Computer-based SBIRT for marijuana use in pregnancy: Planning a Stage II trial

NIDA Grant Number: R34DA036788

Principal Investigator: Steven J. Ondersma, Ph.D.

NIDA Program Official: Jacqueline Lloyd

Draft or Version Number: 2

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STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the NIDCR Clinical Terms of Award. All personnel involved in the conduct of this study have completed human subject protection training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator or Clinical Site Investigator:

Signed: _____ Date: _____

Name: Steven J. Ondersma, Ph.D.

Title: Principal Investigator

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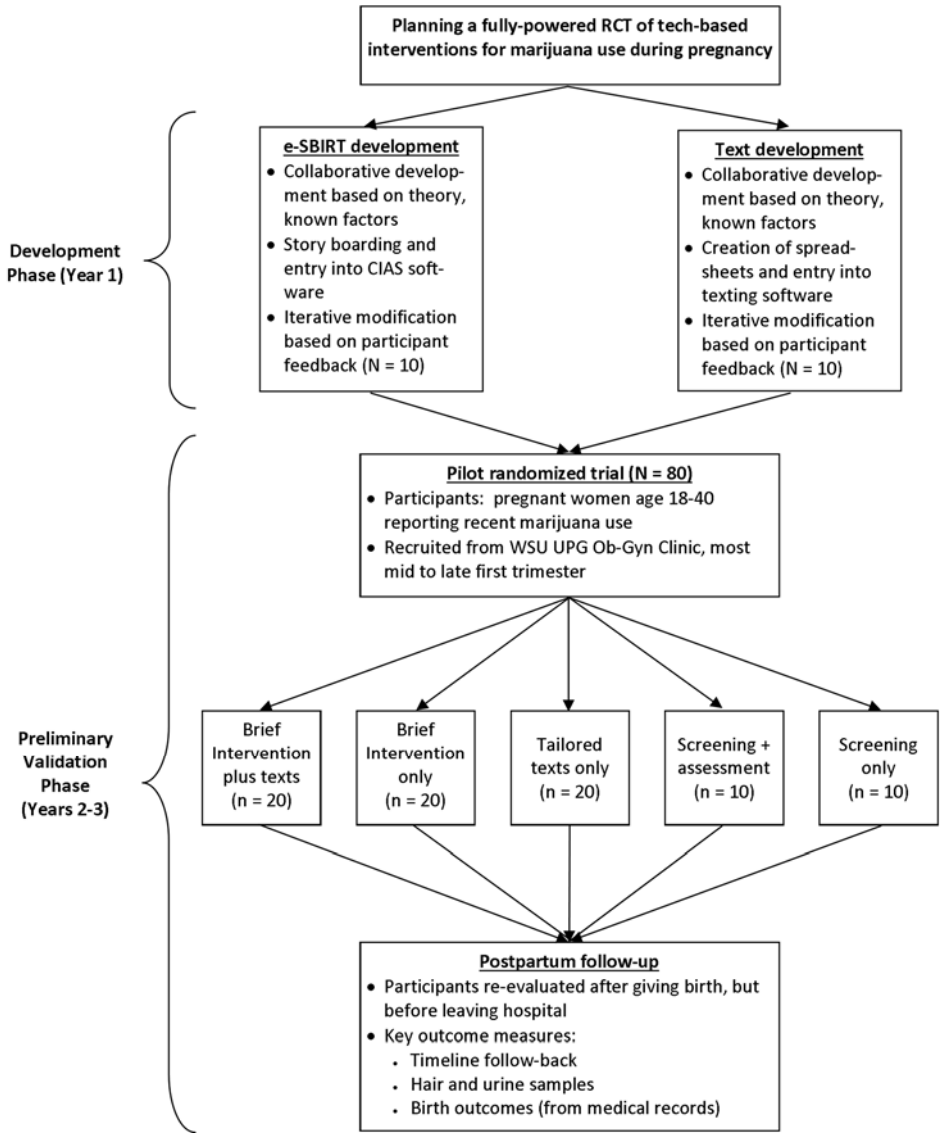
LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CONSORT	Consolidated Standards of Reporting Trials
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FWA	Federalwide Assurance
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IRB	Institutional Review Board
LC-MS/MS	Liquid Chromatography-Tandem Mass Spectrometry
MOP	Manual of Procedures
N	Number (typically refers to subjects)
NIDA	National Institute of Drug Abuse, NIH, DHHS
NIH	National Institutes of Health
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
UP	Unanticipated Problem

PROTOCOL SUMMARY

Title:	Computer-based SBIRT for marijuana use in pregnancy: Planning a Stage II trial
Objectives:	Primary: Co-primary outcomes will include confirmed 7- and 90-day period-prevalence abstinence, and days of marijuana use in the past 90 days. All primary outcomes will be based on participant report during the postpartum timeline follow-back interview; the 7- and 90-day dichotomous abstinence measures will be confirmed using results from urine and hair toxicological analysis, respectively. Evidence of use from either the timeline follow-back interview or toxicological testing will result in that participant being considered non-abstinent. Secondary: Secondary outcomes will include (a) birth outcomes from the Electronic Medical Record (EMR), including birth weight, length of hospitalization, and days in Neonatal Intensive Care; (b) help-seeking, particularly engagement in treatment services for marijuana use; (c) comparisons of the three intervention configurations (SBIRT only, texting only, or combined) to each other, rather than to the control condition; and (d) comparison of time-control and screen-only control participants.
Population:	Participants will be pregnant women age 18 to 40, 20 weeks or less gestation, seeking care at the WSU UPG or Thea Bowman prenatal care clinics.
Number of Sites:	Wayne State University
Description of Intervention:	This R34 clinical trial planning grant proposes the development and preliminary validation of two high-reach and mutually compatible technology-based interventions for marijuana use during pregnancy: an interactive computer-delivered brief intervention, and a tailored text messaging intervention.
Study Duration:	21 months
Subject Participation Duration:	20 – 36 weeks (From prenatal appointment before 20 weeks gestation until follow-up postpartum)
Estimated Time to Complete Enrollment:	21 months

Schematic of Study Design:



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1 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 Backgrou nd Information

The public health impact of marijuana is substantial by any measure, particularly with respect to its use during pregnancy. This is true for at least three reasons. *First*, marijuana is by far the most commonly used illicit drug in the U.S., and marijuana use disorders alone are as prevalent as disorders related to all other drugs combined, including pain relievers (SAHMSA, 2012). This relative prevalence extends to pregnancy: a total of 4.1% of all pregnant women *(7.0% of African-American women)* report use of marijuana in the past month, as opposed to 1.3% for all other illicit drugs combined (SAHMSA, 2012); this is also markedly higher than the rate of binge alcohol use in the past month (2.6%) among pregnant women. *Second*, although non-problem use is common, many marijuana users do experience social and health consequences as a result of their use. For example, in a previous sample of 112 post-partum women who reported any marijuana use prior to pregnancy, 85.7% met World Health Organization/ASSIST screener (Newcombe, Humeniuk, Hallet, & Ali, 2003) criteria for a brief intervention; 71.7% reported daily or almost daily desire to use marijuana, 40.2% reported having a friend or family member express concern about their level of use, and 60.8% admitted to previously trying and failing to control their marijuana use. Frequent marijuana use may also be associated with compromised pulmonary functioning (Tetrault et al., 2007), greater tar deposits than from cigarettes (Mehra, Moore, Crothers, Tetrault, & Fiellin, 2006), increased likelihood/exacerbations of schizophrenia (e.g., Moore et al., 2007), and impairments in executive cognitive functioning (Crean, Crane, & Mason, 2011). *Third*, marijuana use during pregnancy—although inconsistently associated with poor birth outcomes—has been associated with a range of negative neurobehavioral effects (e.g., Minnes, Lang, & Singer, 2011). In addition, ongoing parental use of marijuana after childbirth has also been associated with negative child outcomes, such as increased risk of behavior problems (Chatterji & Markowitz, 2001) and increased marijuana use disorder symptoms at age 18-20 (Buu et al., 2009). *Marijuana use in pregnancy cannot be safely ignored.*

Marijuana use in pregnancy is substantially under-studied. Despite being by far the most prevalent illicit drug of abuse among pregnant women (Substance Abuse and Mental Health Services Administration, 2012), and despite its now eclipsing tobacco use in at least one sample of pregnant women (Beatty, Svikis, & Ondersma, 2012), there are currently no randomized trials evaluating interventions for marijuana use in this crucial population. This is unacceptable: although evaluated in fewer studies, research suggests that the long-term consequences of prenatal marijuana exposure may be similar to that of other drugs of abuse, with evidence for subtle but meaningful long-term effects on IQ (Goldschmidt, Richardson, Willford, & Day, 2008), academic achievement (Goldschmidt, Richardson, Willford, Severtson, & Day, 2012), response inhibition (Smith, Fried, Hogan, & Cameron, 2004), delinquency (Day, Leech, & Goldschmidt, 2011), and later substance use (Porath & Fried, 2005). Further, unique among all

substances of abuse, marijuana is vigorously promoted as safe by a visible grassroots community without a counterbalancing public health message (Beatty et al., 2012). There is tremendous need for an evidence-based response in this area.

Proactive technology-based interventions may be an ideal first element in a comprehensive response to substance use in pregnancy. Often deployed in primary care settings, such interventions have been proven efficacious (for example, see systematic reviews and meta-analyses by Portnoy, Scott-Sheldon, Johnson, & Carey, 2008; Riper et al., 2009; Rooke, Thorsteinsson, Karpin, Copeland, & Allsop, 2010). Technology-delivered interventions are also uniquely applicable with non-treatment-seeking populations, who may refuse extended treatment but accept a minimal, opportunistic intervention. Their privacy, ease of use, and ability to work independently of medical staff give them very high potential reach, and thus the potential for a substantial population impact. Their potential is further enhanced by the relative ease of implementation in the community.

Study aims are to develop theory-based eSBIRT and text messaging interventions with expert and participant feedback; to randomize 80 pregnant women to eSBIRT, text messaging, combined, or control conditions (n = 20 each, with the control condition being further split between time control and screen-only); and to conduct postpartum follow-up to measure marijuana use and other secondary outcomes.

1.2 Rationale

Importantly, results from our lab (the Parent Health Lab) of similar approaches with tobacco use during pregnancy (DA021668) and prenatal alcohol use (AA020056) have been encouraging. This lends support to the feasibility of the present application, as well as to the larger goal of this line of research: the establishment of a single software package that can flexibly and effectively address multiple substances. Additionally, behavioral science appears to have reached a point in the technology adoption life cycle in which early efforts have begun to give way to systematic reviews that can drive the field forward in important ways.

This R34 clinical trial planning grant therefore proposes the development and preliminary validation of two high-reach and mutually compatible technology-based interventions for marijuana use during pregnancy. The first, a theory-based, synchronous, and highly interactive computer-delivered brief intervention, will be based on an emerging knowledge base regarding key elements of efficacious technology-delivered interventions. The second intervention, a series of tailored text messages, will build on the rich literature regarding key tailoring elements. These interventions will be developed and refined with input from pregnant women who report active use of marijuana, as well as from health care providers. They will subsequently be tested—alone and in combination—in a pilot randomized trial involving 80 women actively using marijuana during pregnancy. This Stage IA and IB pilot work would set the stage for a

confirmatory Stage II trial. It would also produce the first high-reach brief interventions for marijuana use during pregnancy.

1.3 Potential Risks and Benefits

1.3.1 Potential Risks

The primary potential risk of this type of research involves legal/child protective services repercussions due to drug (marijuana) use during pregnancy. Some additional risk may be present due to potential distress regarding evaluation of multiple sensitive areas.

We believe that the risks to participants in this study are minimal, particularly given the positive nature of the intervention and the plan to seek a Federal Certificate of Confidentiality. We believe that the minor risks that are present are justified given the tremendous potential of this research to produce: (a) a method of identifying a large proportion of women using marijuana during pregnancy; and (b) two replicable, high-reach, and low-cost interventions that are designed for pregnant women. These interventions, then, could potentially be presented to large numbers of pregnant women in a way that is financially and logistically feasible

1.3.2 Potential Benefits

Just over half of participants in this study will receive one or more brief, positive interventions designed to promote reductions in marijuana use during 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 OBJECTIVES

2.1 Study Objectives/Outcome Measures

2.1.1 Primary

Co-primary outcomes will include confirmed 7- and 90-day period-prevalence abstinence, and days of marijuana use in the past 90 days. All primary outcomes will be based on participant report during the postpartum timeline follow-back interview; the 7- and 90-day dichotomous abstinence measures will be confirmed using results from urine and hair toxicological analysis, respectively. Evidence of use from either the timeline follow-back interview or toxicological testing will result in that participant being considered non-abstinent.

2.1.2 Second ary

Secondary outcomes will include (a) birth outcomes from the Electronic Medical Record (EMR), including birth weight, length of hospitalization, and days in Neonatal Intensive Care; (b) help-seeking, particularly engagement in treatment services for marijuana use; (c) comparisons of the three intervention configurations (SBIRT only, texting only, or combined) to each other, rather than to the control condition; and (d) comparison of time-control and screen-only control participants.

3 STUDY DESIGN

The first year of this project will be devoted to development of the eSBIRT and text messaging interventions, with refinement following feedback from participants meeting the same inclusion and exclusion criteria as the proposed pilot trial (e.g., pregnant and reporting active marijuana use). All activities in this phase will be the result of close collaboration between the PI and the rest of the investigative team, particularly Dr. Resnicow, Dr. Svikis, and Ms. Konkel (Consultants from University of Michigan and Virginia Commonwealth University). The investigative team will meet regularly with the PI, both individually and as a group via Skype or web conferencing using "GoToMeeting" software to facilitate screen sharing.

Overview

We will initiate the *N* = 80 pilot randomized trial following development and modification in response to feedback, after participant ratings have exceeded our a priori criteria for acceptability. The primary goal of this phase will be to pilot test the interventions, alone and in combination, to further evaluate feasibility/acceptability, explore potential mechanisms, and inform effect-size estimation. Even with limited power, 2 X 2 designs are ideal for Stage I trials: they provide richer data to inform Stage II and allow collapsing across factors that prove unrelated to outcome (thus making efficient use of available participants), yet maximize the proportion of participants who receive an intervention (facilitating analysis of feasibility and acceptability). Details are provided below.

Participants

Participants will be 80 pregnant women at less than 20 weeks gestation, recruited from a WSU Ob-Gyn clinic and the Thea Bowman family community health clinic (working with the nurse midwife on staff). Participants will be excluded if they are considering termination of the pregnancy or giving the baby up for adoption, are planning to deliver outside of the DMC Hutzel Hospital (over 90% of patients at this clinic deliver at Hutzel), are deemed unable to understand the consent process, or are unable to understand spoken English. We have had clear success using a similar approach in prior studies. Past samples have been predominantly African-American and low-income (e.g., Ondersma, et al., 2007).

Measures

Given the context of data collection, the overall battery was designed to be thorough yet brief. The brief versions of all measures will be repeated at follow-up, along with more extended assessment in key areas. All measures listed below are well validated, commonly used in NIH-funded trials, have been used successfully in our previous work, and/or are taken from the NIDA Clinical Trials Network (CTN) common assessment battery. Urine samples will be analyzed by Redwood Toxicology, Inc., and hair samples by USDTL Laboratories. All measures will be administered via the CIAS ACASI

functionality, other than the questions about use of technology completed on the paper calendar used for the Timeline Follow-back interview.

The baseline assessment battery below will not be administered at baseline to participants in the screen-only control group; however, all measures will be administered to all groups at follow-up. Finally, note that the follow-up assessment battery includes assessment of the usefulness and impact of the intervention materials, as well as of the timing and reasons behind any attempts to quit or cut down on marijuana use. This information will greatly assist us in evaluating the timing and manner of any intervention-related change, and will assist in planning the subsequent Stage II trial.

Table 2. Study measures at baseline and follow-up	**Baseline**	**Follo w-up**
1. Demographics	X	X
2. Drug-Taking Confidence Questionnaire (marijuana self-efficacy)	X	X
3. ASSIST substance use screener (7 items per substance	X	X
4. CESD-10 (depression)	X	X
5. Motivation Measurement Scales (visual analog)	X	X
6. Satisfaction with CIAS software	X	
7. Short Index of Problems-Revised	X	X
8. Items to inform tailoring (timing/freq, stage, attitudes)	X	X
9. Theory of Planned Behavior & Self-Det. Theory Questions	X	X
10. Pregnancy related anxiety scale	X	
11. Urine & hair sample (tested for drugs)		X
12. Birth outcomes (birth weight, gestation, days in hospital/NICU)		X
13. Substance Use Calendar (TimeLine Follow Back – TLFB)		X
14. Mini International Neuropsychiatric Interview (MINI)		X
15. Cannabis Abuse Screening Test (CAST) and ALAC		X
16. Substance use in home/peer group/significant relationships		X
17. Conflict Tactics Scale (CTS-II)		X
18. Brief Child Abuse Potential Inventory (BCAP)		X
19. Wayne Indirect Drug Use Screener (WIDUS)		X
20. HRBS (HIV risk measure)		X
21. Prescription Drug Use Questions		X
22. Motivation to Change		X
23. Medical Marijuana Use Questions		X
24. Kirby		X
25. Primary Care PTSD Screen (PC-PTSD)		X
26. Satisfaction with Text message & study		X
27. Questions about use of technology		X

3.1 Subject Inclusion/Exclusion Criteria

Inclusion criteria

Age 18 to 40, pregnant, seeking care at the DMC/UHC or Thea Bowman prenatal clinics, able to communicate in English, own a cellphone and willing to receive text messages, willing to allow access to their pending newborn's birth records, less than 20 weeks pregnant, and reporting marijuana use at least twice weekly in the month before becoming pregnant.

Exclusion criteria

Frank cognitive impairment, considering an elective abortion or adoption, not able to communicate in English, not planning to deliver at a DMC hospital, previous or current research participant in a study conducted by Dr. Ondersma, or already a participant with the NICHD Perinatal Research Branch.

3.2 Strategies for Recruitment and Retention

Many techniques and communications are employed to orient each participant from enrollment to completion of participation after follow up appointments. This includes all of the correspondences described in the Correspondence Schedule, some of which are detailed here. About one week after enrollment, a research assistant sends a thank you card by mail or email to the participant. A reminder card is mailed about 14 weeks before the participant's due date reminding them about the follow-up when their baby is born. A phone call is made 8 weeks before their due date to serve as an additional reminder and confirm due date and planned hospital for delivery of the infant. Additionally, holiday, Thanksgiving and birthday cards are mailed or emailed if appropriate given dates between original enrollment and birth of infant. Approval to track participants through their medical records was obtained during consent. We have a DMC nurse who checks census for Hutzel hospital to know when participants deliver. Participants are compensated with a $50 Target gift card at baseline. For the follow-up visit they are compensated with a $50 Target gift card and an additional $25 Target gift card if they provide a hair & urine sample.

3.3 Treatment Assignment Procedures

3.3.1 Randomiz ation Procedures

Randomization is determined by CIAS when first given a computer ID during enrollment and baseline data collection at a rate set by research administrators. All participants who screen eligible for the RCT are randomized to one of four conditions: eSBIRT only, Text message only, eSBIRT and Text message, or Control (split evenly between Screen only or Screen & Assessment). The PI and Project Coordinator monitor the randomization rate to ensure that equal numbers of participants are randomized to each condition: 20 to Control (10 to each Screen and Assessment conditions) and 20 to each Intervention condition (eSBIRT, Text, & Both).

3.3.2 Masking Procedures (if applicable)

This is a blinded study, meaning that outcomes assessor is blinded to the participant's randomization condition, but the PI and Project Coordinator have access to that condition. Participants are informed in the consent form that they will be randomly placed into one of the four conditions. CIAS automatically randomizes all eligible participants to one

condition. At the end of the assessment and intervention package, CIAS delivers a brief summary of the participant's tailoring conditions in order for the research assistant to assure those participants placed into the text message condition receives a welcome text.

3.4 Subject Withdrawal

Participants are free to withdraw from the study without changing any present or future relationship with Wayne State University or any of its affiliates. The PI may withdraw participants as well. If the PI makes this determination, participants will be told. The decision is made only to protect participants health and safety, or because the participant did not follow instructions to take part in the study.

3.4.1 Reasons for Withdrawal

Participants are notified in the consent form that their participation is voluntary and that they may withdraw from the study at any time without affecting their health care. They are not obligated to provide a reason for withdrawing, though suspected reasons might include the sensitive nature of certain questions, health concerns for their infant, lack of ability to receive regular text messages, or a lack of available time to complete baseline appointment.

3.4.2 Handling of Subject Withdrawals or Subject Discontinuation of Study Intervention

If withdrawal occurs due to health concerns or discomfort with questions, this is noted on tracking spreadsheets so that the participant is no longer contacted. If appropriate, sympathy cards are sent to participants who experience traumatic events. Subjects who unofficially withdraw due to loss to follow up are reported during progress reports.

3.5 Premature Termination or Suspension of Study

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and to the Department or Agency Head. [45 CFR 46.113; 38 CFR 16.113 Suspension or Termination of Research.]

To fulfill the regulatory requirements (as noted above), Wayne State University (WSU) has authorized the Institutional Review Board (IRB), the individual Institutional Review Boards (IRBs,Committees) and/or the Committee Chairs or the Assistant/Associate Vice

President for Research (AVPR), to suspend or terminate a research project that is not being conducted in accordance with the IRB's requirements and/or that may pose increased risks and/or unacceptable risks to the safety and welfare of human research subjects. Additionally, any of the above entities or individuals can suspend the human research activities of an investigator who has committed serious or continuing non-compliance in order to assess and/or remediate the problem(s). Suspension or termination would occur when there are issues of continuing or serious noncompliance with IRB and federal requirements, when the research is associated with unexpected serious harm to research participants, or when there are immediate serious issues involving participant safety.

Key Definitions
Committee – Refers to the individual IRBs at Wayne State University.
Designee – A person appointed by the IRB Chair, acting on his/her behalf.
Confirmed Non-Compliance – Non-compliance (as defined below) that has been verified as a result of a for-cause audit or investigation.
Continuing Non-Compliance – A repeated pattern of non-compliance with all federal regulations, including Veterans regulations and guidance, by an individual investigator or research staff member either on a single protocol or multiple protocols.
Non-Compliance – The failure to comply with all federal regulations, including Veterans Administration regulations and guidance, state and local requirements, WSU Policy and determinations of the IRB.
Serious Non-Compliance – The failure to comply with all federal regulations, including Veteran's Administration regulations and guidance, state and local requirements, WSU Policy and determinations of the IRB that involve one or more of the following:

- Harm to research participants;
- Exposing research participants to a significant risk of substantive harm;
- Comprising the privacy and confidentiality of research participants;
- Damage caused to scientific integrity of the research data that has been collected;
- Willful or knowing non-compliance on the part of the investigator; and
- Adversely impacting ethical principles

(See IRB Policy: "Identifying, Defining, and Managing Non-Compliance in Human Research" for specific examples).
Suspension – A suspension occurs when the IRB Committee, IRB Chair, or AVPR places a temporary hold on the research that had been previously approved so that no new participants can be accrued, no research interventions may occur (unless necessary for the safety and well-being of the enrolled participants), and no follow-up can be conducted unless it is in the best interest of the participant and approved by the IRB.

Termination of a previ ously approved protocol – Termination of a previously approved protocol occurs when the IRB Committee, IRB Chair, or AVPR withdraw approval or stop all research activity permanently. No new participants may be enrolled and no additional research interventions can occur. However, future follow-up may be conducted with the approval of the IRB to monitor the well-being and any potential risk to participants.
Termination of activities that have nev er received prior review and approval – On the occasion when research activities have occurred that did not receive prior review and approval from the IRB, the IRB shall stop all such activities permanently. None of the data collected in this activity can be used in any future publication or presentation.
Unexpected Problem – An unexpected problem is associated with any aspect of the research study that may involve not only risks to the participant enrolled in a research study, but to other individuals who may or may not be directly associated with the research study. Unexpected problems may occur in non-clinical (behavioral or social science) as well as clinical research studies (see IRB Policy and Procedure "Unexpected Problems Involving Risk to Participants" for an inclusive list of categories).

IRB Procedures
Prior to, or during, the process of suspending or terminating a previously approved research protocol or research activities that have been conducted without prior approval, a for-cause audit will be conducted. The results of this audit will be provided to the AVPR, the IRB Chairs and Committee Members as a part of their decision to suspend and/or terminate a research protocol (see IRB Policy and Procedure "For-Cause Audit").

When other administrative groups within the University have suspended a research activity for an issue involving human participants, they are required to notify the IRB within 5 business days. An investigation will be done and an audit may be conducted by the IRB as part of their decision to suspend and/or terminate the research protocol. These results of the above actions may range from corrective or educational measures for the researcher up to and including the termination of all research activities. Further, the IRB may suspend the approval of research projects at any time during an inquiry or investigation to assure the protection of human participants.

<u>Suspension of a Research Protocol</u>
When reviewing an unexpected problem, the IRB or IRB designee may determine that the protocol associated with the unexpected problem should be suspended.

In addition, when there is concern that research is being conducted that is not in compliance with an approved research protocol, the IRB or IRB designee may suspend the research protocol until an internal audit has been completed. The completed audit

report will be reviewed by the IRB, to determine whether or not to terminate the IRB approval.

As an alternative to termination, the IRB may impose a suspension and/or remedial actions to bring the research activities into compliance with the IRB requirements and to reduce the risk to participants. When the IRB has determined that all remedial actions have been implemented, the IRB may withdraw the suspension and the research may resume.

Termination of a Research Protocol

A research protocol is terminated:

- When a remedial action plan approved by the IRB has not been implemented; or
- When the IRB determines that it is in the best interest of the research participants.

Due to safety issues and full disclosure (as outlined in the informed consent process), participants in the research must be notified in writing of all terminations. This notification must be approved by the IRB before it is sent to participants. A plan for safe withdrawal of participants from the research is required and should consider their rights and welfare, and must be submitted to the IRB for review and approval. If follow-up of the participants for safety and effectiveness reasons is permitted or required by the IRB, the participants should be informed after obtaining IRB review and approval of the notice. Any unexpected problems or other outcomes identified during follow-up should be reported to the IRB, the research study sponsor, and the FDA, if applicable.

If the investigator wishes to resume a research protocol that has been terminated, it must be submitted as a new protocol.

Terminating Research Activities Prior to IRB Review and Approval

When research activities have occurred without prior review and approval, then all activities must cease immediately and the following process is followed:

- The PI will be required to submit an Unexpected Problem Report/Form regarding the event;
- A for-cause audit of all research documents will be conducted;
- The investigator must verify in writing that none of the data will ever be used for research purposes in the future;
- All paper documents and informed consent forms must be sent to the IRB office to be confiscated;
- All computer files must be destroyed and a signed verification submitted by the PI;
- Mandatory education of the investigator and research team will be conducted;
- Appropriate University, IRB, Agency, and Sponsor entities will be notified.

Reporting of All IRB Suspensions and/or Terminations

The suspension and/or termination of IRB approval of a research protocol will be promptly reported to the investigator by courier within 24 hours and will include a written statement of the reasons for the IRB's actions.

When research has been suspended and/or terminated, the Associate Vice President for Research will report the suspension and/or termination to other appropriate Institutional Officials, Departmental Chairs or Deans and appropriate regulatory agencies (e.g., Offices for Human Research Protection, Food and Drug Administration, Veterans Affairs, Sponsor, etc.) within 60 days of the suspension or termination (see IRB Policy and Procedure "Reporting of Unexpected Problems, Suspensions and Terminations, and Serious and Continuing Non-Compliance and the Institutional Official's Responsibilities"). For VA requirements, in addition to reporting to ORO, the following offices must be notified:

- The Privacy Office, when the report involves unauthorized use, loss, or disclosure of individually identifiable patient information.
- The Information Security Officer when the report involves violations of information security requirements.

PI Recourse

The PI may request a meeting with the AVPR, IRB Committee or IRB Chair or designee regarding any decision to suspend and/or terminate a protocol. This should be accompanied by a written appeal.

Disciplinary Action

While the IRB shall have the authority to suspend and/or terminate a research protocol, or any of an investigator's human research activities, all disciplinary action taken against an individual for being out of compliance with institutional policies regarding the protection of human participants, shall be the responsibility of the institution. The Associate/Assistant Vice President for Research shall be responsible for reporting the termination to other institutional officials (Department Chairs, Deans, the Provost, etc., as required) and to assist in taking appropriate institutional disciplinary action.

4 STUDY INTERVENTION

4.1 Stud y Behavioral or Social Intervention(s) Description

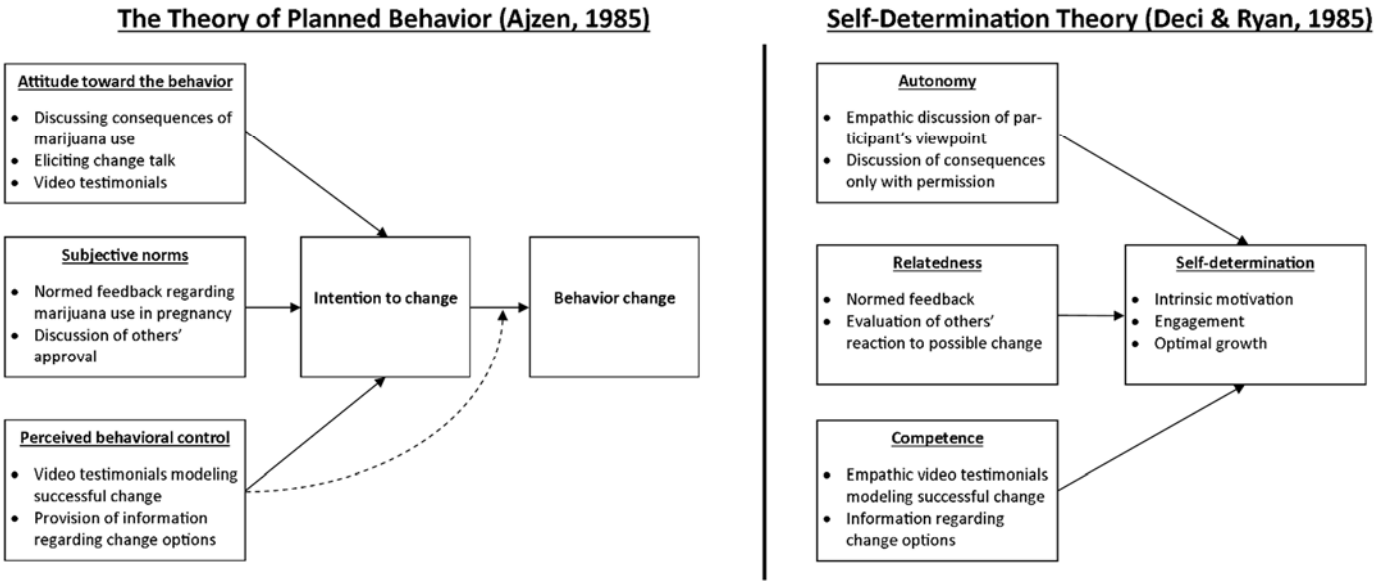
The eSBIRT intervention will be a single highly interactive session, delivered via a touch screen Tablet. The total planned duration of approximately 20 minutes is based on evidence suggesting that "longer" brief interventions (e.g., greater than ten minutes) are associated with stronger effects than shorter brief interventions (Fiore, Jaen, Baker, & et al., 2008), while also being cognizant of time limitations in a busy outpatient clinic. Participants will interact with the CIAS software and its animated narrator via a touch screen and headphones in a private office, prior to or after being seen by medical staff (see below for details regarding participants and recruitment).

The intervention for this project will draw from our previously successful interventions for post-partum drug use and prenatal tobacco use (Ondersma et al., 2007, 2012), from Motivational Interviewing (e.g., Miller & Rollnick, 2002) and brief intervention approaches (e.g., Babor et al., 2007), as well as the growing literature supporting two specific theories of health-related behavior. This solid theoretical foundation will maximize efficacy and enhance our ability to examine mechanisms. This and other key elements of the proposed eSBIRT intervention are described below.

1. Strong theoretical basis. This eSBIRT software will be based on the Theory of Planned Behavior (TPB; Ajzen, 1985) and Self-Determination Theory (SDT; Ryan & Deci, 2000), two theories that have garnered support in the literature and that are consistent with brief interventions for health behavior change. The following list describes the techniques that will be incorporated into the eSBIRT intervention and how those elements relate to one or both of these theories. This information is also summarized in Figure 4, below. Note that the use of multiple techniques is consistent with a recent meta-analysis showing that doing so is associated with stronger outcomes (Webb, et al., 2010).
    a. Empathic exploration of the participant's thoughts regarding their marijuana use (supporting autonomy; SDT)
    b. With permission, provision of information on possible consequences of marijuana use during pregnancy and possible benefits of changing (modification of attitudes toward the behavior, TPB; supporting autonomy, SDT)
    c. Normed feedback and exploration of others' approval of the behavior/potential change (addressing subjective norms, TPB; relatedness, SDT)
    d. Use of Motivational Interviewing strategies to elicit participants' own reasons for change (modification of attitudes toward the behavior, TPB)
    e. Incorporation of video testimonials modeling successful change (modification of attitudes toward the behavior, TPB; perceived behavioral control, TPB; building autonomy and competence, SDT)

f. Provision of information regarding multiple change methods, and optional goal setting (perceived behavioral control, TPB; building autonomy and competence, SDT)

Figure 4. Simplified theoretical framework, with associated eSBIRT change techniques



2. Use of tailoring. Tailored health communications are associated with stronger effects than non-tailored communications (Noar, et al., 2007). Although tailoring has been incorporated into many messaging-based interventions (Hawkins, Kreuter, Resnicow, Fishbein, & Dijkstra, 2008; Resnicow et al., 2009), it has not been as widely implemented in technology-delivered brief interventions—which, although providing personalized feedback, have failed to vary their overall structure to fit each participant. This is critical, as tailored interventions are associated with stronger effects. Even more importantly, interventions tailoring on multiple theoretical, behavioral, and demographic characteristics together have stronger effects than those tailoring on only one of these (Noar et al., 2007). The proposed eSBIRT software will target pregnant women and will provide personalized feedback, but will go far beyond this by tailoring intervention components, order, language, and tone on individual factors such as age, race, motivation to change (e.g., willing to consider quitting vs. not at all open), changes made since learning of their pregnancy, self-efficacy, and social support (variables emerging as important in Noar et al., 2007).
3. Non-specific factors. The therapy outcome literature clearly shows the extent to which non-specific or "common" factors influence outcomes (e.g., Chatoor & Krupnick, 2001). Knowledge of the importance of such factors led to their being central to the very definition of Motivational Interviewing (Miller & Rollnick, 2002). Although of course technology-delivered interventions can never replicate a true, high-quality human interaction, they nevertheless can vary in perceived empathy, optimism, insight, responsivity, alliance, and respect. In part through leveraging the

synchronously interactive talking narrator available in CIAS, the eSBIRT intervention will maximize participant perceptions of empathy, etc., to the extent possible through this medium.

4. Tailored video clips. Our recent computer-delivered intervention for cigarette smoking in pregnancy (Ondersma et al., 2012) included video clips containing information from a physician and a testimonial from a young mother that were embedded within CIAS as part of the intervention flow. These video clips were very well received, and appear to have contributed to the positive results of that intervention. The present intervention for prenatal marijuana use will also include video clips that are tailored based on age, race, current change/motivation status, and self-efficacy.
5. Promotion of self-change and/or treatment-seeking. The overall goal of the eSBIRT intervention will be to promote self-change and/or help-seeking, which it will do in part by providing a range of nearby and accessible options for assistance (one's physician, a faith leader, nearby opportunities for treatment, etc.). Rather than using a severity algorithm to determine which participants should be referred for assistance, this intervention will simply provide a menu of available options to all participants who have indicated some interest in change.

Design and theoretical basis of tailored text intervention

We will use group text messaging software developed within the CIAS program using Twilio to deliver the text messages. Consistent with Self-Determination Theory and Motivational Interviewing, we will seek to maximize autonomy by allowing participants assigned to the tailored text condition to choose the frequency (weekly, twice a week or three times a week) and time (morning, afternoon, evening, or nighttime) of text messages. Text messages will continue until childbirth or until the participant opts out.

Following evidence that even use of a first name may enhance efficacy (Dijkstra, 2005), text messages will make regular use of the participant's first name. As noted above, the text intervention will also tailor on factors such as participant gestational stage, self-efficacy, social support, and will follow the key theoretical principles of the Theory of Planned Behavior and Self-Determination Theory noted in Figure 4 (e.g., text messages will strive to build perceived behavioral control and a sense of competence with regard to avoiding marijuana). We will work closely with Dr. Resnicow and Ms. Konkel in developing the text message language and algorithms. In order to maximize engagement and retention, messages will mix marijuana-targeted content with general content related to a healthy pregnancy (e.g., nutrition), as well as use of appropriate humor and tips for community resources.

Participant protection is always an important consideration. This is especially true when working with pregnant women and illicit drug use, as this can potentially place them at risk for a range of negative consequences. Text messages, which could potentially be viewed in transit or by anyone with access to the participant's mobile phone, present unique challenges in this regard. We carefully considered a number of options for dealing with this, and spoke with other investigators (some of whom are the first to do

texting regarding illicit drug use, albeit not with pregnant women). Although we understand that our ability to affect marijuana use would most likely be maximized by addressing it directly, we believe that (a) we are ethically required to avoid sending text messages that could directly implicate participants in illegal activity that could place them or their custody of their infant at risk; and (b) we can take a number of steps to maximize efficacy while still protecting participants. Therefore, text messages will never refer directly to marijuana in a way that implies its use by the participant. Instead, texts will refer only to “smoking,” without further clarification; the CIAS session for those assigned to the text conditions will clarify that marijuana is the primary focus of this study and that “smoking” is always used to refer specifically to marijuana use. Other texts will make reference to substances in general without presuming use (e.g., “Remember that babies grow best when they don’t get any tobacco, marijuana, alcohol, or other drugs. Moms who avoid these things give their baby a great gift”).

4.2 Administration of Intervention

The computerized intervention is delivered by a tablet with the aid of CIAS. This eliminates fidelity concerns because, pending no software glitches, packages are delivered the same way every time. After a positive screen for eligibility, the RA sets up the participant on the tablet. The appropriate intervention arm is determined by the computer program once the ID number is assigned. Participants then proceed on the tablet as directed to answer assessment questions and then proceeds to the intervention package (if appropriate). Pictures and videos appear on-screen, as well as questions and response options. Feedback regarding satisfaction and change beliefs is collected by the tablet post-intervention. All data collected during tablet administration is transferred to the Wayne State server via an encrypted and protected transmission system.

4.3 Procedures for Training Interventionists and Monitoring Intervention Fidelity

The intervention as described above does not require training interventionists or monitoring intervention fidelity in the traditional sense. Rather, the CIAS-authored intervention is delivered via the internet to the tablet computer for participants to interact and answer questions. CIAS is routinely checked for issues, though none have been found to date that were not easily fixed. Data is also analyzed for out-of-range values or entry errors monthly so that they may be identified, logged, and prevented in the future. This ensures an extremely high level of intervention fidelity and trial administration in general.

5 STUDY SCHEDULE

- Day 1
  - Recruit into study
  - Confirm preference of mail or email correspondence & receipt of text if in text message group
  - Emphasize post-partum follow-up and ask them to call us when at the hospital

- Day 5
  - Send thank you letter (either through postal mail or email)

- 14 weeks before due date
  - Mail reminder card (postal or email) about follow-up appointment post-partum before discharged from hospital

- 12 weeks before due date
  - DMC nurse checks post-partum unit census for participant once a day (alerts project coordinator if any participant listed in census)

- 8 weeks before due date (if hasn't already delivered)
  - Phone call to confirm due date & ask where planning to deliver
  - Check and see if they received reminder card
  - Answer any questions about follow-up appointment
    - Try other contacts if participant not responding or number disconnected

- 4 weeks before due date (if hasn't already delivered)
  - DMC nurse checks post-partum unit census for participant twice a day (alerts project coordinator if any participant listed in census)
  - Phone call to confirm due date, remind of follow-up appointment and ask where planning to deliver
    - Try other contacts if participant not responding or number disconnected

- Follow-up after baby is born, before mother discharged from hospital
  - Mother must
    - Agree to participate
    - Have slept since giving birth
    - Not report distress about birth outcome
    - No narcotic pain medications within past 3 hours
  - TLFB completed first (paper calendar filled out with personalized dates first)
  - CIAS assessment battery completed after TLFB complete
  - Hair & urine collected when appropriate

- Other mailings (postal mail or email depending on participants preference) during study - only if occurs while enrolled in study
  - Hard to contact mailing – when can't reach by phone or through other contacts
  - Birthday card – sent 3 days before birthday

- Happy Holidays card
  - Sent 3 days before Thanksgiving
  - Sent in the middle of December for New Years and other holidays during this time

5.1 Screening

Participants will be 80 pregnant women at less than 20 weeks gestation, recruited from a WSU UPG Ob-Gyn clinic or Thea Bowman. Participants will be excluded if they are considering termination of the pregnancy or giving the baby up for adoption, are planning to deliver outside of the DMC Hutzel Hospital (over 90% of patients at this clinic deliver at Hutzel), are deemed unable to understand the consent process, or are unable to understand spoken English. Note that participation in this phase will be anonymous, and will use an informed consent information sheet rather than written consent, since collecting identifying information would present unnecessary risk (45 CFR 46.117). We have had clear success using a similar approach in prior studies. Past samples have been predominantly African-American and low-income (e.g., Ondersma, et al., 2007).

Screening and recruitment

Participants will be given a flyer by clinical staff at the clinics, alerting them to the existence of a voluntary study. Medical staff will indicate that the flyer describes a voluntary research project that involves 5-10 minutes to determine eligibility for a larger study and that they will receive a small gift for their baby if they choose to participate. Those showing tentative interest will be introduced to the research assistant, who will pre-screen for age, weeks gestation, ability to understand spoken English, and ability to receive and comfort receiving text messaging. Women passing this pre-screen process will be brought to a private room within the clinic where pre-screening will continue (i.e., intention to carry pregnancy to term). Those meeting this final pre-screen criterion will then be helped to review an informed consent information sheet (as used in prior NIH funded and IRB-approved studies; see 45 CFR 46.117). Those providing consent will use a Tablet PC with headphones (with disposable sanitary covers) to complete a brief screener evaluating a range of pregnancy-related health behaviors and emotions (e.g., nutrition, sleep, exercise, depression, anxiety, alcohol use, and smoking), as well as a key question regarding any marijuana use in the month prior to pregnancy. (See recruitment script in section 3.2)

The validity of this key question—any marijuana use in the month prior to pregnancy—has been supported; in a recent study from our lab, it was shown to be significantly more accurate than the Drug Use Screening Test (Skinner, 1982) in predicting drug use during pregnancy, as measured by hair and urine toxicology (Ondersma, Svikis, LeBreton, et al., 2012). In unpublished results specifically focused on marijuana use, only indirect screening (that is, screening that does not address marijuana use in any way) achieved higher sensitivity in predicting hair and urine toxicology. Notably, other

screening tools typically achieve high sensitivity and specificity values, but only when using a self-report gold standard, a methodology that can lead to inflated accuracy estimates when under-reporting is present, as it often is during pregnancy (Grekin et al., 2010; Ondersma, Svikis, LeBreton, et al., 2012). This under-reporting also means that sensitivity and reach can be maximized by asking about use prior to pregnancy. We will also seek to minimize under-reporting by contextualizing the drug use question within a broader screening process; through the use of Audio Computer-Assisted Self-Interview (ACASI) technology for the key eligibility criterion, as these approaches are associated with greater disclosure of drug use (e.g., Newman et al., 2002); and by ensuring anonymity at this step (Chase, Beatty, & Ondersma, 2011; Durant, Carey, & Schroder, 2002).

Recruitment Script Introduction

Initial contact with potential participants sets the tone for the interaction between researcher and research participant. The research assistant (RA) must approach the participant with respect, consideration for personal time and space, and with awareness of the need to maintain confidentiality.

Pregnant women will be recruited at or before 20 weeks gestation. The medical staff member (medical assistant, nurse, doctor, midwife or ultrasound technician) will ask the patient if they are interested in talking with the research assistant and either have the RA begin in the room while the patient waits to see the doctor, or give the patient a flyer and let them know where to find the RA. Recruitment, screening and participation will occur as detailed below.

Survey Phase

1. The RA will briefly introduce the study and ask the participant if they are willing to be screened for eligibility. The RA may use the following script:

> *Hi, Congratulations on your pregnancy! My name is _____; I'm from Wayne State University. We are looking for pregnant woman to help with a research study. It will take 5-10 minutes to complete. First off the study is completely voluntary. Whether or not you participate will not affect your care at the clinic in any way. Also, no information that you give us will be shared with any of the staff. It's completely anonymous, which means your name is not recorded anywhere. You also get a gift for your baby for participating. All family members must wait in the waiting room until we're done, and we ask this of everyone that participates. Does this sound like something you'd be interested in?*

If the potential participant agrees, the RA may continue with screening:

Great! The first step is to just ask a couple questions to make sure you are eligible (ask age, due date, acceptance of texting, etc.). Now I can get you set up on the tablet. Normally we would go through an information sheet together; however, the tablet will read the information sheet to you. As you go along, if you have any questions or concerns please stop and ask me. The tablet will then ask you a range of questions related to your health and any substances you may or may not use.
This portion will help determine whether you are eligible for a study; if you are eligible, I'll tell you all about it when you are done. You can decide then if you're interested. I will stay in here just in case you have any questions.

2. Begin the Qualtrics screener. Give the participant the tablet and headphones. Show them where the volume controls are.

3. After the participant is done, Qualtrics provides a message saying *"You are all done with this screener. Thank you very much for answering these questions! Please just give this computer to the research assistant. RA – please press continue."* When you press continue you will either see Ineligible or a color. If there is a color, they are eligible. Press continue again to receive their Qualtrics ID (it will be a 14 digit alphaneumeric id). Write both the color and ID number on the checklist; they will need to be entered into CIAS.

4. If participant is not eligible, RA thanks the participant, gives her a small baby gift, information sheet, and moves on.

5. If the participant is eligible and is interested in the RCT, the RA will give the participant the informed consent for Clinical Trial.

Thanks so much. We appreciate your help very much. It looks like you are eligible the study. This is also completely voluntary; it would take up to 45 minutes today, and involves a follow-up at the hospital after your baby is born. You would receive a $50 Target gift card for participating today and up to $75 in gift cards at the follow-up visit. Would you like to hear more?

If "no" say:
Thanks again for participating in the first part with us. Make sure they know how to get where they are going (front desk for next appointment, lab, etc.)

Inclusion Criteria:

1. Is the participant between 18 and 40 years old? Yes _____ No_____*

2. Does the participant communicate in English? Yes _____ No_____*

3. Is the participant at 20 weeks gestation or less? Yes _____ No_____*

4. Does the participant have a cell phone & is she willing to receive text messages? Yes __ No__*

*If **NO** to any of the remaining questions, participant is **NOT** eligible to participant*.

Exclusion Criteria:

1. Is the participant enrolled in any studies with the Perinatal Research Branch? Yes ___* No_

2. Has the participant been involved in any other research involving Peedy? Yes __* No__

*If **YES** to any of the above questions, participant is **NOT** eligible to participant*.

5.2 Enrollment/Baseline

Participants meeting all eligibility criteria will be offered participation in the pilot clinical trial. Those providing written informed consent will again be given the Tablet PC and headphones. Participants will then be randomized to one of the five conditions by the CIAS software. Total time spent for each participant will be approximately 10-30 minutes, depending on condition, with the exception of those in the screen only condition (who will be done sooner). Randomization will be stratified on race, age, and frequency of marijuana use prior to pregnancy. This study will include five conditions with an *n* of 20 per intervention condition (e-SBIRT only, texting only, or combined) and 10 per control condition (assessment only or screen only). This reduced *n* for the control conditions will simultaneously allow us to (a) focus analyses on feasibility and acceptability, given that 75% of participants will receive one or more interventions; (b) obtain a full control group for primary analyses, at minimal additional cost/effort, by collapsing the two control conditions (if they—as expected—do not differ significantly from each other); and (c) pilot the addition of a screen-only control group in order to identify any practical or procedural challenges prior to a future Stage II trial.

Table 1. Study arms and associated components

Condition	Screening	Assessment battery	Text preferences	eSBIRT	Tailored texting
1. Screen only control	x				
2. Assessment control	x	x			
3. eSBIRT only	x	x		x	
4. Tailored text only	x	x	x		x
5. eSBIRT + Tailored text	x	x	x	x	x

After determining eligibility by the previously mentioned screening procedures and having the participant indicate interest in continuing, the RA reads through the Trial consent form.

> *OK great. Here's a form describing this second study in detail. Let's go over it together. If you decide you want to participant in this study you will need to sign 2 copies of this form. You will keep one copy and one copy will be kept in a locked file cabinet at WSU in Dr. Ondersma's office.*

Allow the participant time to read, review, and ask questions. Once all questions are answered participant must sign 2 copies of the form and answer the quiz to determine they understand the study.

Consent Quiz

		Correct answers
1.	Is your participation voluntary? _____	Yes
2.	If you decide not to take part in this study, will the care you receive at UPG, Thea Bowman, or the DMC be affected? _____	NO
3.	How many visits will you be asked to participate in for this study? _____	2
4.	When will the second visit occur? _____	after delivery

If participant does not provide correct answer, record the answer and review the consent form. Repeat quiz; Questions 1 and 2 must be answered correctly on first or second attempt to continue in the study.

Have participant complete (and RA review):

a) Future Research Contact form

- *Dr. Ondersma often has new studies that you might be interested in; we want to know if we can contact you about studies in the future. We would only contact you to tell you about a new study. If you're interested you will go through a consent process just like this. On a separate page is a box for you to check telling us whether or not we have your permission to contact you about future studies.*

b) Contact Form

Once all forms are complete and her questions are answered say:

- *OK let's get started. The next part is to use the program on the tablet. It will walk you through it just like before and let you know what group you have been put in. Here are the headphones. If you get stuck, or have any questions, just ask me. Ready…*

6. Open the tablet to the .mobi site and put in participants first name (spelled correctly), the Qualtrics ID (under MISC), and your initials (under staff initials). Here you will need to enter the participant's phone number in case they are placed in a text message group. Please let the participant know that the computer will place them into the group and tell them which group they are in. Since we do not know yet their group, you need to put in everyone's phone number. They will only get messages if they are in a texting group.

   Ask them what days of the week and times during the day are okay to receive text messages. The texts will only come during the selected days and times. Ask them the frequency they said on the screener and select from the drop down menu from opt-in days (once/week, twice/week, three times/week).
   Also, make sure you select US/Eastern time zone at the bottom.

   Press login, write down the CIAD ID and start the program. You will need to re-enter the Qualtrics ID number in the text box and select the color. Then you can hand the tablet & headphones to the participant. (Hit next, select full screen).

7. Once the participant is done with the program there will be a screen that says "Please give the tablet back to the research assistant" You will press on the button that says "For RA only". This will take you to a slide that either says "No Text Messages" or "Yes Text Messages"

   If they receive text messages please say the following.
   "You are in one of the groups where you get text messages. I need to let you know a few things before you leave. We use "smoking" to refer to marijuana use with all of

the text messages. Since we do not know who has access to your phone or how much they know about you, we are doing this to provide further protection. Also, you can type "STOP" to the phone number at any point to stop receiving the text messages and "START" if you change your mind and want to receive them again."

8. Once you log out of the program the participant should get a message that says "Welcome to the Healthy Parenting Study!" from (313) 444-8802. Please verify that this happens and let Jessi know right away if it doesn't.

9. At the end of the recruitment process the RA will complete the recruitment log.

HPS Clinical Trial Checklist
(for use with all participants who agree to screening)

Time started:_____ Time end:_____

Completed Recruitment log.

_____ Participant Questions:

How far along are you in your pregnancy (must be 20 weeks or less)?
_____

Due date? _____

How long ago did you find out you were pregnant? _____

How old are you? _____

Did you smell cigarette smoke on the participant? Yes Maybe No

Did you smell marijuana smoke on the participant? Yes Maybe No

Did you smell alcohol on the participant's breath? Yes Maybe No

_____ Qualtrics ID# _____

_____ What color did the participant get assigned? _____

_____ Gave participant information sheet.

_____ Gave participant baby gift.

_____ **Eligibility for clinical trial** *(use Eligibility page to determine)*

_____ Read ICF for pilot clinical trial with participant

Participant Agreed _____ Yes _____ No

Participant passed consent Quiz _____ Yes _____ No

Completed Eligibility & Quiz form _____ Yes _____ No

Kept a signed copy of ICF _____ Yes _____ No

Gave participant a signed copy of ICF _____ Yes _____ No

Did participant initial each page of ICF _____ Yes _____ No

_____ Participant Question:

If we send you text messages how often would you like to receive them and what time of day is best for you (go over options in CIAS login page)

_____ cell number

_____ CIAS/Computer ID Clinical Trial # _____

_____ In Clinical Trial package enter your initials in “Staff Initials” and the Qualtrics ID# in “Miscellaneous Info.”

_____ (If in the text message group) Did the participant receive the welcome text message from (313) 444-8802? _____ Yes _____ No

If yes, did you go over details about text messaging? (smoking language, STOP, etc.) _____ Yes _____ No

_____ Gave participant referral guide _____ Yes _____ No

_____ Distribute Gift card(s) -- participant and RA sign receipt

_____ Completed Consent for Future Research Contact

_____ Completed Contact Form

_____ Record gift card #

$50 (baseline) _____

5.3 Follow -up (Final) Visit

This study is designed to maximize the follow-up rate in what is typically a difficult population to track. As part of study consent, we will obtain permission to check each participant's electronic medical records once per day beginning 12 weeks from their due date and twice per day beginning 4 weeks before their due date, to determine when they have been admitted to the Labor and Delivery Unit of Hutzel Women's Hospital. Checking of medical records will only occur with full approval of the WSU/Detroit Medical Center IRB, consent of the participant, and HIPPA authorization from the participant. This process will allow us to complete follow-up evaluations with a very high proportion of participants without the need for arranging follow-up visits. We have successfully used this approach in a different health care system for an ongoing NIAAA project involving eSBIRT for alcohol use in pregnancy.

Once we learn of a participant's admission to the hospital, we will make contact and arrange a time to complete follow-up assessment, taking care to insure first that the participant has slept, is comfortable, and has not recently been given prescription pain medication (within the past 3 hours). All hospital rooms are private. Should medical staff require access to the participant, the nurse research assistant will simply pause data collection and finish when the participant is again available. The nurse research assistant conducting follow-up evaluation will be blind as to the participant's group assignment.

We also try to schedule at a time when family or friends will not be visiting. If someone is staying at the hospital with the participant, we ask if they would mind leaving during the visit to assure confidentiality. Participants complete a paper copy of a calendar from the past 90 days to fill out any important dates. This calendar is used on the computerized version of the Timeline Follow Back interview that asks about any marijuana use in the past 90 days. After that is complete the participant answers additional questions (see study measures in Section 3 – Study Design) on the tablet. Hair and urine samples are collected during the visit if the participant is willing to provide them. Participants receive a $50 Target gift card for completing the visit and an additional $25 Target gift card if they provide biological samples.

HPS Clinical Trial Follow-up Checklist

Time started:_____ Time end:_____

_____ Checked to make sure good time for participant

Participant Agreed _____ Yes* _____ No

Participant slept since giving birth _____ Yes* _____ No

Reporting any distress about birth outcome _____ Yes _____ No*

Received narcotic medication within last 3 hours _____ Yes _____ No*

_____ Date & time baby born: _____

_____ Baseline CIAS ID _____
(enter in MISC in CIAS)

Baseline date _____

_____ Qualtrics TLFB ID# _____

_____ CIAS/Computer ID follow-up # _____

Entered Baseline number in Misc _____ Yes _____ No

_____ Agreed to give a urine sample _____ Yes _____ No

_____ Urine Collected (30 mL)

_____ ID number written on sample (use today's CIAS#)

_____ Agreed to give a hair sample _____ Yes _____ No

_____ Hair Collected

_____ ID number written on sample (use today's CIAS#)

_____ Gave participant referral guide _____ Yes _____ No

_____ Distribute Gift card(s) -- participant and RA sign receipt

_____ Record gift card #

$50 (follow-up) _____

$25 (bio sample) _____

6 STUDY PROCEDURES /EVALUATIONS

6.1 Laboratory Procedures/Evaluations

6.1.1 Clinical Laboratory Evaluations

Urine Results (Redwood Toxicology)

Screening Panel testing for:

Alcohol (Ethanol) 0.04 g/dL; Amphetamines 1000 ng/mL; Barbiturates 200 ng/mL; Benzodiazepines 200 ng/mL; Cocaine (Benzoylecgonine) 300 ng/mL; Cotinine (Nicotine Metabolite) 250 ng/mL; Opiates 300 ng/mL; THC (Marijuana) 50 ng/mL

Hair Results (USDTL; United States Drug Testing Laboratories, Inc.)

All categories confirmed by LC-MS/MS, with Cannabinoids tested first

AMPHETAMINES

Amphetamine 100 pg/mg; Methamphetamine 100 pg/mg; MDA 100 pg/mg; MDMA 100 pg/mg; MDEA 100 pg/mg

COCAINES

Benzoylecgonine 50 pg/mg; Norcocaine 50 pg/mg; Cocaine 100 pg/mg; Cocaethylene 50 pg/mg

OPIATES

Morphine 100 pg/mg; Oxymorphone 100 pg/mg; Hydromorphone 100 pg/mg; Codeine 100 pg/mg; Oxycodone 100 pg/mg; Hydrocodone 100 pg/mg; 6-MAM 100 pg/mg

PCP

Phencyclidine 100 pg/mg

CANNABINOIDS

Carboxy-THC GC/MS 0.05 pg/mg

6.1.2 Specimen Preparation, Handling, and Storage

Urine:

The following information should be recorded on the bottle label:

- Date of collection
- Donor's identification number
- Collector's initials

Provide the donor with a clean, unused urine specimen collection container and instruct the donor to fill the container at least 1/3 full (minimum of 30 mL's)

Allow the donor to enter and maintain privacy within the stall or partitioned area

- Complete the remainder of the test request form while the donor is collecting the specimen
- Urine Drug Screen Type: check the box corresponding to the reason the donor is being tested.
- Security Seal: after collecting the specimen, tighten the bottle cap. Place the security seal over the top of the cap and down the sides of the bottle.
- Specimen Label: Indicate which test or panel is to be ordered by placing a check mark in that box.
- Indicate donor identification number, collection date, and collector, if you have not already done so.

Accept the specimen from the donor, aided by the use of disposable gloves

Hair:

RA fills out the Custody and Control Form (CCF). Be sure to include the CIAS FU # in Step 1, Section B and specify "Research" for Step 1, Section C. Leave Step 2 and 3 blank. Complete Step 4.

Remove the Sample Acquisition Card (SAC).

- Open it and remove the foil, integrity seal and alcohol pad.
- Fold the foil in half lengthwise and open. Sign and date the integrity seal.
- Copy the donor ID# from the CCF to the SAC.
- Sign the SAC and fill in the date and time.
- Decide where the hair sample is going to be collected from and check the appropriate box on the CCF.

Collect the hair sample as appropriate:

- Clean the scissors and hair clip with the alcohol pad.

- Select the area where the hair will be collected and note this on the CCF.
- Grasp a small lock of hair visibly equal to ½ inch wide by 1-2 strands deep when held flat across your finger.
- Cut as close to the scalp as possible, taking the sample from an area on the head that is cosmetically undetectable to the donor.

Put the hair sample in the foil with root ends aligned and pinch it closed.
Put the sample in the SAC with the root ends to the left.
Seal the SAC by removing the adhesive strip from FLAP A and folding it over to meet the designated spot on the SAC. Repeat this process for FLAP B.
Complete sealing the SAC by removing the backing from the Integrity Seal and placing it over the designated spot on the SAC creating a secure seal across FLAPS A and B.
Remove the bar code label from the CCF and place it on the SAC in the designated spot.

6.1.3 Specimen Shipment

Urine samples are shipped within 1-2 days of collection; each sample is logged prior to shipment along with location of mailing; hair samples are collected for longer periods of time prior to shipment (until 8 samples have been collected) so that bulk mailing can be employed as directed by the company; between shipments, hair samples are stored in the Project Coordinator's locked desk drawer. Hair sample identification numbers are logged for each shipment.

7 ASSESSMENT OF SAFETY

During recruitment it is explained to the participant that this is a research study. They are also told the types of questions that will be asked and that they have the right to decline participation or withdrawal at any time. Participants are also explained the potential risk of distress due to the sensitive nature of the questions. The participant is explained their rights and what the study is clearly and a brief quiz/ questions will be asked of them to ensure that the patient understands clearly. Lastly, they are informed that a Federal Certification of Confidentiality has been obtained to further protect participants against forced disclosure of data.

The IRB determined that the PI's potential conflict of interest arising from his co-ownership of the software company which provides the screening, assessment, and intervention platforms merited a Data and Safety Monitoring Board and disclosure in publications and informed consent forms. As such, amendments were made to the informed consent forms to notify participants of this potential conflict of interest prior to their enrollment. The DSMB was established to periodically review study progress, any noteworthy incidents or adverse events, and participant demographics, among other information. The Board is comprised of 3 members. Should any of these members believe that an issue requires attention, a meeting will be sought within several weeks to provide more information and determine the proper course of action to prevent further issues or rectify any that have occurred.

7.1 Specification of Safety Parameters

7.1.1 Unanticipated Problems

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects 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 IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject 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 subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.1.2 Adverse Events

An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

7.1.3 Serious Adverse Events

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity

7.2 Characteristics of an Adverse Event

7.2.1 Relationship to Study Intervention

To assess relationship of an event to study intervention, the following guidelines are used:

1. Related (Possible, Probable, Definite)
    a. The event is known to occur with the study intervention.
    b. There is a temporal relationship between the intervention and event onset.
    c. The event abates when the intervention is discontinued.
2. Not Related (Unlikely, Not Related)
    a. There is no temporal relationship between the intervention and event onset.
    b. An alternate etiology has been established.

7.2.2 Expectedness of SAEs

The Study PI will be responsible for determining whether an SAE is expected or unexpected. An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention.

7.2.3 Severity of Event

The following scale will be used to grade adverse events:

1. Mild: no intervention required; no impact on activities of daily living (ADL)
2. Moderate: minimal, local, or non-invasive intervention indicated; moderate impact on ADL
3. Severe: significant symptoms requiring invasive intervention; subject seeks medical attention, needs major assistance with ADL

7.3 Reporting Procedures

7.3.1 Unanticipated Problem Reporting to IRB and NIDA

Incidents or events that meet the OHRP criteria for unanticipated problems require the creation and completion of an unanticipated problem report form. OHRP recommends that investigators include the following information when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB:

- appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number;
- a detailed description of the adverse event, incident, experience, or outcome;
- an explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem;
- a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:

- Unanticipated problems that are serious adverse events will be reported to the IRB and to NIDA within 1 week of the investigator becoming aware of the event.
- Any other unanticipated problem will be reported to the IRB and to NIDA within 2 weeks of the investigator becoming aware of the problem.
- All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB's receipt of the report of the problem from the investigator.

7.3.2 Serious Adverse Event Reporting to NIDA

Procedures and timeline for reporting AEs to NIDA.

AEs will be reported to the NIDA PO at least once per year as a part of the annual progress report. These reports will describe the event, when it occurred, the study arm of the participant, and the outcome/resolution. If there are no AEs in a given year, the report will include a statement to this effect.

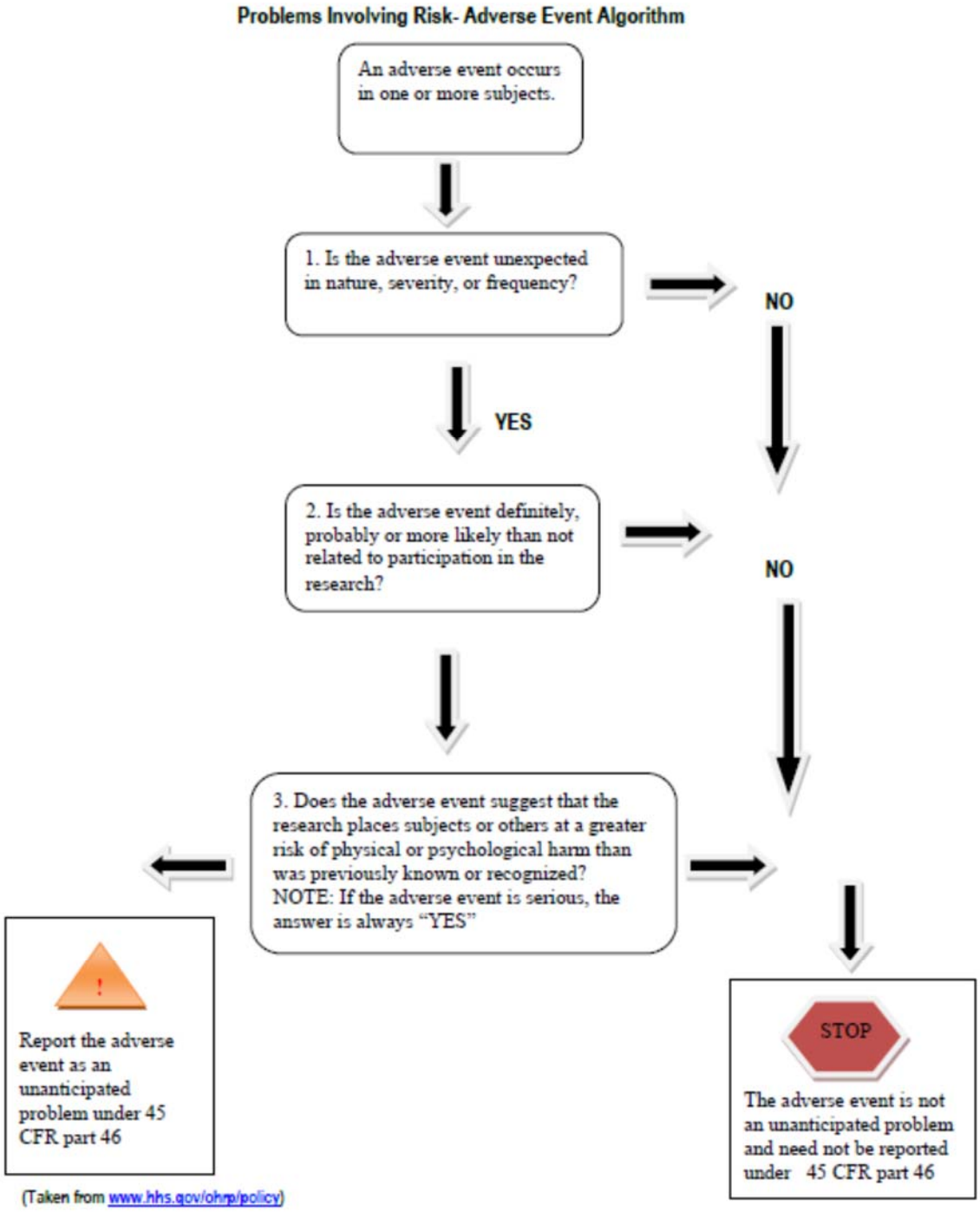
Procedures and timeline for reporting SAEs to NIDA.

SAEs, whether or not anticipated, will be reported to the NIDA PO within 24 hours of the event by email. This 24 hour notification will include a brief explanation of the SAE and when it occurred. A written follow up will be sent within 72 hours of the event. This written follow up will include information on the date of the event, what occurred, actions taken by project staff, planned follow up (if any), the intervention group/study arm of the affected participant, whether the event appears to be related to the intervention, and whether participant will continue in the study.

Reporting of IRB actions to NIDA.

Follow-up reports to the NIDA program official—made within 48 hours of IRB actions—will specify IRB actions related to study shut-down or changes. We will follow Wayne State University policy in the handling of all AEs and SAEs; see Appendix 1 for algorithm from the WSU IRB, which will be followed in all respects except with regard to unanticipated SAEs, which **will** be reported to NIDA.

Wayne State University Risk-Adverse Event Algorithm:


Problems Involving Risk- Adverse Event Algorithm
An adverse event occurs in one or more subjects.
1. Is the adverse event unexpected in nature, severity, or frequency?
NO
YES
2. Is the adverse event definitely, probably or more likely than not related to participation in the research?
NO
3. Does the adverse event suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized?
NOTE: If the adverse event is serious, the answer is always "YES"
Report the adverse event as an unanticipated problem under 45 CFR part 46
STOP
The adverse event is not an unanticipated problem and need not be reported under 45 CFR part 46
(Taken from www.hhs.gov/ohrp/policy)

8 STUDY OVERSIGHT

In addition to the PI's responsibility for oversight, this study will use a DSMB to be consistent with a Financial Conflict of Interest (FCOI) management plan from Wayne State University, resulting from the PI's part ownership of the company that markets the software intervention authoring tool that will be used in this study. (Other elements of this management plan include ensuring that the PI's grants are never charged for use of the software, disclosing the potential COI on all publications and presentations, and noting the potential COI in consent documents.) Members of the DSMB assembled for this study include:

i. Theresa Winhusen, PhD, University of Cincinnati School of Medicine. Dr. Winhusen has conducted multiple NIH-funded clinical trials, many under the auspices of NIDA's Clinical Trials Network, and one of which was a study seeking to reduce drug use among pregnant women.
ii. David Ledgerwood, PhD, Wayne State University School of Medicine. Dr. Ledgerwood has led or been part of multiple NIH-funded clinical trials for smoking or gambling, and as a clinician supervises treatment of opioid-dependent pregnant women.
iii. Grace Chang, MD, Harvard University Medical School/VA Boston Healthcare System. Dr. Chang is a leader in brief intervention trials for alcohol use in pregnancy.

Charge of the Board DSMB (e.g., advising PI, sending report to IRB, etc.). The DSMB will review all aspects of the study, including recruitment rate, randomization, AEs, protocol violations, unexpected events, etc., and will advise the PI in terms of maintaining participant safety and confidentiality. They will also be asked to verify that study conduct is not influenced by any potential FCOI. They will be asked to approve a report to be sent to the IRB and to NIDA.

Statement of no conflicts of interest. All DSMB members will sign a form verifying that they have no conflicts of interest with respect to the proposed study. None of the DSMB members are involved in any way in carrying out this study.

Frequency of meetings. The DSMB will receive reports and meet at least annually. Additional meetings may be called, as needed, to respond to SAEs or any other study-related challenges.

PI acknowledgement of requirement to report DSMB activity as part of Annual Progress Report to NIDA. All DSMB activity will be reported to NIDA as part of the annual progress report, as required.

In addition to being made aware of possible risks during the informed consent process, participants will be protected against these potential risks in a number of ways. As noted in the Human Subjects section of this application, we will not collect information about drug use during pregnancy (other than for participants in the cross-validation subsample, whose data in this regard will be anonymous and unavailable until after the participant has left the hospital). Further, we have sought and obtained a Federal Certificate of Confidentiality, and will utilize ACASI technology which makes the RA blind as to all participant data.

9 STATISTI CAL CONSIDERATIONS

9.1 Stud y Hypotheses

Data analysis will seek to (1) verify intervention feasibility and acceptability, (2) obtain preliminary efficacy estimates as measured by confirmed self-report (as recommended by an expert panel convened by NIDA; Donovan et al., 2012); and (3) also measure efficacy in terms of a quantitative measure of drug using days. Details on these three analytic elements are provided below. All significance tests will follow standard procedures for evaluating distributional assumptions, disproportionate or biased follow-up, and randomization success, and will utilize transformations and replacement of missing data using multiple imputation as appropriate. Manuscripts based on these results will be written and submitted during quarter 12 (the end of project year three). This work will form the basis of the R01/Stage II study application to follow, ***unless*** the results suggest that more Stage 1 work is needed before proceeding to a fully powered trial. We see the proposed Stage 1 project as a true test of whether these approaches, alone or in combination, merit further evaluation.

Feasibility will be demonstrated if a high proportion of participants receive the intervention as intended, and ***acceptability*** will be demonstrated if participant ratings show a high degree of satisfaction and usability. *Hypothesis 1a:* 90% or more of participants assigned to the eSBIRT conditions will successfully complete the intervention at the same clinic visit at which they are recruited. *Hypothesis 1b:* 90% or more of participants assigned to the tailored texting conditions will report receiving and reading at least five text messages. *Hypothesis 1c:* Based on prior standards (e.g., Ondersma et al., 2013), we predict that participants assigned to the intervention conditions will rate them as highly acceptable, helpful, and easy to use (mean of ≥ 4.5 on a 1-5 scale ranging from “not at all” to “very much”).

9.2 Sample Size Considerations

Power is neither required nor expected to be adequate in Stage I pilot trials. In an exploratory power analysis, we show power of 0.8 to detect a medium to large effect (*d* = 0.69), which we do not expect. We do expect the strongest effects to be between the combined intervention and the control group.

9.3 Final Analysis Plan

This analysis will make use of two point prevalence outcomes (7-day and 90-day), both of which will be dichotomous measures of drug use that will take advantage of the windows of detection of the two toxicological measures included in this study. Marijuana use in the 7 days prior to follow-up will be defined as either self-report of use in the past 7 days (per the timeline follow-back interview) or evidence of marijuana use on the urine drug screen. Marijuana use in the 90 days prior to follow-up will be defined as self-report of use in the past 90 days (per the timeline follow-back interview) or evidence of

marijuana use per hair analysis. Generalized linear models using a binary logistic link function will be used to assess differences in marijuana use between conditions. The main predictor will be group membership with ***4*** levels (collapsing the two control conditions, if not significantly different). Control variables will include baseline frequency of marijuana use as well as any baseline characteristics not controlled through randomization. *Hypotheses 2a and 2b:* Trends will favor the intervention conditions on confirmed 7-day and 90-day point prevalence, with Logit d effect sizes of at least .30 (see Hasselblad & Hedges, 1995, for details on Logit d, a Cohen's d analog for dichtomous outcomes).

For all efficacy outcomes, we will test interaction terms between baseline characteristics (e.g., baseline severity of marijuana use) and group membership to determine if baseline characteristics moderate the effects of the intervention. We will also evaluate whether treatment-related changes in marijuana use are mediated by changes in theoretical mechanisms hypothesized by the TPB or SDT. To assess mediation, the above analyses will be run in Mplus; changes in TPB and SDT mechanisms will be included as predictors of the outcomes as well as mediators for the effect of the intervention. Bootstrapped standard errors will be used to assess the significance of the mediation.

Days of marijuana use in the past 90 days (per timeline follow-back interview) will be the third efficacy-related primary outcome of the pilot trial. To assess changes in days of marijuana use, generalized linear models using a Poisson loglinear link function will be employed. The main predictor in the analyses will be group membership with ***4*** levels (again, collapsing across the two control conditions). Control variables in the analyses will include baseline frequency of marijuana use as well as any baseline characteristics not controlled by randomization. For these analyses we are also interested in whether baseline characteristics moderate intervention effects or if changes in TPB- and SDT-related constructs mediate the effect. Similar steps as outlined in Section D.c will be used to test these moderating and mediating effects. *Hypothesis 2c: Trends will favor the intervention conditions on days of use in the past 90 days (timeline follow-back), with a Cohen's d effect size of at least .30.*

Most studies suggest that marijuana's effects are stronger on later neurobehavioral outcomes than on birth outcomes such as birth weight. However, at least two large studies (combined N > 19,000) have found marijuana-related effects on birth weight (El Marroun et al., 2009; Fergusson, Horwood, & Northstone, 2002). We will use analyses similar to those described above in section D.d. to evaluate group-related differences in birth weight, length of hospitalization, and days in Neonatal Intensive Care. Results of these analyses will be important in informing any potential cost-related elements of the subsequent Stage II trial. In additional secondary analyses, we will also examine intervention-related effects on help seeking, and will evaluate whether group differences in marijuana use—if any—can be partially explained by differences in help seeking, especially treatment seeking. Finally, secondary analyses will examine effect size

differences for eSBIRT, texting, and combined interventions, and for the screen- vs. assessment-only control groups. Regardless of significance, any clear differences (or the lack thereof) will inform considerations of which conditions to include in Stage II.

10 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Study staff will maintain appropriate medical and research records for this study, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Study staff will permit authorized representatives of NIDA and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

Incentive Storage

Gift cards are stored in 4 main locations: a safe and a lockbox behind a locked door in the Lab, in locked file cabinet drawer in the Lab, and in a locked file cabinet at the Thea Bowman clinic (only the PC and 3 RAs have keys to it). Only 3 of each card denomination is kept in the file cabinets, to be used if participants are eligible and enroll in the study. The RAs move the gift cards to and from the UPG clinic each day there is recruitment at that clinic. The lockbox maintains approximately 5 of each card denomination for restocking purposes. The safe holds all other cards. Only the Project Coordinator has access to the safe, while the PI and PC have access to the lockbox. Electronic tracking logs are kept on Dropbox with the location of all gift cards and a detailed description of when cards change location (including date and locations before/after).

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11 QUALITY CONTROL AND QUALITY ASSURANCE

The accuracy with which data input matches data output using the software was exhaustively checked prior to beginning the trial (using sample protocols).We have never found data coding errors on the part of the software in all previous trials. Although no problems are expected given past experiences with this technology, any evidence of errors in data recording by the ACASI will result in dropping all participants since the last quality check. Data will be checked once per month for out of range values and other quality issues. Data from participants collected at Hutzel Hospital will be accessible only with appropriate passwords known only to the PI and project coordinator. All biological samples will be marked with a unique subject identification number only.

The PI, the project manager, and the RA will meet regularly and review all data collection procedures, as well as recent data, to ensure that study procedures are being followed appropriately and all data are present.

12 ETHICS/PROTECTION OF HUMAN SUBJECTS

12.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

12.2 Institutional Review Board

The Wayne State University Internal Review Board (IRB) oversees research to ensure the safe and ethical conduct of human participant research by all faculty, staff, and students of WSU. This includes reviews of proposed research, oversight committees, continuing oversight for compliance with regulations and policy, quality assurance, and education and training for investigators, staff, and committee members. The IRB is initially notified of proposed research prior to securement of funding and works with investigators to optimize study design, data collection, and associated consents and information sheets. After approval of study protocols, any changes must be submitted to the IRB via amendments. A yearly continuation is necessary so long as research is active; at this time, staff update the IRB of currently approved forms, enrollment figures, participant demographics, preliminary results (if applicable), and other pertinent information that allows the Board to determine study execution success and participant safety and protections. Upon discovering any adverse events, the Coordinator and PI are required to file a report with the IRB and perform any suggested response actions. Finally, the IRB assists staff in closing the study once data collection has been finalized.

12.3 Informed Consent Process

An informed consent information sheet will be utilized for (a) the feedback phases of this research, for both pregnant women and medical staff; and (b) as a screening consent for the pilot clinical trial. As noted in 45 CFR 46.117, part 'c:' "An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds…that the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality." There is no need to record the participant's name in these two aspects of this particular study (intervention feedback, and clinical trial screening), and the risk from **the process of** answering questions is less than the potential harm from the results of this process being linked to a person’s identity. The participant intervention feedback and pilot trial screening informed consent information sheets will be presented and reviewed by the Tablet computer. The information sheet for medical staff will be presented by a research assistant. The research assistant will review the consent document and will offer to read it aloud, and will also check for comprehension. All

informed consent information sheets will include all elements necessary for full consent, including information regarding requirements, risks, the voluntary nature of the research, and the ability to quit at any time. In all cases involving an informed consent information sheet, choosing to participate will be considered evidence of having consented. Additionally, the Tablet computer-based information sheet will utilize a "Check here if you understand and are willing to participate" button.

For the pilot randomized trial, we will utilize written informed consent for those who meet all inclusion and exclusion criteria. This consent form will be summarized by the research assistant and also read, if the participant wishes; a brief verbal quiz will check for understanding, and those failing the quiz twice will not be included in the study. The consent form will describe the nature of the two possible interventions, the kinds of questions that will be asked, the request for consent to allow limited access to their and their child's electronic medical records, follow-up procedures taking place post-partum (including being asked to give urine and hair samples to be tested for marijuana as well as cotinine, cocaine, amphetamines, barbiturates, and opiates), the participant's right to decline or quit at any time, and the possibility of distress as a result of some of the questions or material. Participants will also be told that their data will be identified by a code number only, with the only link between that code and their data being a single form kept locked in the PI's office. We have obtained a Federal Certificate of Confidentiality in order to protect participants against forced disclosure of their data; participants will be told of this additional protection, presuming our application is successful. Finally, although we will not ask any questions that might elicit reportable information in these areas, the consent form will clearly note the possible need to breach confidentiality should the investigators become aware of reportable information regarding child abuse, neglect, suicide risk, or infectious disease.

12.4 Inclusion of Women and Minorities (Special Populations)

Inclusion of Women

The proposed research is focused exclusively on women in the prenatal and post-partum period. The sample selected will be representative of this and other urban obstetric services. Men will not be included as primary study participants, given the focus on prevention of drug use in pregnancy. (However, note that approximately have of the 10 medical staff included as focus group members will be men.)

Inclusion of Minorities

Based on the demographics of Detroit, and of previous samples recruited in a similar manner from Wayne State University/Detroit Medical Center clinics, it is expected that the sample recruited in the proposed research will be primarily composed of racial and ethnic minorities. Specifically, we expect approximately 85% of participants to be African-Americans, 10% of participants to describe themselves as "Other" or to select

multiple racial categories, and 5% of participants to be White; approximately 10% will be of Hispanic ethnicity.

This sample, while not generalizable to the entire U.S. population, will be quite similar to other samples found in urban health care settings. Such a population, in and of itself, is worthy of study given (a) the increased rate of marijuana exposure among children of African-American mothers; (b) the clear disparities in the likelihood with which African-Americans and other minorities receive services related to substance abuse; and (c) the confluence of risks to children being delivered in urban hospitals serving low-income populations. If the data gathered for this clinical trial justify future research, that research will seek to validate technology-based screening and computerized intervention with tailored text messages in other samples of women using marijuana during pregnancy.

12.5 Subject Confidentiality

Subject confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and any study information relating to subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor. The authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study subjects. The clinical study site will permit access to such records.

Breaches of confidentiality will be prevented in a number of ways. First, we will strictly separate identifying information and data, connecting them only via a linking table (with a hard copy kept in a locked file cabinet in the PI's lab, and a password-protected electronic version kept on a secure WSU server). Old versions of the paper linking table will be shredded; the table will only be accessible by the PI and Project Coordinator. Second, breaches will also be prevented by encrypting all ACASI data in transit using AES-256 encryption (the highest level possible). Third, breaches will be prevented by further protecting saved data with extremely strong passphrases (combining capital letters, lowercase letters, and numbers, using at least 12 characters, and changing them monthly). Fourth, all study computers will be protected with a very strong passphrase.

Should a breach be discovered, it will be reported within 24 hours to the WSU IRB and to NIDA officials, followed by a written report within 72 hours. In addition to addressing

and correcting the source of the breach, discussions with the IRB, the study DSMB, and NIDA will determine whether study participants must be notified of the breach.

Certificate of Confidentiality

To further protect the privacy of study subjects, a Certificate of Confidentiality has been obtained from the NIH. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to subjects.

13 DATA HANDLING AND RECORD KEEPING

13.1 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents and laboratory reports must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems and adverse events must be reviewed by the investigator or designee.

13.2 Data Capture Methods

Most data will be collected using computer-based self-interview (ACASI) technology on a Tablet computer, with data being encrypted in transit and stored on a secure server; further, all data in the ACASI system will only be identified only with a non-identifying ID number for the participant. A single paper copy of the table linking this number to the participant's name will be kept locked in a file cabinet in the PI's lab, with a password protected electronic version stored on a secure WSU server with restricted access, such that only the PI and the Project Coordinator will have access to the server and to the passwords for the linking table file. The PI's lab is kept locked, in a locked and alarmed secure building on campus.

Three additional sources of data will not be collected directly from the participant using the ACASI system. First, data will also be obtained from hair and urine testing performed at follow-up. These samples will also be identified only using the non-identifying participant ID number; the commercial labs doing testing the samples will never obtain identifying information on any participant. Further, data from this testing will not be available until after the participant has been discharged from the hospital, further limiting the potential for any negative consequences relating to prenatal drug exposure. Second, data will be obtained by DMC clinic staff from the neonate's electronic medical record (EMR). We will provide this staff person—who will already have access to clinic medical records—with the participant's name and date of birth, the infant's name and date of birth, and other information as needed so that she can accurately identify the infant in question. She will record birth weight, length of stay, and number of days in neonatal intensive care (if any) on a paper form containing only the participant ID number.

13.3 Data Entry

Data entry for all self-report measures will be completed directly by the participant onto a tablet computer using the ACASI software. Data from the two additional sources—urine and hair data, and EMR data are entered into Excel spreadsheets at the PI's lab.

All non-ACASI data are entered by two research assistants separately into identical, pre-formatted Excel spreadsheets. The Project Coordinator then combines the entries

and uses a simple, pre-formatted row of subtraction cells to verify that all entries are identical (yielding a value of zero). Any non-zero values trigger analysis of the source data to resolve the discrepancy.

Regarding the ACASI: the accuracy with which data input matches data output will be exhaustively checked prior to beginning the trial, using sample protocols. (Note: we have never found data coding errors on the part of the software in all previous trials.) Further, we will test a randomly chosen sample protocol monthly following trial initiation. Although no problems are expected given past experiences with this technology, any evidence of errors in data recording by the ACASI will result in dropping all participants since the last quality check. In addition, data will be checked once per month for out of range values and other quality issues. All data will be accessible only with appropriate passwords known only to the PI and project coordinator.

13.4 Schedule and Content of Reports

PI, the project manager, and the RA will meet at least monthly while data collection is ongoing, to review all data collection procedures, as well as recent data, to ensure that study procedures are being followed appropriately and all data are present.

13.5 Stud y Records Retention

Study records will be maintained for at least three years from the date that the grant federal financial report (FFR) is submitted to the NIH.

13.6 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol, Good Clinical Practice, or Manual of Procedures requirements. The noncompliance may be on the part of the subject, the investigator, or study staff. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly.

These practices are consistent with investigator and sponsor obligations in ICH E6:

- Compliance with Protocol, Sections 4.5.1, 4.5.2, 4.5.3, and 4.5.4.
- Quality Assurance and Quality Control, Section 5.1.1
- Noncompliance, Sections 5.20.1 and 5.20.2.

All deviations from the protocol must be addressed in study subject source documents and promptly reported to NIDA and the local IRB, according to their requirements.

14 PUBLICATION/DATA SHARING POLICY

This study will comply with the *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 also follows the policy that requires that all clinical trials be registered in a public trials registry such as *ClinicalTrials.gov*, which is sponsored by the National Library of Medicine. The Clinical Trials registration number for this study is **NCT02191605**.

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