The University of Vermont Committees on Human Research

For Committee Use Only
PROTOCOL NUMBER

Human Subjects Research Protocol

The Common Human Subjects Protocol Cover Form **must** be completed and **attached** to the front of this form. This Protocol form should be completed for any human subjects research proposal that does not have a specific "protocol," such as a grant application. This form must be submitted along with a copy of the complete grant proposal and all the information in this form **must** be consistent with that proposal. This protocol form, once IRB approved, will be the working protocol for that research. **When completing this document, do not refer to page numbers within your grant**. If revisions are necessary during the course of the research, amendments should refer to this protocol form, not the grant proposal. Enter responses for all sections. Check N/A if the section does not apply.

PROTOCOL SUMMARY

Project: Title (Should match the title entered on the face page of any associated grant proposal.)

Improving effective contraceptive use among opioid-maintained women: Stage II

Principal Investigator: Sarah H. Heil, Ph.D.

Grant Sponsor: National Institute on Drug Abuse Grant Number: 27822
(For grants routed through UVM, indicate the OSP Proposal ID # located at the top of the OSP Routing Form)

Lay Language Summary: *(Please use non-technical language that would be understood by nonscientific IRB members to summarize the proposed research project. The information must include: (1) a brief statement of the problem and related theory supporting the intent of the study, and (2) a brief but specific description of the procedure(s) involving the human subjects. Please do not exceed one single-spaced 8 ½ X 11" page.)*

The rate of unintended pregnancy among opioid-dependent women is striking: nearly 9 of every 10 pregnancies are unplanned. Despite this dismal statistic, we know of no controlled studies examining the efficacy of interventions for decreasing unintended pregnancy among opioid- or other drug-dependent women. Under an R34 Clinical Trials Planning Grant from the Behavioral & Integrative Treatment Development Program, we developed and are pilot-testing a contraceptive-management intervention designed to promote use of more effective contraceptives among opioid-maintained (OM) women. The intervention combines (1) the World Health Organization's (WHO) contraception protocol with (2) financial incentives for attendance at protocol visits. At the first visit, OM women receive assistance with choosing a prescription contraceptive method, are provided structured educational counseling about and a free supply of their preferred method, and are offered the option of initiating it immediately. At subsequent visits, they receive support to manage side effects and problem-solve compliance problems, free refills of their chosen contraceptive method, and assistance with switching methods when indicated. Participants earn financial incentives contingent on their attendance at each of these regularly scheduled visits. Our ongoing Stage IB pilot trial data strongly support the feasibility and initial efficacy of this intervention, with 3-times more OM women assigned to the experimental intervention using prescription contraceptives at the end of the 6-month intervention compared to those assigned to a usual-care-control condition.

Building on these promising pilot data, the present proposal has one primary and two secondary aims:

Primary Aim 1: Conduct a fully randomized controlled Stage II clinical trial to rigorously evaluate the efficacy and cost-effectiveness of this innovative contraceptive-management program.

OM women at risk for unintended pregnancy (N=195) will be randomly assigned to one of three study conditions: (1) the WHO contraception protocol + financial incentives for attendance; (2) the WHO contraception protocol alone; or (3) usual care (information about contraceptive options and contact information for contraceptive service providers in the community). Contraceptive use by all participants

will be evaluated at follow-up assessments scheduled 1, 3, 6, and 12 months after trial intake. The primary outcome will be biomarker-verified period-prevalence use of prescription contraceptives at 6 months. Incremental cost-effectiveness ratios that take into consideration the costs of each opioid-exposed pregnancy and birth avoided will be calculated and compared between conditions. We hypothesize a graded outcome in terms of efficacy, with WHO + incentives > WHO alone > usual care. Regarding cost-effectiveness, we hypothesize the WHO + incentives and WHO alone conditions will dominate the usual care condition. This design will allow us to more fully assess the efficacy and cost-effectiveness of the intervention while also isolating the contributions of the financial incentives, both key objectives of Stage II intervention development.

Secondary Aim 1: Characterize contraceptive and sexual decision-making in OM women. Participants will complete questionnaires (e.g., survey of attitudes and beliefs about sex, contraception, and unplanned pregnancy) and tasks (e.g., a novel sexual discounting task) to quantify impulsivity in contraceptive and sexual decision-making in this high-risk population. Growing evidence in the field of behavioral economics suggests there are fundamental biases in the way people make choices that increase impulsivity and contribute to vulnerability to risky health behaviors. Characterizing these basic predispositions as they relate to contraceptive and sexual decision-making in OM women has potential to influence the future development of this and other interventions aimed at decreasing unintended pregnancy and transmission of sexually transmitted infections.

Secondary Aim 2: Evaluate biochemical and self-report measures of adherence to combined prescription contraceptives. While use of contraceptive injections, implants, and intrauterine devices (IUDs) is objectively verifiable, adherence to combined prescription contraceptives (birth control pills, patches, and rings) is most often assessed by self-report, which may be subject to demand characteristics. Assessing the relationships between biochemical markers (e.g., contraceptive steroid levels, hormone-sensitive binding globulins) and self-report will help establish the adequacy of each of these measures for assessing pill, patch, and ring adherence in trials like this one.

Overall, the proposed project will significantly advance our overarching goal of developing an intervention to increase more effective contraceptive use in OM women. This research has tremendous promise for impacting public health by developing efficacious interventions with the potential to reduce the vast economic and societal costs associated with unintended pregnancy among opioid-dependent and possibly other drug-dependent women. The project may also enhance understanding of contraceptive decision-making and biomarkers of contraceptive method adherence. This project has considerable potential to advance public health efforts to reduce unintended pregnancy in vulnerable populations.

PURPOSE AND OBJECTIVES

Purpose: *The importance of the research and the potential knowledge to be gained should be explained in detail. Give background information.*

The rate of unintended pregnancy among opioid-dependent women is extremely high: nearly 9 of every 10 pregnant opioid-dependent women report that the current pregnancy was unintended. Opioid-exposed neonates have an increased incidence of poor birth outcomes (e.g., premature delivery, low birth weight, neonatal abstinence syndrome) that often require extended hospitalization. It is estimated that the costs of medical care for opioid-exposed infants is more than $700 million annually in the US alone. More generally, bearing a child in disadvantaged circumstances like those of most OM women significantly diminishes the future wellbeing of both the child and the mother. Bringing the contraceptive use of this special population in line with their conception desires is a public health imperative.

The proposed project is the second step towards our overarching goal of developing an efficacious, empirically based contraceptive management program that can be disseminated to drug treatment facilities throughout the country. The proposed research also holds significant potential for impacting public health in general, as development of efficacious programs will help reduce the vast economic and societal costs associated with unintended pregnancy among drug-dependent and non-drug-dependent women alike.

References*. Include references to prior human or animal research and references that are relevant to the design and conduct of the study.*

Armstrong KA, Kennedy MG, Kline A, and Tunstall C. (1999). Reproductive health needs: comparing

women at high, drug-related risk of HIV with a national sample. J Am Med Womens Assoc, 54(2):65-70.
Black KI, Stephens C, Haber PS, and Lintzeris N. (2012). Unplanned pregnancy and contraceptive use in women attending drug treatment services. Aust N Z J Obstet Gynaecol, 52:146-50.
Heil SH, Jones HE, Arria A, Martin P, Fischer G, Stine S, Coyle M, Selby P, and Kaltenbach K. (2011). Unintended pregnancy in opioid-abusing women. J Subst Abuse Treat, 40: 199-202.
Patrick, S.W., Schumacher, R.E., Benneyworth, B.D., Krans, E.E., McAllister, J.M., Davis, M.M. (2012). Neonatal abstinence syndrome and associated health care expenditures; United States, 2000-2009. JAMA, 307: 1934-40.
World Health Organization. (2005). "Decision-Making Tool for Family Planning Clients and Providers" prepared by the World Health. Organization and the INFO Project at the Johns Hopkins Bloomberg School of Public Health/Center for Communication Programs. Geneva, World Health Organization, and Baltimore, Johns Hopkins. Bloomberg School of Public Health/Center for Communication Programs.
World Health Organization. (2007). World Health Organization Department of Reproductive Health and Research (WHO/RHR) and Johns Hopkins Bloomberg School of Public Health/ Center for Communication Programs (CCP), INFO Project. Family Planning: A Global Handbook for Providers. Baltimore and Geneva: CCP and WHO.
World Health Organization. (2009). Medical eligibility criteria for contraceptive use. Department of Reproductive Health, World Health Organization.
Zieman M, and Hatcher RA. (2012). Managing Contraception. Tiger, GA: Bridging the Gap Foundation.

Objectives: *Clearly state the primary and secondary objective(s) of the study.*

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Secondary Aim 2: Evaluate biochemical and self-report measures of adherence to combined prescription contraceptives. While use of contraceptive injections, implants, and intrauterine devices (IUDs) is objectively verifiable, adherence to combined prescription contraceptives (birth control pills, patches, and rings) is most often assessed by self-report, which may be subject to demand characteristics. Assessing the relationships between biochemical markers (e.g., contraceptive steroid levels, hormone-sensitive binding globulins) and self-report will help establish the adequacy of each of these measures for assessing pill, patch, and ring adherence in trials like this one.

Overall, the proposed project will significantly advance our overarching goal of developing an intervention to increase more effective contraceptive use in OM women. This research has tremendous promise for impacting public health by developing efficacious interventions with the potential to reduce the vast economic and societal costs associated with unintended pregnancy among opioid-dependent and possibly other drug-dependent women. The project may also enhance understanding of contraceptive decision-making and biomarkers of contraceptive method adherence. This project has considerable potential to advance public health efforts to reduce unintended pregnancy in vulnerable populations.

METHODS AND PROCEDURES

Study Design: *Describe the research design, including a description of any new methodology and its advantage over existing methodologies.*

Randomized controlled trial

Procedures: *Describe all procedures (sequentially) to which human participants will be subjected. Identify all procedures that are considered experimental and/or procedures performed exclusively for research purposes. Describe the types, frequency and duration of tests, study visits, interviews, questionnaires, etc. Include required screening procedures performed before enrollment and while on study. Please provide in table, list or outline format for ease of review. (describe and attach all instruments)*

Note: A clinical research protocol may involve interventions that are strictly experimental or it may involve some aspect of research (e.g., randomization among standard treatments for collection and analysis of routine clinical data for research purposes). It is important for this section to distinguish between interventions that are experimental and/or carried out for research purposes versus those procedures that are considered standard therapy. In addition, routine procedures performed solely for research purposes (e.g., additional diagnostic/follow-up tests) should be identified.

All procedures will be performed for research purposes.

Intake Assessment

All potential participants will complete an intake assessment battery comprised primarily of questionnaires and interviews that are described in detail in the next section below. Potential participants will also undergo physiological testing at intake including blood pressure measurement and a urine pregnancy test. We will apply for a Certificate of Confidentiality to protect the privacy of participants. Each participant will earn $35 for completing the intake assessment.

Treatment conditions

One hundred ninety-five participants will participate in the proposed study and be assigned to (1) usual care; (2) WHO contraception protocol; or (3) WHO contraception protocol + incentives (described below). Randomized participants will be frequency matched on their preferred prescription contraception method (short- (pills, patch, ring) vs. long-acting (injections, implants, IUDs)), age (< 35 vs. 35), and on whether they have intentions of starting a prescription contraceptive method now or in the near future, smoke, or have a primary/steady partner (all Yes/No). Having intentions of starting a method and not having a primary/steady partner are associated with higher rates of initiation (Clarke et al., 2006). Older age and not smoking are associated with higher rates of continuation (Westhoff et al., 2007, 2009).

Usual care condition. Participants assigned to the usual care condition will be given general information about contraceptive options (Facts About Birth Control, Planned Parenthood, 2010) and contact information for local clinics and providers of contraceptive services.

WHO contraception protocol alone condition. Participants in this condition will receive the WHO contraception protocol over the 6-month study period.

Visit 1. The first visit will occur after the intake assessment or on another day shortly after. At this visit, the study nurse practitioner and participant will use the WHO's Decision-making Tool for Family Planning Clients and Providers (2005). This flip-chart tool helps providers systematically implement four empirically validated recommendations that improve contraceptive initiation by reducing barriers, including taking a limited medical history, providing structured counseling about the participant's chosen method, giving the participant supplies of the chosen method, and offering the participant the option to initiate the chosen method immediately in the clinic. For research reasons, the medical history will be completed as part of the study intake assessment to ensure all participants are medically eligible to initiate prescription contraceptives.

When choosing a method, participants will be reassured that they can try a method to see how they like

it (WHO, 2005). Importantly, a woman who chooses an IUD will be screened for Chlamydia and gonorrhea on the day of IUD insertion and those who test positive will be treated for the infection(s) (ACOG, 2011). Also of note, to facilitate our secondary aim of evaluating biomarker and self-report measures of combined prescription contraceptives (see below), we will preferentially offer the two brands of birth control pills used by Westhoff et al. (2013) in their study of the relationship between serum levels of steroid hormones and binding globulins and self-report, although the study nurse practitioner will prescribe other brands when medically indicated. Any participant who chooses a combined prescription contraceptive method (pills, patch, or ring) will provide a blood sample prior to initiating the method to establish baseline levels of CBG and TBG (see below).

Structured counseling will include describing how the method works, how to use it, common side effects and how to manage them, and side effects that require immediate medical attention. It also includes providing reassurance that side effects will likely resolve over time and are not harmful to the patient's health and encouraging the patient to contact the clinic if they have any problems, concerns, or questions. Participants will also be reassured that if they are dissatisfied with their chosen method, they can choose to switch methods (WHO, 2005). Participants will be given written highlights of the structured counseling to take home with them.

Participants who have chosen a method will then be provided with a supply of this method free of charge and given the opportunity to start it immediately. All prescription methods can be initiated immediately as long as the participant has a negative pregnancy test. If the first visit does not occur on the same day at the intake assessment, the pregnancy test will be repeated. If a participant reports unprotected sex in the last 5 days, we will also offer her Plan B/Ella emergency contraception for use at this visit to prevent an unintended pregnancy (Westhoff et al., 2002, 2007). If menstrual bleeding started more than 5 days ago or the participant is amenorrheic, she will be advised that she will need to abstain or use a back up method for 7 days while her chosen method reaches efficacy levels (Zieman et al., 2010).

Participants who choose not to initiate a prescription contraceptive method at Visit 1 will be reassured that they can contact study staff at any time during the study to schedule a visit to repeat any portion of Visit 1.

All participants will be offered condoms and Plan B/Ella emergency contraception at this and all future visits.

Visit 2. The next visit will be scheduled for 1 week after Visit 1. Since side effects are the primary reason women in the general population discontinue contraceptive use and they peak during the early weeks and months of prescription contraceptive use (Moreau et al., 2007; Rosenberg & Waugh, 1998; Rosenberg et al., 1995; WHO, 2007), we anticipate that more frequent visits shortly after initiation of prescription contraceptives will facilitate efforts to help manage side effects, problem-solve compliance problems, and switch methods when indicated with fewer disruptions in contraceptive use. We also anticipate that providing women who have not initiated prescription contraception with additional opportunities to initiate will facilitate use. At Visit 2, participants will complete a TLFB assessment of sexual activity and contraceptive use (both prescription and non-prescription methods) since Visit 1 and a urine pregnancy test. Collecting information about use of prescription and non-prescription methods using a TLFB assessment will generate specific and useful event-level information that will allow us to examine not only whether use of prescription contraceptives alters condom use, but also the time course of any changes, instances of dual protection, etc. Potential side effects and compliance problems will also be assessed. Following the WHO protocol, women who are taking pills, for example, will be asked about common side effects (e.g., spotting or irregular bleeding, mood changes), serious side effects (e.g., chest pains, severe leg pain), changes in medical status that may affect medication efficacy (e.g., new medications), and medication compliance issues (e.g., ever forgotten pills, often forgotten pills). Study medical staff will use the recommendations provided in the WHO's Family Planning Handbook (2007) to help manage minor side effects as well as side effects that may indicate the need to switch methods (e.g., migraine headaches) or more serious side effects that may require more thorough followup and/or discontinuation of methods (e.g., a viral hepatitis flare). In addition to providing support to manage side effects and problem-solving compliance problems, participants will also be given refills of their chosen method and provided assistance switching methods when indicated. Women who have discontinued their method will be offered the opportunity to repeat any portion of Visit 1.

Visits 3-14. The frequency and timing of the remaining visits was developed based on discontinuation

rates in the general population (Nelson et al., 2008). Since 30% of discontinuation in the general population occurs during the first 4 weeks after starting a prescription contraceptive, scheduled program visits for OM women will continue weekly. In weeks 5-12, rates of discontinuation in the general population begin to slow somewhat (10% every 4 weeks), so starting at week 8, scheduled program visits for OM women will decrease from weekly visits to every other week. Continued frequent contact early in the program provides an opportunity for patients to switch methods if they are dissatisfied with their first choice. In the general population, women who are not completely satisfied with their method are more likely to use that method inconsistently (Frost & Darroch, 2008). In weeks 13-24, rates of discontinuation in the general population decline further (5% every 4 weeks), so starting at week 16, scheduled program visits for OM women will decrease from twice-monthly to once-monthly visits. Beyond 6 months, the rate of discontinuation in the general population is estimated to be low (1.5% every 4 weeks), so scheduled program visits for OM women will end after the 24-week visit. Throughout the program, additional patient contacts in the form of brief phone calls or in-person sessions will be encouraged as needed. The same routine from Visit 2 will be utilized at Visits 3-14. At Visit 14, participants will be given a 6-month supply of their current prescription contraceptive method, as appropriate, to facilitate continuation through the 12-month assessment.

WHO contraception protocol + incentives condition. Participants in this condition will receive the WHO contraception protocol as described above plus financial incentives contingent on attendance at regularly scheduled protocol visits. Incentive values will start at $15 and escalate in value by $2.50 for each consecutive visit attended. Missed visits will result in the voucher value for the next visit being reset back to the initial value of $15, but two consecutive visits will restore the voucher value back to its pre-reset value. This reset contingency helps promote consistent attendance and has been used in other studies using vouchers to reinforce appointment attendance (e.g., Svikis et al., 2007). No cash will be provided to participants; rather, participants will be able to purchase retail items and services in the local community by submitting requests to research staff. Research staff will have the right to veto any request on ethical grounds (e.g., requests for alcoholic beverages will be vetoed). This system has worked well in other voucher programs by our group and we anticipate few instances where a veto will be necessary. Nevertheless, retaining veto power is important to maintaining the integrity of the incentive program against instances of poor judgment in the use of vouchers that could reflect poorly on all involved. Maximum possible earnings will be $437.50.

Follow-up assessments

Appropriately modified versions of the intake battery will be competed 1, 3, 6 and 12 months after intake with all participants from all three study conditions. All participants will be compensated $35 per assessment independent of their contraceptive status to assure high compliance. This level of compensation has permitted us to achieve high levels of follow-up compliance in our pilot study (100%) and in our other treatment development studies (~90%). We anticipate no difficulties achieving the same or better here.

At the 5-month follow-up visit, any WHO + incentives and WHO alone condition participants reporting prescription contraceptive use will have that use verified. Participants using injections, implants, or IUDs will have that use verified by medical record review, palpation, and ultrasound, respectively. Use of combined prescription contraceptives will be scheduled to come to the clinic for weekly blood draws to assay steroid hormone levels (levonorgestrel for pill users, etonorgestrel for ring users, and norelgestromin for patch users) in the last month of the study. For usual care control condition participants, study staff will contact them at the 5-month mark to schedule their 6-month assessment. They will be asked during the call if they are using prescription contraceptives; those reporting combined prescription contraceptive use will also be scheduled for weekly blood draws. Draws will be scheduled to ensure they occur during weeks the participant reports being in the active portion of each method (i.e., weeks 1-3 of active pills, patch or ring) and not during the week of placebo pills or when patch or ring have been removed to permit withdrawal bleeding. All participants will be compensated with $15 per blood draw. Per the literature, participants with levonorgestrel levels >1.0 mcg/mL, norelgestromin levels > 0.7 ng/mL, or etonogestrel levels > 500 ng/L for at least 2 of the 3 samples collected during this month will be considered biomarker-verified at the 6-month assessment (Abrams et al., 2002; Westhoff et al., 2012, 2013). Serum samples will also be assayed for CBG and TBG. While opioids are known to increase serum levels of TBG, we do not anticipate this will be a problem as the levels observed in OM women (32 mcg/mL compared to 21 mcg/mL in non-drug-using controls; English et al., 1988) are still far below peak levels. For example, levels of 59-66 mcg/mL are commonly observed during pregnancy

(Mayo Medical Laboratories). All samples will be drawn, processed, and assayed by Fletcher Allen Health Care laboratories. Samples will be assayed for the method-specific progestins described above and CBG and TBG levels. Regarding the binding globulins, baseline levels will be subtracted from levels ascertained during weeks the participant reports being in the active portion of each method. Increases of > 25 mcg/mL in CBG levels and > 6.2 mcg/mL in TBG levels will be considered adherent (Westhoff et al., 2013). To parallel verification in participants using injections, implants, or IUDs, administration/insertion of these methods will be confirmed at the 5-month follow-up visit and again at the 5-month assessment by medical record review, palpation, and ultrasound, respectively.
After the 12-month assessment when study participation is complete, all participants will be offered assistance in transitioning contraceptive care to a community provider using a protocol developed by Shlay et al. (2003). Assistance in transitioning the participant will consist of: helping her select a provider, taking into consideration personal preferences, financial circumstances, etc.; scheduling the appointment for the participant if possible; contacting the participant after the scheduled appointment to determine whether she attended; and, if the first appointment was missed, attempting to make another appointment.

For research involving survey, questionnaires, etc.: *Describe the setting and the mode of administering the instrument and the provisions for maintaining privacy and confidentiality. Include the duration, intervals of administration, and overall length of participation. (describe and attach all instruments)*

☐ ***Not applicable***

All questionnaires and interviews will be completed in a quiet office in UHC. The instruments to be collected at intake are as follows:

(1) Demographics including age, race/ethnicity, yrs of education, marital status, and social standing (MacArthur Foundation Ladders). **(2) Sexual, reproductive and contraceptive history** including a locally developed Reproductive History Interview that assesses sexual history (e.g., number of sexual partners in the past 3 months, history of sexually transmitted infections, HIV+), reproductive history (e.g., history of pregnancies and unintended pregnancies, age at first and subsequent pregnancies), and contraceptive history (e.g., methods used, consistency of use, benefits/side effects). A modified version of the Time-Line Followback (TLFB) interview adapted to assess sexual activity and contraceptive use will also be used to collect this information for the 90 days prior to intake (Weinhardt et al., 1998; 2002). The Risk Assessment Battery (Metzger et al., 1993) will also be collected to assess risky sexual behavior. **(3) Medical history** to identify potential contraindications to prescription contraceptives including smoking status/rate, history of migraines, current or history of breast cancer, any type of cancer in genital organs, trophoblastic disease, or pelvic tuberculosis; recent or history of stroke, blood clot in legs or lungs, or heart attack, taking medication for tuberculosis, seizures, or HIV/AIDS, gall bladder disease, liver disease or jaundice, history or current high blood pressure, history or current diabetes, and history of lupus. **(4) Substance abuse and mental health** including current and past use of substances (Addiction Severity Index, McLellan et al., 1985) and current symptoms of depression (Beck Depression Inventory). **(5) Impulsivity and decision-making** including the Barrett Impulsiveness Scale (BIS-11; Patton et al., 1995), Pleasant Events Schedule (PES; adapted from MacPhillamy & Lewinsohn, 1976), delay discounting tasks for money and cigarettes (Johnson & Bickel, 2002), the National Campaign to Prevent Teen and Unplanned Pregnancy survey on knowledge, attitudes, beliefs, and behavior related to sexual activity and contraception (2009), and a sexual discounting task (Johnson & Bruner, 2012).

Appropriately modified versions of the intake battery will be competed 1, 3, 6 and 12 months after intake with all participants from all three study conditions.

Statistical Considerations: *Delineate the precise outcomes to be measured and analyzed. Describe how these results will be measured and statistically analyzed. Delineate methods used to estimate the required number of subjects. Describe power calculations if the study involves comparisons. Perform this analysis on each of the primary and secondary objectives, if possible.*

Experimental conditions will be compared on demographics and other baseline characteristics using analyses of variance for continuous variables and chi-square tests for categorical variables. If specific characteristics differ significantly across conditions and are predictive of outcome, they will be considered as potential covariates in subsequent analyses. Primary analyses will be based on all participants randomized to experimental conditions independent of early dropout, noncompliance, etc., consistent with an intent-to-treat approach to clinical trials (Armitage, 1983). For the intent-to-treat

analyses, it will be assumed that participants who miss scheduled visit are not using prescription contraceptives.

The primary outcome measure for Aim 1 will be biomarker-verified period-prevalence use of a prescription contraceptive at the 6-month assessment. Use will be defined as a self-report of adherence to a prescription contraceptive for the past 28 days + biomarker verification based on serum hormone levels (pill, patch, ring), medical record review (injection), palpation (implant), or ultrasound (IUD). Chi square tests will be used to compare contraceptive use at this time point, and at the 1-, 3-, and 12-month assessment points which will be defined as a self-report of adherence to a prescription contraceptive for the past 28 days. Comparison between conditions on period prevalence at each time point will be based on chi-square tests. Additionally, robust GEE methods for repeated measures analyses of categorical data (SAS, PROC GENMOD) will be used to compare treatment conditions across assessment points on contraceptive use. In initial GEE analyses, missing assessments will be considered non-adherent with prescription contraceptives and in a secondary set of analyses, missing assessments will be considered missing. Additional secondary outcomes will include percent of subjects who ever initiate a prescription contraceptive method, and means weeks of pregnancy protection from prescription contraceptive use. Initiation will be defined as a self-report of ever using a prescription contraceptive method on the TLFB interviews. Mean weeks of pregnancy protection from prescription contraceptive use will be determined using the TLFB interviews. Study staff will examine each day of TLFB data to determine whether the participant's use of prescription contraception protected her from pregnancy that day using standard clinical guidelines (Zieman & Hatcher, 2013). For example, the first seven days of use will not count as protected as women are routinely advised to abstain or use a back up method while the new method reaches efficacy levels (Zieman & Hatcher, 2013). This additional comparison will be based on analyses of variance with chi square tests utilized for the categorical outcome of ever using a prescription contraceptive method.

For the economic evaluation, we will use the standard practice of calculating incremental cost-effectiveness ratios (ICERs; Drummond et al. 2005). This procedure evaluates the incremental effectiveness of WHO alone and WHO + incentives relative to their incremental costs. The cost under each condition includes the direct and indirect hospital and other costs for the care of NAS infants from the antenatal period to the point of discharge. These will be derived by allocating hospital costs based on the proportion of time or space utilized by the programs, e.g., treatment facility costs, following procedures developed for WHO by the economic co-investigator (Shepard et al. 2000). Nearly all OM women receiving treatment in our area also deliver at our university-affiliated hospital and, with maternal consent, we will have access to all prenatal care, delivery, and infant care records. Over >10 years, 100% of women in our trials with pregnant cigarette smokers have provided permission to review maternal and infant medical records and we anticipate being able to achieve a similarly high rate of consent in the proposed trial. The total cost per treatment episode will be individual-specific.

The costs under each condition will also include costs that vary by patient engagement and contraceptive status (e.g., contraceptive supplies, incentives). Any costs incurred by the patient will be measured by the Brief DATCAP, widely accepted in addiction projects utilizing incentives (Knealing et al., 2008). The Brief DATCAP survey data will supplement healthcare costs to include the opportunity cost of the patient's time while in treatment (Salomé et al., 2003; French 2005) and will allow us to adopt the societal perspective for the period under study (i.e., from intake to discontinuation or program completion; Drummond et al., 2005). The cost of all research-specific resources consumed will be excluded from the evaluation, with all costs and benefits expressed in a common dollar year without the need for discounting.

Data from the EuroQol EQ-5D-3L collected at each follow-up assessment will ensure our cost and outcome measures are comprehensive (Szende et al., 2007). This questionnaire will capture quality of life gains and losses from avoiding possible pregnancy complications, such as nausea, and possible adverse events related to some contraceptive methods. Each follow-up EuroQol observation will be weighted by the number of months since the preceding observation (i.e., 1, 2, 3, and 6). The result will be the number of quality adjusted life years (QALY) enjoyed by each woman in the 12 months following randomization (Zeckhauser & Shepard, 1976). These QALY impacts will be considered as part of the costs and savings of averting pregnancies and part of the cost part of ICER (Drummond et al. 2005). Therefore, these net QALYs will be converted into their cost equivalents by valuing each QALY based on US per capita gross domestic product based on the criteria for "very cost-effective" (WHO, 2001). We will then adjust incremental costs of each comparison by adding these cost-equivalents to the routine

care costs amount to the existing care costs.
In the final analysis, outcomes in this cost-effectiveness analysis will be the incremental cost or cost savings of each additional opioid-exposed pregnancy prevented. This ICER is the difference in costs across conditions divided by the difference in each outcome (e.g., additional opioid-exposed pregnancy and additional opioid-exposed birth avoided). These ICERs will be calculated for several comparisons: usual care vs. WHO alone (to value the net impact of the WHO component), WHO alone vs. WHO + incentives (to evaluate the net impact of the incentives component), and usual care vs. WHO + incentives (to evaluate the combined effect of the WHO and incentive components). The robustness of ICERs and cost savings so calculated will be determined by employing nonparametric bootstrapped standard errors and replications (Claxton et al., 2005; Drummond et al. 2005). This process will generate a distribution of results so that the mean, median, and probability distribution of net savings and 95% confidence intervals on the ICERs can be estimated. Additional sensitivity analyses will explore alternative assumptions, such as alternative values for time lost and quality adjustments and procedures for excluding or imputing missing data.
These economic findings will also be compared to economic studies on the costs of unintended pregnancy and the cost-effectiveness of other efforts to reduce them (Trussell, 2007; Trussell et al., 1997). We hypothesize the WHO alone and WHO + incentives conditions will both dominate usual care.
Statistical analyses for Secondary Aim 1 will quantitatively characterize this population in relation to normative data on knowledge, attitudes, beliefs, and behavior related to sexual activity and contraception and behavioral tasks designed to specifically characterize contraceptive and sexual-decision-making discounting. For dichotomous items (e.g. “In life, things just seem to happen to me”, “I worry about STI’s more than I do pregnancies”), exact binomial tests will be used to compare the observed rates of endorsement for OM women to those obtained in the National Survey. T-tests and non-parametric tests will be used for comparisons on continuous outcomes. Repeated measures analyses of variance (or alternatively, Friedman’s tests) will be used to compare sexual discounting outcomes (e.g. AUC, estimated hyperbolic discounting parameter *k*) across conditions (e.g., individual most vs. least likely to have an STI). Sexual discounting outcomes of OM women will also be compared to those of matched control non-drug-using women. Pearson r and Spearman’s r will be used to examine the relationship between sexual discounting, impulsivity and beliefs and knowledge about contraception.
Analyses of Secondary Aim 2 will evaluate the concordance between biomarker and self-report measures of adherence to combined prescription contraceptives. Area under the ROC curve analyses will be used to examine sensitivity and specificity of corticosteroid-binding globulin (CBG) and thyroxine-binding globulin (TBG) with serum levels of the specific steroid hormone used as the gold standard. Based on these analyses optimal cutpoints will be developed to discriminate between compliant and non-compliant women. Assessing the concordance between biomarkers and self-report will help establish the adequacy of each of these measures for assessing pill, patch, and ring adherence in future trials.
All statistical analyses will utilize SAS statistical software Version 9.3 (SAS Institute, Cary NC).

Confidentiality Measures and Secure Storage of Data or Tissue: *Describe how the data/tissue will be collected. Will there be identifiers or will the data/tissue be coded? Describe where the data/tissue will be stored and how it will be secured. Describe who will have access to the data/tissue or the codes. If subject data/tissues with identifiers will be released, specify to whom. Describe what will happen to the data/tissues when the research has been completed.*

☐ ***Not Applicable***

A Certificate of Confidentiality will be applied for once IRB approval is received.
Study data will come from interviews, questionnaires, and physiological testing. All data collected will be labeled with a study ID code and stored in a locked filing cabinet in a locked office at the Substance Abuse Treatment Center. The master list for study ID codes will be kept in a locked file cabinet in a different locked office from where data are stored and will only be accessible by the PI and the project coordinator. The data will be accessible by the PI, project coordinator and the data entry and analysis team. Following American Psychological Association (2001) guidelines, all samples and data will be maintained for 5 years after publication of the data.

Risks/Benefits: *Describe any potential or known risks. This includes physical, psychological, social, legal or other risks. Estimate the probability that given risk may occur, its severity and potential reversibility. If the study involves a placebo or washout period, the risks related to these must be addressed in both the protocol and consent. Describe the planned procedures for protecting against or minimizing potential risks and assess their likely effectiveness. Where appropriate, discuss*

plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. Discuss the potential benefits of the research to the subjects and others. Discuss why the risks to the subjects are reasonable in relation to the anticipated benefits to subjects and others. Discuss the importance of the knowledge gained or to be gained as a result of the proposed research and why the risks are reasonable in relation to the knowledge that reasonably may result. If there are no benefits state so.

Potential Risks

This study, like all research studies involving human participants, is not devoid of risk. (a) There is a risk that contraceptive management program participants will experience side effects from using prescription contraceptives. (b) A potential risk to all subjects is that an unauthorized person would obtain access to the information contained in their study files during study participation. (c) There is a risk that some participants may misuse vouchers or the monetary compensation for completing the baseline and follow-up assessments. (d) Participants may experience some distress or personal embarrassment related to urine collection or in answering questions about sensitive topics (sexual behavior, drug use) during the assessments. (e) There is a small risk of bruising, pain and infection at the site of a blood draw.

Protection Against Risk

(a) Contraceptive management program participants will be carefully screened prior to initiation of prescription contraceptives. Importantly, a woman who chooses an IUD will be screened for Chlamydia and gonorrhea on the day of IUD insertion and those who test positive will be treated for the infection(s) (ACOG, 2011). In addition, only skilled, experienced providers (e.g., Dr. Meyer, Co-I on the proposed study) will perform IUD insertions. Following prescription contraception initiation, contraceptive management program participants will be monitored closely for side effects and at a frequency greater than in usual clinical care. They will be counseled about side effects that require immediate medical attention and helped to manage more minor side effects. More common but minor side effects include: menstrual irregularities (e.g., irregular bleeding; longer, heavier bleeding; spotting between periods; amenorrhea); cramping or backache; nausea and/or vomiting; sore breasts; changes in sex drive; headache; changes in appetite or weight gain; hair loss or increased facial/body hair; depression; vaginal discharge, irritation, or infection; discoloring or scarring of skin (implant only); and pain at insertion site (implant only). Many of these side effects resolve with time. Rare but serious side effects include: heart attack; stroke; blood clots; high blood pressure; liver tumors; gallstones; yellowing of the skin or eyes; and uterine perforation (IUD only). More generally, the risks associated with prescription contraceptive use are less than the risks associated with pregnancy (Zieman et al., 2010). (b) All study files will be stored in locked filing cabinets. (c) All voucher purchases must be approved in advance by project staff who retain veto power. Misuse of vouchers has not been a problem in prior studies at our clinic or in the literature (e.g., Dempsey et al., 2008; Festinger et al., 2005, 2008). (d) Participants will have the opportunity to meet with the PI and/or other investigators to discuss their discomfort. Participants will also be offered the opportunity to obtain feedback on their assessment data following completion of the study. (e) Using trained personnel and sterile techniques on all blood draws minimizes the risk of bruising, pain and infection.

Therapeutic Alternatives: *List the therapeutic alternatives that are reasonably available that may be of benefit to the potential subject and include in the consent form as well.*

☐ ***Not Applicable***

Participants can avoid an unintended pregnancy by not having sex or by practicing safer forms of sex (e.g., mutual masturbation). In addition, contraceptives and other family planning services are available at local clinics (e.g., Planned Parenthood) and from local medical providers (e.g., primary care physicians, OB/GYNs).

Data Safety and Monitoring: *The specific design of a Data and Safety Monitoring Plan (DSMP) for a protocol may vary extensively depending on the potential risks, size, and complexity of the research study. For a minimal risk study, a DSMP could be as simple as a description of the Principal Investigator's plan for monitoring the data and performance of safety reviews or it could be as complex as the initiation of an external, independent Data Safety and Monitoring Board (DSMB). The UVM/FAHC process for review of adverse events should be included in the DSMP.*

Our overall monitoring plan consists of ongoing, close monitoring of data and safety issues at the UVM site by the PI, Co-Investigators, and other project staff as well as monitoring outside the UVM site by a Data and Safety Monitoring Board (DSMB). We provide more detail below regarding particular areas recommended by Notice OD-00-038.

Monitoring at the UVM site.

Patient eligibility and status. All recruitment will be managed by trained research staff under the supervision of the PI using specialized forms and procedures. Research staff will contact potential participants about scheduling and completing the intake assessment. Following the intake assessment, eligible women will provide informed consent with the PI or a person designated by the PI. The status of all active participants will be reviewed weekly at staff meetings between the PI, Co-Investigators and trained support staff.

Rigorous data management/quality assurance. Study data will come from participant screening and intake sessions, urine specimen collections, follow-up visits, and follow-up assessments. Study data collection will be primarily with paper questionnaires that will be manually double-entered into computers for analysis. The two coded data sets will be compared against each other for agreement and discrepancies will be resolved and corrected using source materials. Current compared data sets from will be delivered electronically to the UVM Bioinformatics Facility on a regular basis where they will again be reviewed for accuracy. Any apparent errors will be resolved and corrected under supervision of the biostatistician and using source materials. The biostatistician and PI will discuss any problems at monthly data meetings.

Auditing procedures. Review of any problems related to quality of data collection, transmission or analyses and of any AEs and SAEs that occurred during the past week will occur at weekly research staff meetings. Interim analyses of data will be conducted when half the subjects have been entered or at other times based on the discretion of the PI and biostatistician.

Reporting mechanisms of AEs and SAEs to the UVM IRB and Funding Agency. AEs and SAEs will be assessed at each subject visit by a trained staff member and copies of all reports noting AEs and SAEs will be kept in a central file as well as in the individual subject's chart. AEs will be discussed at the weekly research staff meetings. Any SAE will be brought to the attention of the PI or a Co-Investigator as soon as possible and not longer than 24 hours. Any death that is unexpected AND related to the protocol will be reported to the UVM IRB within 48 hours of the PI learning of the event. All SAEs, study or non-study related, require reporting to NIDA and DSMB within 72 hours of the PI learning of the event; unexpected and related SAEs require reporting to the IRB within 7 days of the PI learning of the event. All SAEs will be followed through ongoing consultation with the physician caring for the patient until they resolve, result in death, or stabilize and are not expected to improve. Any non-serious AE that is unexpected AND related requires reporting to the UVM IRB within 7 days of the PI learning of the event.

Monitoring outside the UVM site.
A Data and Safety Monitoring Board (DSMB) has been established to oversee the safety and ethics of this study. The following policies and procedures relate to the DSMB process that will be employed to assure an appropriate level of monitoring for a study with a vulnerable population.

1. Authority: Decisions of the DSMB are advisory to the trial and its investigators. However, special circumstances and documentation are required when DSMB recommendations are not followed.

2. Responsibilities of the DSMB: The DSMB is charged with monitoring and evaluating three aspects of the clinical trial. These include:

Safety: Reviewing interim data for a trial in order to assure the continuing safety of subjects. The DSMB may review adverse events and serious adverse events reported to the sponsor or IRB as applicable.

Study Progress: Outcome data will be reviewed to assure that the study can be completed in a reasonable time frame to be of significant clinical relevance.

Efficacy: Reviewing interim analyses of outcome data prepared by the study statistician to assure that the data are consistent with identifying clinical efficacy.

The trial will continue to be reviewed by the DSMB until all interventions are discontinued and issues raised by the Board are concluded to the Board's satisfaction.

3. Membership: Biographical information for the three DSMB members follows below.

Hendree E. Jones, Ph.D. (Chair). Dr. Jones is Professor of Obstetrics and Gynecology and Director of UNC Horizons at UNC Chapel Hill. She is an internationally recognized expert in research and clinical issues pertaining to opioid-dependent women and their families. Most recently, she was the Principal Investigator of a NIDA-funded, multi-site, randomized controlled trial comparing the safety and efficacy of methadone and buprenorphine for the treatment of opioid dependence during pregnancy, where she worked successfully with a six-member DSMB. Dr. Jones serves on NIH review panels and as a consultant to the U.S. State Department, the United Nations, and the World Health Organization and has more than 115 peer-reviewed journal articles and other scholarly contributions to her credit.

Ira M. Bernstein, M.D. (Member). Dr. Bernstein is Professor and Chair of Obstetrics, Gynecology and Reproductive Sciences and Senior Associate Dean for Research at the University of Vermont (UVM). He is board certified in Obstetrics and Gynecology and Maternal Fetal Medicine. Dr. Bernstein is also an NIH-funded researcher with expertise in maternal physiology and fetal growth and has authored more than 80 peer-reviewed publications. In addition, Dr. Bernstein has more than 15 years of experience with clinical research regulation and adverse event monitoring, having served as the chair or vice-chair of such committees at both the UVM Institutional Review Board and General Clinical Research Center.

Laura J. Solomon, Ph.D. (Member). Dr. Solomon is a Research Professor of Psychology (Emeritus) and Family Medicine and is affiliated with the Office of Health Promotion Research at UVM. She has conducted numerous intervention studies designed to modify behaviors that place people, especially low-income women, at risk for illness and disease. Examples relevant to the proposed study include studies testing voucher-based incentives to promote smoking cessation among low-income pregnant women and other behavioral interventions to promote nicotine replacement use among low-income female smokers, safer sex practices among women in low-income housing, and breast cancer screening in community samples. She is the author of more than 100 journal articles and has edited two books.

4. Meetings: The DSMB will meet at least once annually or more frequently as dictated by issues as they arise. Meetings of the DSMB will be coordinated by the PI. Interim data reports will be supplied to the DSMB by the PI at least two weeks prior to each meeting. Data will be supplied in tabular and electronic forms per request of the DSMB. Examples of acceptable interim reports will be made available to investigators to facilitate their interaction with the DSMB. In addition, any new information from external sources that could alter the DSMB's perception of the trial, for example, findings published from a similar trial or regarding the intervention used in the trial, will be assembled and summarized with respect to the PI's perception of its importance.

5. Meeting Procedure: Prior to each formal meeting, it is the responsibility of the chair (Hendree E. Jones) of the DSMB to assure that the required data have been submitted with appropriate explanations. This material will be mailed to board members at least two weeks prior to the DSMB meeting. The formal meeting of the DSMB for the trial shall consist of three parts. The first part is an open session in which members of the research team, including the Principal Investigator, medical Co-Investigators (e.g., Dr. Meyer) and the study statistician, are available to review data with the DSMB. Following the open session, the DSMB may hold a closed session. The study statistician must be available to discuss the results with the DSMB during the closed session. The third phase of each meeting is a final executive session involving only voting DSMB members and may be held to allow the DSMB to discuss general conduct of the trial and all outcome results, including adverse events, to develop recommendations, and to take votes as necessary.

Clerical support will be provided by the UVM site as requested by the chair of the DSMB. Following each DSMB review, the chair shall prepare a written report to be finalized within 20 working days following the formal meeting and be sent to the PI.

6. Recommendations from the DSMB: Following each study review, the DSMB will recommend either:

   a. Continuation of the trial using the current protocol and statistical plan.
   b. Continuation of the project with modifications as outlined by the board.
   c. Immediate suspension of the trial for safety reasons with a recommended plan of follow-up to minimize subject harm.
   d. Placing a clinical hold on the trial. This should include freezing further accrual. Subjects may continue on their assigned treatments until clarifications requested by the Board are resolved.
   e. Termination of the trial because of: 1) treatment effectiveness demonstrated earlier than expected ("early stopping"); 2) futility of further accrual to meet the trial's goal; 3) discovery of new information that precludes completion of the trial; and/or 4) structural problems in trial execution that are not amenable to correction.

7. Other Issues:

   Release of outcome data. The DSMB will review outcome data. Outcome data will not be made available from the DSMB until accrual has been completed, all patients have completed their treatment, and the interpretations of the outcome data has been agreed upon by the DSMB, the statistician and Principal Investigator. Any release of outcome data prior to the DSMB's recommendation for general dissemination of results must be reviewed and approved by the DSMB.

   Confidentiality: No communications, either written or oral, of the deliberations or recommendations of the DSMB will be made outside of the DSMB except as provided by written policy. Outcome results are strictly confidential and must not be divulged to any nonmember of the Board except as indicated by policy.

   Conflict of Interest: Individuals invited to serve on the DSMB will disclose any potential conflict of interests, whether real or perceived, to the Principal Investigator, the chair of the DSMB, or institutional officials in accordance with UVM policy.

Adverse Event and Unanticipated Problem (UAP) Reporting: *Describe how events and UAPs will be evaluated and reported to the IRB. All protocols should specify that, in the absence of more stringent reporting requirements, the guidelines established in the Committees on Human Research "Adverse Event and Unanticipated Problems Reporting Policy" will be followed. The UVM/FAHC process for review of adverse events and UAPs to subjects or others should be included in the DSMP.*

AEs will be reported as described on the prior page in the Data and Safety Monitoring section using procedures that are consistent with the UVM IRB's Unanticipated Problems Reporting Policy. This policy will also be followed in terms of evaluating and reporting unanticipated problems.

Withdrawal Procedures: *Define the precise criteria for withdrawing subjects from the study. Include a description of study requirements for when a subject withdraws him or herself from the study (if applicable).*

Participants may withdraw from the study at any time. If they withdraw before the study is completed, they will be compensated for their participation up to that time.
Participants may also be withdrawn from the study. Possible reasons for withdrawing participants include an event that makes their continued participation unsafe (e.g., development of a medical condition that precludes prescription contraceptive use) or an inability to work with study staff (e.g., threatening study staff). If participants are withdrawn from the study, they will be compensated for their participation up to that time.

Sources of Materials: *Identify sources of research material obtained from individually identifiable human subjects in the form of specimens, records or data. Indicate whether the material or data will be obtained specifically for research purposes or whether use will be made of existing specimens, records or data.*

The research material will be obtained from interviews, questionnaires, and physiologic testing. All data collection will be specifically for research purposes.

DRUG AND DEVICE INFORMATION

Investigators are encouraged to consult the FAHC Investigational Pharmacy Drug Service (847-4863) prior to finalizing study drug/substance procedures.

Drug (s) [X] ***Not applicable***

Drug name – generic followed by brand name and common abbreviations. Availability – Source and pharmacology; vial or product sizes and supplier. If a placebo will be used, identify its contents and source. (attach investigational drug brochure)

Preparation: Reconstitution instructions; preparation of a sterile product, compounded dosage form; mixing guidelines, including fluid and volume required. Identify who will prepare.

Storage and stability – for both intact and mixed products.

Administration – Describe acceptable routes and methods of administration and any associated risks of administration.

Toxicity – Accurate but concise listings of major toxicities. Rare toxicities, which may be severe, should be included by indicated incidence. Also adverse interactions with other drugs used in the protocol regimen as well as specific foods should be noted. Address significant drug or drug/food interactions in the consent form as well. List all with above details.

Is it FDA approved: (include FDA IND Number)

1. *in the dosage form specified? If no, provide justification for proposed use and source of the study drug in that form.*
2. *for the route of administration specified? If no, provide justification for route and describe the method to accomplish.*
3. *for the intended action?*

Device (s) [X] ***Not applicable***

Device name and indications (attach investigational device brochure)

Is it FDA approved: (include FDA IDE Number)

1. *for indication specified? If no, provide justification for proposed use and source of the device.*

Risk assessment (non-significant/significant risk) - PI or sponsor needs to assess risk of a device based upon the use of the device with human subjects in a research environment.

SUBJECT CHARACTERISTICS, IDENTIFICATION AND RECRUITMENT

Subject Selection: *Provide rationale for subject selection in terms of the scientific objectives and proposed study design.*

The rate of unintended pregnancy among opioid-dependent women is extremely high, with nearly 9 of every 10 pregnant opioid-dependent. Despite these dire statistics, there is a dearth of scientific knowledge about contraceptive use in this population. The limited research available indicates that 75% of opioid-maintained women either use no contraception (45%) or less effective methods like condoms (30%). The modest increases in condom use produced by existing interventions underscore the need to develop other approaches that promote use of more effective contraceptives (e.g., birth control pills, IUDs, implants) in this special population.

Vulnerable Populations: *Explain the rationale for involvement of special classes of subjects, if any. Discuss what procedures or practices will be used in the protocol to minimize their susceptibility to undue influences and unnecessary risk (physical, psychological, etc.).*

[ ] ***Not applicable***

The proposed intervention targets opioid-maintained women given the extremely high rate of unintended pregnancy in this group. We have extensive experience working with drug-dependent populations generally and with opioid-dependent women specifically. The protocol calls for careful monitoring of women assigned to the experimental conditions, monitoring that is more extensive than they would receive in routine clinical care. The Data and Safety Monitoring Board that will regularly review the safety and progress of the proposed trial provides additional protection.

Number of Subjects: *What is the anticipated number of subjects to be enrolled at UVM/FAHC and in the case of a multi-center study, with UVM/FAHC as the lead, the total number of subjects for the entire study.*

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Inclusion/Exclusion Criteria: *Eligibility and ineligibility criteria should be specific. Describe how eligibility will be determined and by whom. Changes to the eligibility criteria at a later phase of the research have the potential to invalidate the research.*

For inclusion, participants must (1) be 18-44 years of age, (2) be pre-menopausal and have no history of a tubal ligation or hysterectomy, (3) have had heterosexual vaginal sex in the past 3 months, (4) have no plans to become pregnant in the next 6 months, (5) be medically eligible to use prescription contraceptives, (6) report no recent prescription contraceptive method use (i.e., no use of pills, patch, ring, implant, or IUD in the past 7 days or depot injection in the past 3 months), (7) have been in opioid maintenance treatment for at least the past 30 days, (8) have no plans to leave the geographic area in the next 12 months, (9) not be facing imminent incarceration, and (10) be English-speaking. Only failure to meet the aforementioned criteria or refusal to participate will be reasons for exclusion.

Inclusion of Minorities and Women: *Describe efforts to include minorities and women. If either minorities or women are excluded, include a justification for the exclusion.*

Because this study involves women of childbearing age, no adult males will be enrolled. Minority representation is anticipated to parallel the minority distribution of the population of Burlington, VT and surrounding areas, where minorities (primarily American Indians and African Americans) comprise approximately 8% of the general population. Members of minority groups will not be excluded.

Inclusion of Children: *Describe efforts to include children. Inclusion is required unless a clear and compelling rationale shows that inclusion is inappropriate with respect to the health of the subjects or that inclusion is inappropriate for the purpose of the study. If children are included, the description of the plan should include a rationale for selecting or excluding a specific age range of children. When included, the plan must also describe the expertise of the investigative team in working with children, the appropriateness of the available facilities to accommodate children, and the inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose of the study.* ***If children are excluded*** *then provide appropriate justification. Provide target accrual for this population.*

Women between the ages of 18-21 will be included in the study. Federal regulations require that patients receiving opioid maintenance be at least 18 years old.

For protocols including the use of an investigational drug, indicate whether women of childbearing potential have been included and, if not, include appropriate justification.

If HIV testing is included specifically for research purposes explain how the test results will be protected against unauthorized disclosure. Include if the subjects are to be informed of the test results. If yes, include the process and provision for counseling. If no, a rationale for not informing the subjects should be included.

X ***Not applicable***

Recruitment: *Describe plans for identifying and recruitment of subjects. All recruitment materials (flyers, ads, letters, etc) need to be IRB approved prior to use.*

Initial recruitment efforts will focus on the Chittenden Clinic, the methadone maintenance clinic at UHC. All women who have been in treatment for at least 30 days will be given a screening form when they arrive at the clinic for their methadone dosing and counseling appointments. Those who (1) indicate on the screening form that they are not pregnant now and do not want to get pregnant in the next 6 months and (2) sign the screening form will be contacted by study staff to arrange an intake assessment.

FINANCIAL CONSIDERATIONS

Expense to Subject: *If the investigation involves the possibility of added expense to the subject (longer hospitalization, extra studies, etc.) indicate in detail how this will be handled. In cases where the FDA has authorized the drug or device company to charge the patient for the experimental drug or device,* ***a copy of the authorization letter from the FDA or sponsor must accompany the application. Final approval will not be granted until the IRB receives this documentation.***
There are very limited circumstances under which study participants may be responsible (either directly or via their insurance) for covering some study-related expenses. If the study participant or their insurer(s) will be billed for any portion of the research study, provide a justification as to why this is appropriate and acceptable. For example, if the study involves treatment that is documented standard of care and not investigational, state so. In these cases, the protocol and the consent should clearly define what is standard of care and what is research.

NA

Payment for participation: *Describe all plans to pay subjects, either in cash, a gift or gift certificate. Please note that all payments must be prorated throughout the life of the study. The IRB will not approve a study where there is only a lump sum payment at the end of the study because this can be considered coercive. The amount of payment must be justified. Clarify if subjects will be reimbursed for travel or other expenses.*

[ ] ***Not applicable***

All participants will receive $35 in cash for completing the intake assessment and each assessment at 1, 3, 6, and 12 months after study entry.
Participants in the WHO contraception protocol + incentives condition will also have the opportunity to earn voucher-based incentives each time they attend follow-up visits. Voucher values will start at $15 and escalate in value by $2.50 for each consecutive visit attended. Missed visits will result in the voucher value for the next visit being reset back to the initial value of $15, but two consecutive visits will restore the voucher value back to its pre-reset value. This reset contingency helps promote consistent attendance and has been used in other studies using vouchers to reinforce appointment attendance (e.g., Svikis et al., 2007). No cash will be provided to participants; rather, participants will be able to purchase retail items and services in the local community by submitting requests to research staff. Research staff will have the right to veto any request on ethical grounds (e.g., requests for alcoholic beverages will be vetoed). This system has worked well in other voucher programs by our group and we anticipate few instances where a veto will be necessary. Nevertheless, retaining veto power is important to maintaining the integrity of the incentive program against instances of poor judgment in the use of vouchers that could reflect poorly on all involved. Maximum possible earnings will be $390.

Collaborating Sites*. When research involving human subjects will take place at collaborating sites or other performance sites when UVM/FAHC is the lead site, the principal investigator must provide in this section a list of the collaborating sites and their Federalwide Assurance numbers when applicable. (agreements may be necessary)*

[X] ***Not applicable***

INFORMED CONSENT

Consent Procedures*: Describe the consent procedures to be followed, including the circumstances under which consent will be obtained, who will seek it, and the methods of documenting consent.*

Note: Only those individuals authorized to solicit consent may sign the consent form confirming that the prospective subject was provided the necessary information and that any questions asked were answered.

Consent will be obtained by key personnel in a quiet, private office at UHC with unlimited time for questions.

Information Withheld From Subjects: *Will any information about the research purpose and design be withheld from potential or participating subjects? If so, explain and justify the non-disclosure and describe plans for post-study debriefing.*

[X] ***Not applicable***

Consent, Assent, and HIPAA Authorization. *Specify the form(s) that will be used e.g. consent (if multiple forms explain and place identifier on each form), assent form and/or HIPAA authorization (if PHI is included). These form(s) must accompany the protocol as an appendix or attachment.*

Screening ICF
Study ICF

Summary of important changes after trial commencement:

- Added a quiz to the consent process to ensure participants understand their assigned condition
- Added "at least 8 weeks postpartum" as an inclusion criterion so that the clinical practice of reviewing or initiating contraceptive use at the 4-6 week postpartum visit (ACOG, 2012) did not inadvertently influence trial outcomes
- Changed inclusion criterion from "being in OMT for at least 30 days" to "being in OMT" to be more inclusive
- At the 6-month assessment, changed from verifying pill/patch/ring use using serum hormone levels to verifying using pill counts, visual inspection, and pelvic exam, respectively, and from verifying IUD use using ultrasound to verifying via a pelvic exam due to issues around the feasibility of the original verification procedures
- Added method verification at 12-month assessment