informed consent process. Study staff will email electronically signed informed consents to the participant upon completion of the informed consent process. Participants will also be asked to provide their mailing address for any necessary follow-up by mail (e.g., for retention purposes), to send nail kits*, and to contact them for retention purposes if needed. The consenting process is expected to take approximately 30 minutes. (*Note: per an IRB protocol modification submitted 9/19/2024, biospecimen collection and analysis has been discontinued.)

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, and regulatory authorities. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance of study staff to the protocol (i.e., significant protocol violations)

- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency, sponsor, IRB, or other relevant regulatory or oversight bodies.

10.1.3 CONFIDENTIALITY AND PRIVACY

The informed consent information sheets for this study will be delivered via Qualtrics (information sheet for the screening portion of this study) and DocuSign (informed consent information sheet for the Phase 1 feedback and Phase 2 trial portions of the study). After reading the information sheet during screening via their own electronic device, participants will be asked to provide overt, active consent by clicking a button saying "I agree." Informed consent information sheets for Phases 1 and 2 of the study will be presented electronically to participants via DocuSign by a study staff member, who will authenticate the participant's identity using two-factor authentication, review the form by telephone while the participant simultaneously views it page-by-page, obtain the participant's initials on each page and e-signature to document consent, provide study staff member e-signature, and email a signed copy of the consent form to the participant.

A total of three separate informed consent information sheets will used for this study: (1) the first will obtain consent to participate in the electronically-delivered, ***anonymous*** eligibility screening for both the feedback and clinical trial phases; (2) for those who are eligible, a separate informed consent information sheet will be presented for participation in the intervention feedback phase of this study (n = 20); and (3) during the clinical trial phase, participants who meet all inclusion and exclusion criteria will be presented with an informed consent information sheet regarding the factorial trial (n = 384). These informed consent information sheets will carefully describe the study, time involvement, and potential risks, including possible guilt or inadvertent disclosure of responses. The two risks noted above (distress, and possible risk of answers becoming known) will be emphasized in the feedback and factorial trial information sheets. Participants who complete the anonymous screening will be asked to provide their name and contact information (phone and email address) so that a study staff member can contact them for eligibility verification and notification. They will also be informed that, if they provide contact information, their name will then be connected to their screening responses. This information will be included on the screening information sheet. Ineligible women will be asked if they wish to be contacted about other studies for which they may be eligible and, if so, they will be directed to a separate survey to provide their contact information so that it is not connected to their screening survey. They may be provided with such information, including study contact information and/or study link. Additionally, those who consent to participate in the full trial (Phases 1 and 2) will be asked to provide their mailing address so that we may send them a small gift (nail art) for collection of their nail samples*, the nail collection kit, and to contact them for retention purposes if needed. They will also be asked to provide

1-2 collateral contacts during the informed consent process. (*Note: per an IRB protocol modification submitted 9/19/2024, biospecimen collection and analysis has been discontinued.)

For participants who consent to participate in the factorial trial (Phase 2), language authorizing the release of participant state birth data for the research team to obtain birth outcome data will be included on the informed consent form.* This form will be presented electronically to participants at the time of consent by a study staff member, who will review the form by telephone, obtain the participant's signature, and email a signed copy to the participant. (*Note: per an IRB protocol modification submitted 9/19/2024, state birth data will no longer be collected.)

The use of computer technology for gathering self-report data enhances participant protection, in that participant data or group assignment will not be available to anyone in the participant's clinic or hospital setting. Even the research assistant is unable to access participant responses or information about group assignment. The web-based CIAS software in this study uses 256-bit AES encryption in order to protect data in transit from the participant's electronic device to the dedicated and secured server on which the software resides. CIAS resides on a HIPAA-compliant server with data encryption at rest, dual-factor authentication, malware protection, 24 x 7 monitoring of event notification, and a dedicated and fully managed firewall with active intrusion detection and prevention and access tracking. The data center itself (from Online Tech in Ann Arbor, Michigan) is independently audited annually for compliance with HIPAA (OCR HIPAA Audit Protocol), and features multiple levels of physical security plus two-factor authentication, N+1 redundancy across core network and security systems, natural gas and diesel generator backup, redundant network connections, and VLAN configuration to isolate individual instances. Further, data will be backed up regularly on highly secure Michigan State University servers with a multi-tier firewall system, active threat protection, and access tracking. In addition, web-based Qualtrics software in this study has similar data security features. Qualtrics uses 256-bit AES encryption to protect data in transit between the remote device (participant's electronic device). It uses Hypertext Transfer Protocol Secure (HTTPS) access and HTTP Strict Transport Security (HSTS). Data from surveys is processed by Qualtrics servers and stored on database servers. The Qualtrics platform supports Transport Layer Security (TLS) for all interaction with the platform. Additionally, Qualtrics uses dual level encryption keys, generating unique keys on each server or data storage volume, encrypting the software volt where they are stored, and rotating the keys when data storage volumes are rebuilt. Qualtrics conducts annual risk management assessment and its information security management system is International Standards Organization (ISO) and Federal Risk and Authorization Management Program (FedRAMP) compliant. Qualtrics also holds the following security certifications: ISO 27001Security Management Controls, FedRAMP Government Data Standards (moderate), Cyber Essentials Cyber Threat Protection, and HITRUST CSF v9.1. The physical building security features controlled access (biometrics and card reader), 24/7 on-site guards, and annual independent auditing of the data center and data systems. External vulnerability scans are performed nightly and internal vulnerability scans are performed weekly. Further, data will be backed up regularly on highly secure University servers with a multi-tier firewall system, active threat protection, and access tracking.

The Computerized Adaptive Testing-Mental Health (CAT-MH®) is an adaptive test of mental health status that rapidly provides summary scores that are highly predictive of DSM-5 diagnoses. CAT-MH® modules are accessed via the CIAS application and are protected by the same security and encryption used to gather other self-report data using CIAS technology. Individual log-ins are utilized by the research team to access the site. No PHI is communicated with the CAT-MH® system and the linkage between the participant and their CAT-MH® assessment results are solely accessible within the CIAS system.

The informed consent information sheets will explicitly acknowledge the limited security of text messages, both because they are not encrypted, and because the participant's phone itself may be accessible to others. Further, text messages—although tailored—will be written in a way that does not imply any details of the participant's alcohol use; that is, they will look like general advice that might be provided to any pregnant woman. Notably, text messaging for substance use and other health-related behaviors is becoming increasingly common, in the research literature as well as in the NIH portfolio. Further, the National Cancer Institute participated in development of, and actively promotes, a free and publicly available text-messaging service for smoking in pregnancy (SmokeFreeMom). Their approach to privacy and security issues is very similar to that taken in this study: participants are provided with information regarding the limited security of text messaging (SMS), and have the option to accept or decline based on that information. Finally, participants will be informed that they can end the text messaging plan at any time by texting back "STOP."

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data will be kept on secure servers until manuscripts are written. There are some identifiable data that cannot be destroyed without compromising our ability to write manuscripts (e.g., date of delivery cannot be deleted but will not be linked with other identifiable data). All other data will be stored in statistics software packages, such as SAS, and Excel and scrubbed of other information that may allow disclosure of maternal information. Additionally, the NIAAA data sharing agreement requires that de-identified data be uploaded to their data archive ($NIAAA_{DA}$), where it will be stored indefinitely. As with manuscript data, some identifiable data, such as date of delivery, cannot be deleted, but will not be linked with other identifiable data.
Genetic testing will not be performed.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Principal Investigator**	**Medical Monitor or Independent Safety Monitor**
Steven J. Ondersma, PhD, Professor, Department of Obstetrics & Gynecology Division of Public Health	Kimberly Yonkers, MD, Professor of Psychiatry, Epidemiology and of Obstetrics, Gynecology & Reproductive Sciences	NA
Michigan State University	Yale University	
200 East 1st Street	40 Temple Street, Suite 6B	

Flint, MI 48502	New Haven CT 06510	
(810) 600-5658	(203)764-6621	
	kimberly.yonkers@yale.edu	

10.1.6 SAFETY OVERSIGHT

A Data Safety and Monitoring Board (DSMB) will be responsible for monitoring this trial. A summary of the DSMB report will be provided to NIAAA annually along with the progress report. This report will include information regarding participant age, race/ethnicity, and socioeconomic status; expected vs. actual recruitment; follow-up rates, regulatory or quality issues that occurred during the past year, and a summary of any adverse events (whether AE or SAE) that took place in the past year (along with any resulting actions or changes to the protocol). The DSMB report to NIAAA will also include, when available, the results of any efficacy data analysis conducted.

10.1.7 CLINICAL MONITORING

N/A

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Data quality assurance will be facilitated in five ways. First, most data will be collected by direct participant entry using secure technology (CIAS and Qualtrics). This eliminates any intermediate data entry error. Further, CIAS takes multiple steps to achieve a high degree of security and reliability. For example, it uses 256-bit AES encryption in order to protect data in transit from the remote device to the dedicated and secured server on which the software resides. CIAS also resides on a HIPAA-compliant server with data encryption at rest, dual-factor authentication, malware protection, 24 x 7 monitoring of event notification, and a dedicated and fully managed firewall with active intrusion detection and prevention and access tracking. The data center itself is independently audited annually for compliance with HIPAA (OCR HIPAA Audit Protocol), and features multiple levels of physical security plus two-factor authentication, N+1 redundancy across core network and security systems, natural gas and diesel generator backup, redundant network connections, and VLAN configuration to isolate individual instances. In addition, web-based Qualtrics software in this study has similar data security features. Qualtrics uses 256-bit AES encryption to protect data in transit between the remote device (participant's electronic device). It uses Hypertext Transfer Protocol Secure (HTTPS) access and HTTP Strict Transport Security (HSTS). Data from surveys is processed by Qualtrics servers and stored on database servers. The Qualtrics platform supports Transport Layer Security (TLS) for all interaction with the platform. Additionally, Qualtrics uses dual level encryption keys, generating unique keys on each server or data storage volume, encrypting the software volt where they are stored, and rotating the keys when data storage volumes are rebuilt. Qualtrics conducts annual risk management assessment and its information security management system is International Standards Organization (ISO) and Federal Risk and Authorization Management Program (FedRAMP) compliant. Qualtrics also holds the following security certifications: ISO 27001Security Management Controls, FedRAMP Government Data Standards

(moderate), Cyber Essentials Cyber Threat Protection, and HITRUST CSF v9.1, The physical building security features controlled access (biometrics and card reader), 24/7 on-site guards, and annual independent auditing of the data center and data systems. External vulnerability scans are performed nightly and internal vulnerability scans are performed weekly. Further, data will be backed up regularly on highly secure Michigan State University servers with a multi-tier firewall system, active threat protection, and access tracking.

Second, other key outcomes will be collected via external sources and double-entered by research staff in order to ensure accuracy. These outcomes include record review (birth data* from the participant's state of residency, where obtained) and web analytics (completion of text messages and remote booster sessions; time spent in each booster session; etc.). (*Note: per an IRB protocol modification submitted 9/19/2024, state birth data will no longer be collected.)

Third, to further protect participants, full names and other identifying information (other than cellphone number) will not be entered into CIAS. Further, data files containing CIAS, state birth data*, or web analytics data will be stripped of all identifiers, including cellphone number. These files will be encrypted and stored on a secure University server with access only by Dr. Ondersma and his approved designees. (*Note: per an IRB protocol modification submitted 9/19/2024, state birth data will no longer be collected.)

Fourth, we will manage all regulatory and data management elements of this trial via the Ripple clinical trial management system, which facilitates regulatory compliance, participant safety, data management, and communication. Ripple will be be used to store identifiable participant information as well as a linkage list that includes participant names and study IDs.

Fifth, data quality will be monitored regularly by coordinator Ms. Todd, in concert with biostatistician Ms. Gilstad-Hayden. All data will be checked once per month for out of range values and other quality issues. We will also conduct regular reviews of participant records to ensure that consent is documented for all, that the correct informed consent information sheet was used, that eligibility checklists are present and complete for all participants; and that follow-ups (and booster session invitations) are taking place within the pre-established time frame.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data.

Data recorded in the electronic case report form (eCRF) derived from source documents will be consistent with the data recorded on the source documents.

Most data will be collected by direct participant entry using secure technology (CIAS and Qualtrics). This eliminates any intermediate data entry. Only the subject completing the interview can read the interview questions and her selected responses on the screen. Once entered, responses to the questions are disaggregated from the questions for purposes of data storage.

Participant data, including results of laboratory tests*, state birth data*, subject lists, progress through the study, and web analytics (completion of text messages and remote booster sessions; time spent in each booster session; etc.), will be coded by subject number only and will be stored on secure servers. All data entered via electronic devices by participants contain a subject ID uniquely assigned to this subject, and randomly generated by a computerized list. The data do not contain any identifiable personal health information. Computers are double password protected. In this way, sensitive data will not be linked with participant information that could lead to a breach of confidentiality. (*Note: per an IRB protocol modification submitted 9/19/2024, biospecimens and state birth data will no longer be collected.)

Access to computers is encrypted, password-protected and limited to research study staff

10.1.9.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 3 years. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of Drs. Ondersma & Yonkers. It is the responsibility of Drs. Ondersma & Yonkers to inform the investigators when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- Section 4.5 Compliance with Protocol, subsections 4.5.1, 4.5.2, and 4.5.3
- Section 5.1 Quality Assurance and Quality Control, subsection 5.1.1
- Section 5.20 Noncompliance, subsections 5.20.1, and 5.20.2.

It will be the responsibility of the site investigator to use continuous vigilance to identify and report deviations within [specify number] working days of identification of the protocol deviation, or within [specify number] working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to [specify NIH Institute or Center (IC)] Program Official and [specify Data Coordinating Center or sponsor]. Protocol deviations must be sent to the reviewing IRB per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Additionally, deidentified data from this study may be requested by other researchers indefinitely after the completion of the primary endpoint by contacting the NIAAA Data Archive ($NIAAA_{DA}$). Considerations for ensuring confidentiality of these shared data are described in Section 10.1.3.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the [specify NIH Institute or Center (IC)] has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS AND SPECIAL TERMS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance

QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
2.0	Investigator Signatures; Sections 1.1, 1.3, 4.1, 5.1, 5.2, 5.3, 5.4, 5.5, 6.3, 6.4, 7.3, 8.1, 8.2, 10.1.1.1, 10.1.1.2, 10.1.3, 10.1.4, 10.1.8, and 10.1.9; miscellaneous formatting corrections and revisions.	Updated pg. 5 to include co-investigator signature. 1.1: Revised study description for clarity; updated study population and "Description of Sites/Facilities" to include descriptors relevant to remote (online) recruitment; corrected number of participants from 336 to 384; changed the age range from 18 and older to 18-35 years; reformatted "Description of Study" table (previously partially cut off); and changed study duration for Phase 1 from 4 weeks to 6 weeks to include timing of fingernail specimen collection. 1.3: Updated "Schedule of Activities" table and associated notes to reflect changes to remote study participation, replacement of "MINI" measure with the "Brief DSM-5 AUD Assessment"; included measures not previously listed (prescription drug use, readiness rulers); change to specimens collected for EtG lab (fingernails instead of urine); and change to postpartum timepoint (now "34 weeks" instead of "end of 3rd trimester"). 4.1: Changed the age range from 18 and older to 18-35 years. Revised design from in-person recruitment and study participation to online recruitment for phase 1 and phase 2 (using community flyers and social media ads); included information on e-signatures for electronic consent; updated inclusion criteria; updated postpartum assessment to indicate that it is a "34-week assessment"; and procedures for collecting nail clippings for the EtG lab. 5.1: Changed the age range from 18 and older to 18-35 years. Added state of residence and completion of baseline assessment (for enrollment) to inclusion criteria. 5.2: Removed hospital delivery from a participating site from exclusion criteria. 5.3: Revised considerations to reflect remote study implementation (electronic brief intervention) and	Change to remote recruitment because of COVID-19.

		remove reference to clinic appointments; included provision of fingernail clippings and collection of birth data from state agencies instead of electronic medical records. 5.4: Eliminate option for individuals to be rescreened if they do not meet participation criteria (to limit fraudulent enrollment). 5.5: Changed gift from rattles and onesies to nail art; revised to include strategies for online recruitment (using community flyers and social media ads) based on best practices provided by consultant, Dr. Jaimee Heffner; changed compensation debit cards to Tango Cards with Reward Genius; removed postpartum assessment during post-delivery hospitalization. 6.3: Changed the name of the intervention session from “feedback” to “brief intervention”; changed randomization from conducted by CIAS computer program to conducted by statistician; and stratification by state instead of by site. 6.4: Revised description of the immediately postpartum data collection to a 34-week data collection, removed references to in-person data collection, and included remote (online) data collection procedures; specified that follow-up questionnaires will be completed via Qualtrics; revised the time to complete this data collection to 40 minutes; included revised compensation for the 34-week data collection and nail clippings, plus bonuses for timely completion of these two study activities; specified compensation for phase 1 participants; changed compensation debit cards to Tango Cards with Reward Genius; added protocol for sending assessment links and reminders. 7.3: Revised lost to follow-up procedures to focus on failure to complete the 34-week assessment rather than failure to attend at least 3 scheduled clinic visits and loss of contact. Removed clinic staff procedures for contacting participants. 8.1: Revised procedures for electronic screening and assessment in Phases 1 and 2; corrected the number of participants in Phase 1 (10 followed by feedback,	

		then another 10 after changes made based on feedback; previously indicated 5 at each site followed by another 5 at each site; the total number for Phase 1 remains the same at 20); replaced a measure, updated the list of assessment measures per timepoint, changed the postpartum assessment to 34 weeks gestation assessment; changed EtG lab from urine to fingernail or toenail clippings; and revised medical records checks to gathering of birth certificate information (or vital statistics information) from the state for all trial participants postpartum (Phase 2 participants); clarified that participants will be recruited online (using community flyers and social media ads) and will complete electronic consents; changed the name of the intervention session from "feedback" to "brief intervention." 8.2: Revised to reflect Lisa Todd as project coordinator. 10.1.1.1 – 10.1.1.2: Updated consent documentation and procedures to reflect online consenting processes, inclusion criteria, use of e-consent and e-signatures, and gathering contact information. 10.1.3: Updated to include limits of anonymous screening, e-consent and e-signature, use of Qualtrics, Qualtrics security, and revisions to remote and in-person procedures. 10.1.4: Included data storage in $NIAAA_{DA}$ (data archive) 10.1.8: Revised to include Qualtrics data quality assurance, reflect Ripple as study management software, reflect collection of state birth data, change location of linkage data storage, and reflect Ms. Todd as project coordinator. 10.1.9: Revised to change location of data storage, reflect use of Qualtrics, and reflect collection of state birth data. Miscellaneous: Minor updates to formatting of tables, spacing, and line breaks throughout the document to improve readability.	

v.3.0	3-11-2022	Title page: Added National Clinical Trial (NCT) number. 1.3: Revised Table 3b to remove unused measures and updated the overall timeline. 4.1: Clarified efforts to aid blinding of study staff and updated unit of measure used for EtG detectability. 4.1, 5.5, 8.1, and 10.1.1.2: Revised social media recruitment description to include ads and posts. 6.4 and 7.3: Clairfied applicability of reminder schedule for participant completion of study activities and its applicability to retention. 6.4 and 8.1: Updated the frequency of text messages in Phase 1 (20 participants) from twice a week to once a day for 4 weeks.	Reduction of participant time burden, correct lab units of measurement, provide clarification where needed for procedures and study staff blinding efforts, more fully describe the different types of study information dissemination social media platforms, increase frequency of text messages for feedback group to to obtain sufficient feedback on content.
v.4.0	4-28-2022	4.1 and 10.1.1.2: Updated the overall design to indicate additional efforts to reduce fraudulent enrollment (i.e., visible and invisible survey questions). 4.1, 5.5, and 8.1: Revised the online recruitment description to more broadly indicate online advertising for via multiple platforms that may appear as banners, text, images, video, and/or URL links to the study website, which further links to the screening survey. Examples of digital platforms include social media such as Facebook, Instagram, and Twitter; search engines/Google AdWords; digital flyer and ad placement on organization websites such as local health departments and non-profits serving the target population, listservs, message boards, forums, and blog websites.	Additional fraud detection measures were added to aid early detection and improve data integrity. Advertisement policies and platform popularity change frequently. We have learned from initial online recruitment efforts and expert consultation that, successful online recruitment of difficult to find potential participants, requires flexible efforts to keep up with rapid changes in the digital world. Ads become “stale” on digital platforms very quickly if they are not updated or the general content becomes too familiar to users.
V6.0	1.1, 1.3, 4.1, 6.1, 6.3, 6.4, 7.2, 8.1, 8.2, 10.1.3, 10.1.9.1	Revised study synopsis graphic to better reflect use of multimedia content in Baseline and Boosters (section 1.1). Revised Table 3b to include the CAT-MH in the baseline assessment (section 1.3). Updated language from “reside” to “planning to give birth” in the target states to more clearly reflect	Revised study synopsis graphic to reflect changes to multimedia. Added the CAT-MH as a new assessment measure and moved follow-up surveys

		eligibility criteria (section 4.1). Revised language for sending boosters to include email as a possible send method (sections 4.1, 8.1). Revised language referring to testimonials to broaden the description, removing reference to "a mother" (section 6.1). Updated language referring to linking table storage to indicate use of a secure server (section 6.3). Revised delivery of follow-up surveys for data collection to indicate delivery via CIAS rather than Qualtrics (section 6.4). Clarified language regarding participant withdrawals and missed sessions (section 7.2). Added a new example of referral guide content to the safety assessment (section 8.2). Added a description of the CAT-MH technology and access (section 10.1.3). Updated the description of computer security to remove the portion referring to computers being stored in offices (section 10.1.9.1).	from Qualtrics to CIAS. Minor updates to language were made to improve consistency with prior protocol revisions (eligibility criteria, use of text and/or email, secure storage), broaden the description of testimonial content so that content is not limited to other mothers, and updated safety assessment section to reflect example of new referral guide resources..
V.7.0	5.5, 10.1.1.2, 10.1.3, 10.1.8	Updated online advertisement strategies including targeted audience advertising and use of digital tags/code, such as Meta Pixel (section 5.5). Added additional language to specify use of participant mailing addresses to mail nail collection kits (10.1.1.2 and 10.1.3). Described electronic storage of participant information, including a separate participant linkage list in Ripple, a clinical trial management system (section 10.1.8).	Strategies to improve efficiency and accuracy of online recruitment efforts were recommended by advertising consultants. Language in other sections indicated that nail kits would be mailed to participants, but this information was not specified where uses of the mailing addresses were listed. Use of Ripple software for secure electronic study data storage, including the linkage list, will make study operations more efficient given that study staff have remained primarily remote. Participant management and protection is cumbersome without electronic access to this information.
V.8.0	1.1, 1.3, 4.1, 5.1, 5.3, 5.5, 8.1	Revised the description of geographic locations in which recruitment and enrollment will take place to indicate the "United States" (previously just Connecticut, Massachusetts, and Michigan; sections	Expansion of recruitment locations to include the United States in whole is expected to greatly

		1.1, 4.1, 5.1). Revised Table 3b and its associated notes to include the Birth Data Self-Report measure in the baseline assessment and clarify that state birth data will not be collected from all states (sections 1.3, 5.3, 8.1). Revised the description of recruitment and use of recruitment materials to include the use of smaller community handouts, plus recruitment assistance from organizations such as Wayturn or Qualtrics; sections 4.1, 5.5, 8.1).	improve recruitment rate, but makes obtaining state birth data from all states less feasible because it would add significant cost and paperwork burden. Research literature supports the use of self-report birth data and some state level data will still be gathered for comparison. Community recruitment resources not previously described (handouts) have been added to provide 'take away' materials, and ad/recruitment assistance from organizations that connect researchers and potential participants is needed to improve recruitment rate.
V.9.0	4.1, 5.5	Revised the study recruitment strategies to include examples of how community flyers may be distributed and by whom (sections 4.1, 5.5).	Clarified activities by those distributing flyers to demonstrate that they are not engaged in human subjects research by distributing the flyers.
V.10.0	4.1, 5.5	Updated recruitment and retention strategies to include the use of Calendly for participant and potential participant self-scheduling as an option (sections 4.1, 5.5).	Added use of Calendly to facilitate appointment scheduling.
V.11.0	1.3, 4.1, 5.3, 6.4, 7.3, 8.1, 10.1.1.2, 10.1.3, 10.1.8, 10.1.9.1	Revised protocol in sections 1.3 (Table 3b notes), 4.1, 5.3, 6.4, 7.3, 10.1.1.2, 10.1.3, and 10.1.9.1 to indicate that biosamples (nail clippings) will no longer be collected and analyzed, and revised protocol in sections 1.3 (Table 3b notes), 5.3, 8.1, 10.1.3, 10.1.8, and 10.1.9.1 to indicate that state birth data will no longer be collected, per an IRB modification submitted on 9/19/24 . Added language to indicate that ineligible people who wished to be informed of other studies may be provided with basic information such as study contact information and/or study link (sections 4.1, 10.1.3).	Due to changes in feasibility, nail specimen collection and analysis, as well as state birth data collection have been discontinued, effective upon the approval of the IRB modification submitted on 9/19/24. Language was needed per IRB consultation to indicate that basic information about other

			studies could be provided to ineligibles.

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