PROTOCOL TITLE:

Nitrous Oxide versus IV Sedation for Anesthesia (NOVIA)

Protocol ID: 16-101

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REGULATORY FRAMEWORK:

Please indicate all that apply:

☐	DOD (Department of Defense)
☐	DOE (Department of Energy)
☐	DOJ (Department of Justice)
☐	ED (Department of Education)
☐	EPA (Environmental Protection Agency)
☐	FDA (Food and Drug Administration)
☐	HHS (Department of Health and Human Services)
☒	Other: Society of Family Planning

Is this a clinical trial under ICH-GCP E6? ☒ Yes ☐ No

If yes, please confirm that the research team is familiar with and agrees to comply with the investigator requirements cited in ICH-GCP E6. ☒ Yes ☐ No

ICH-GCP E6 can be accessed by copying and pasting this URL into your browser: http://www.fda.gov/downloads/Drugs/Guidances/ucm073122.pdf

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1. Objectives

1.1. We propose a multi-site, double-blinded, randomized, noninferiority clinical trial of inhaled nitrous oxide with oxygen (N_2O/O_2) versus intravenous (IV) sedation, with fentanyl and midazolam, for pain management in adult women having an abortion procedure between 12 and 16 weeks gestational age. We will evaluate whether nitrous oxide is a feasible and acceptable alternative to IV sedation for pain management during early second trimester D&E. We will measure maximum procedural pain using a visual analog scale (VAS) and satisfaction with anesthesia using the Iowa Satisfaction with Anesthesia Scale (ISAS).

1. 2.The contribution of the proposed research is to determine if nitrous oxide is a safe and effective alternative to intravenous (IV) sedation for second trimester abortion. We hypothesize that women receiving nitrous oxide anesthesia will have non-inferior pain and satisfaction scores compared to women receiving IV sedation.

1.2.1. *Primary Objective 1:* To compare women's maximum procedural pain measured on a visual analog scale during a surgical abortion between 12 weeks 0 days to 16 weeks 0 days gestational age between women randomized to nitrous oxide versus intravenous sedation. Our ***hypothesis*** is that women receiving nitrous oxide will report non-inferior pain scores as compared to women receiving intravenous sedation.

1.2.2. *Primary Objective 2:* To compare women's satisfaction with procedural pain management measured on the Iowa Satisfaction with Anesthesia Scale (ISAS) following a surgical abortion between 12 weeks 0 days to 16 weeks 0 days gestational age between women randomized to nitrous oxide versus intravenous sedation. Our ***hypothesis*** is that women who received nitrous oxide will report non-inferior satisfaction scores as compared to women receiving intravenous sedation.

1.3. **Secondary Objectives:** To compare duration of time from procedure completion to ready for clinic discharge, as determined by having an Aldrete score of 8 or greater, between the two groups. To compare duration of procedure, defined as time from speculum insertion to post-procedure speculum removal, between the two groups.

2. Background

2.1. Second trimester abortion is a painful procedure(1). Despite the importance of pain management in abortion care, options for anesthesia in the outpatient setting are limited. According to North American members of the National Abortion Federation, the most common pain management offered for second trimester abortion is a combination of local anesthesia and moderate IV sedation(2). With IV sedation, the American Society of Anesthesiologists recommends fasting for 6 hours prior to the procedure and extended post-procedure monitoring(3). Safety considerations also require that women have a ride home from the clinic creating a burden for those with limited resources or who travel long distances. An ideal anesthetic would offer women adequate pain relief while meeting her need for privacy, rapid recovery, and safety.

Nitrous oxide is an inhaled gas which can be titrated in conjunction with oxygen. Nitrous oxide is attractive in the outpatient clinic setting because delivery systems are relatively inexpensive, training is not burdensome and administration of the gas is non-invasive. Its onset of action is almost immediate and effects can be rapidly reversed with administration of 100% oxygen with minimal to no residual side effects. Prior research utilizing nitrous oxide for abortion is limited.

2.2. Two studies have evaluated the use of nitrous oxide (50% nitrous oxide/50% oxygen) for first trimester abortion. Both studies used nitrous oxide in addition to IV medications. Kan et al found that a 50:50 mix of nitrous oxide/oxygen did not additionally reduce pain in women already

receiving IV sedation in an operating room setting(4). Agostini et al evaluated nitrous oxide versus oxygen alone in women undergoing first trimester abortion with local anesthesia and IV paracetamol in an office setting(5). There was no difference in mean operative pain scores between the study and intervention groups. Our proposed study differs from both those studies in the use of a higher concentration of nitrous oxide and in its use as the primary agent for pain management.

One pilot study has examined the use of nitrous oxide as an alternative to oral sedation in first trimester abortion with promising results. Mean pain scores were similar between groups with maximum procedural pain rated 55.7mm ± 20.8 for women randomized to nitrous oxide and 61.3mm ± 20.2 for oral sedation along a 100mm visual analog scale(6). The follow up randomized clinical trial evaluated maximum pain scores in an oral sedation group versus a nitrous oxide group. The manuscript is under review; personal communication with the principal investigator reveals the following preliminary results: Mean maximum procedural pain was similar between groups (60.75mm [SD= 24.36] in the oxygen group and 55.7mm [SD=20] in the nitrous group). A limitation of this study is that pain was evaluated in the study group after the nitrous oxide dissipated while pain was evaluated in the control group while still under the effects of oral sedation. In our proposed study, pain will be evaluated immediately after the procedure, while both groups are still under the influence of the sedation agent.

Additional studies have been performed at the University of New Mexico (UNM) utilizing nitrous oxide for intrauterine device (IUD) insertion in nulliparous women as well as for transcervical sterilization. These manuscripts are pending publication however personal communication has revealed the following information. In the IUD study, fixed 50:50 ratio of nitrous oxide was compared to 100% oxygen with pain measured after nitrous oxide had dissipated. Women who received nitrous oxide did not report lower pain scores however, they reported higher rates of satisfaction with pain control. In a randomized study of women undergoing transcervical sterilization, a 70:30 nitrous oxide concentration group was compared to an oral sedation group. Pain scores were evaluated while women were still under the influence of medications. This study demonstrated significantly lower pain scores (22.8mm compared to 54.5mm control) in the nitrous oxide group. Total procedure time for transcervical sterilization was notably shorter for women who were randomized to nitrous oxide; however, both groups

experienced longer procedure times than IUD insertion and first trimester abortion.

These studies have informed the proposed research by showing that:

(1) Women are willing to participate in studies of alternative forms of anesthesia, including nitrous oxide.

(2) Fixed 50:50 dosing of nitrous oxide is likely inadequate at providing pain relief; rapid titration is a superior methodology.

(3) Timing of pain score collection is important and should be standardized across groups.
(4) Nitrous oxide appears to be more effective for longer procedures.

2.3. The contribution of the proposed research is to add to the limited literature on novel anesthetic options for second trimester abortion and, specifically, to evaluate the effectiveness of nitrous oxide as a more patient-centered alternative to IV sedation for second trimester abortion. This contribution to the literature is significant because current anesthetic options are limited and insufficient.

3. Study Design

3.1. Selection of Participants/ Target Population:
We propose a multi-site, double-blinded, randomized, non-inferiority clinical trial of inhaled nitrous oxide versus intravenous sedation for pain management in adult women receiving an abortion between 12 and 16 weeks gestational age. Our study will be conducted at two clinical sites: the University of New Mexico Center for Reproductive Health Clinic and University of Colorado Comprehensive Women's Health Center. All study endpoints will be collected on the date of procedure and thus, no follow up will be necessary. In order to be able to show that nitrous oxide is non-inferior on both primary endpoints we will recruit 150 women at two treatment sites.

3.2. Study randomization will occur just prior to initiation of the abortion procedure to nitrous oxide or IV sedation. The research coordinator, participant and providers will be masked to the treatment allocation. The only unmasked member of the team will be the nurse administering the medications. Investigators will utilize a centralized stratified block randomization with allocation listed as "study drug 1" and "study drug 2".

Study coordinators will determine allocation and discuss this with clinic nurses. The meanings of these labels will be separately revealed to clinical nursing staff responsible for administration.

4. Inclusion and Exclusion Criteria

4.1. In order to be able to show that nitrous oxide is non-inferior on both primary endpoints we will recruit 150 women at two treatment sites. This study will be conducted at two separate clinics, both of which provide pregnancy termination services up to 22 weeks gestational age. In New Mexico, participants will be recruited from the University of New Mexico Center for Reproductive Health (CRH) clinic and in Colorado, participants will be recruited from the Comprehensive Women's Health Center (CWHC). These are both outpatient clinics where Family Planning fellows, faculty and Ob/Gyn residents perform second trimester procedures. Only Attendings and Fellows will perform procedures for study participants.

Eligibility for participation will be determined by clinic staff at initial encounter. In order to recruit efficiently, all women seeking pregnancy termination between 12w0d and 16w0d gestational age will be approached about possible study participation. Women presenting for abortion will be screened by clinic providers for eligibility. If determined to be eligible for participation and interested, women will meet with trained research staff in a private clinic room. The research staff will review the study as well as risks and benefits of participation.
Patients will have ample time to read the study consent and consider participation. Patients will be given the opportunity to ask questions regarding study participation. Potential participants will be reassured their clinical care will not be affected by their decision. If patients choose not to participate, they will not be approached again unless they broach the subject.

Recruitment materials in the form of flyers/brochures (in both English and Spanish) will be posted at UNM's CRH clinic. These materials will summarize the study and include a phone number for participants to contact research staff to inquire for more details about the study. Should the participant contact research staff prior to their appointment at CRH, the research coordinators will consult with the patient's provider to ensure eligibility. OB/GYN healthcare providers at UNM will also be provided with a flyer describing the study. The flyer will list eligibility criteria and will allow the providers to discuss the study with their patients should they show interest and meet criteria.

4.2. Eligibility criteria include women who desire an outpatient abortion and are at least 18 years of age, with a gestational age between 12 weeks 0 days and 16 weeks 0 days as determined by ultrasound crown rump length (for gestations up to 13 weeks) and biparietal diameter and femur length (for gestations exceeding 13 weeks), able to read and understand English or Spanish, and obtain reliable post-procedure transportation and observe fasting guidelines of 6 hours prior to procedure. The gestational age range of 12 to 16 weeks was elected as later second trimester abortions (>16 weeks) contain more heterogeneity of cervical preparation.

Exclusion criteria include contraindications to outpatient abortion that will significantly increase medical risk, such as major medical illness or concern for invasive placentation, contraindications to nitrous oxide (pernicious anemia, current treatment with bleomycin chemotherapy, active upper respiratory illness, or COPD), intrauterine fetal demise, chronic narcotic use or known adverse reaction to Fentanyl, Versed, or nitrous oxide. Additionally, women who are not felt to be able to safely receive the starting dose of IV sedation due to low body mass index may be excluded based on provider judgement.

4.3. In order to decrease medical risk and side effects, the study will also exclude patients who have recently undergone middle ear or ocular eye surgery, have sinusitis, ear problems, head trauma, bowel obstruction, and/or pneumothorax. This study will not recruit adults who are unable to consent or women who are currently incarcerated.

4. 4.This study will be recruiting women who can speak and read English and/or Spanish fluently.

5. **Number of Subjects**

5.1. We propose a multi-site, double-blinded, randomized, non-inferiority clinical trial of inhaled nitrous oxide versus intravenous sedation for pain management in adult women receiving an abortion between 12 and 16 weeks gestational age. Our study will be conducted at two clinical sites: the University of New Mexico Center for Reproductive Health Clinic and University of Colorado Comprehensive Women's Health Center. All study endpoints will be collected on the date of procedure and thus, no follow up will be necessary. In order to be able to show that nitrous oxide is non-inferior on both primary endpoints we will recruit 150 women at two treatment sites.

5.2. Through the University of New Mexico Center for Reproductive Health Clinic, we will recruit 75 participants.

5.3. Previous studies using the ISAS showed a mean score of 2.0 with a standard deviation of 1.3 in their treatment group and a difference of 0.6U between their group (7). This study evaluated patients who had received monitored anesthesia care (MAC), local anesthetic block plus or minus dexmedetomidine for different outpatient elective procedures. Our goal was to demonstrate non-inferiority between the two treatment groups and therefore, we calculated our sample size using a 1-sided, 2group test of non-inferiority. With a sample size of 150 (75 in each arm), we can detect a difference of 0.6U with 80% power and a Type I error of 5%.

With regard to the outcome of pain we looked to the literature on medical termination of pregnancy. A previous study studies reported pain scores for expulsion of a second trimester fetus during medical induction, with or without fentanyl for pain control. Median pain on a 100-mm VAS scale was reported as 70 mm (IQR=50, 80) (7). This approximately translates into a mean VAS score = 66.7mm and a SD = 22.2mm. Our goal was to demonstrate non-inferiority between the two treatment groups and therefore, we calculated our sample size using a 1-sided, 2-group test of non-inferiority. With a sample size of 100, we can detect a noninferiority margin of 15mm with 80% power and a Type I error of 5% for the outcome of pain. We plan to recruit 150 participants to assess the outcome of satisfaction. Further, we suspect average maximum VAS among patients having a surgical abortion may be less than for those undergoing second trimester induction. Therefore, we calculated differences that could be detected with 75 participants in each arm. If we estimate that our IV sedation group will have an average maximum VAS pain score of 50mm, and our nitrous group 54.8mm (with a SD of 25mm), we will preserve a non-inferiority margin 15mm and maintain 80% power with a Type I error of 5%.

6. Study Timelines

6.1. Investigators of this study anticipate that recruitment will be possible beginning as early as the Spring of 2016. Based on prior studies and chart review, investigators estimate that the University of New Mexico clinic performs approximately ten abortion procedures between 12 and 16 weeks gestational age a month. Additionally, The University of Colorado clinic performs approximately 15 procedures per month in this gestational age range. Investigators assume 80% enrollment based on prior abortion studies at the University of New Mexico utilizing nitrous oxide(6). Using this information, we approximate that recruitment would be complete in 8 months. We anticipate another month of data cleaning following end of recruitment and three months of data analysis.

This procedure may take one or two days. This would be the case regardless of whether or not the participant chose to enroll in the study. The extra time needed to participate in this study will be related to the amount of time needed to fill out study related questionnaires. We estimate this will take a total of less than two hours.

7. Study Endpoints

7.1. All study endpoints will be collected on the date of procedure and thus, no follow up will be necessary. In order to be able to show that nitrous oxide is non-inferior on both primary endpoints we will recruit 150 women at two treatment sites.

8. Research Setting

8.1. Our study will be conducted at two clinical sites: the University of New Mexico Center for Reproductive Health Clinic and University of Colorado Comprehensive Women's Health Center. These are both clinical sites well versed in managing the competing demands of a busy clinical schedule and robust research. These two sites have previously collaborated as part of a large multi-center study evaluating cervical preparation for intrauterine device insertion and have published on this experience(8). Both sites are part of a Clinical Translational Science Center and projects at both sites will be overseen by well respected members of the family planning community in conjunction with family planning fellows. Progress on the project will also be followed by the Fellowship in Family Planning as part of fellowship graduation requirements.

Clinically, both sites are also well suited for this project. The UNM Center for Reproductive Health and the University of Colorado Comprehensive Women's Health Center are both staffed by providers specialized in reproductive health and family planning. Additionally, nurses at both locations are well versed in outpatient moderate sedation. At the Center for Reproductive Health, nurses are trained in intravenous sedation and moderate sedation, maintain Advanced Cardiac Life Support (ACLS) certification and participate in quarterly safety drills. In order to provide nitrous oxide for this study, nursing staff and providers will also be responsible for reading material on the provision of nitrous oxide, attending a didactic course and successfully completing a test to establish proficiency.

8.2. This study will be conducted at two separate clinics, both of which provide pregnancy termination services up to 22 weeks gestational age.

In New Mexico, participants will be recruited from the University of New Mexico Center for Reproductive Health (CRH) clinic and in Colorado, participants will be recruited from the Comprehensive Women's Health Center (CWHC).

9. Resources Available

9.1. Our study will be conducted at two clinical sites: the University of New Mexico Center for Reproductive Health Clinic and University of Colorado Comprehensive Women's Health Center. These clinics are staffed with medical providers well versed in abortion care as well as outpatient anesthesia. All providers of nitrous oxide will complete education in administration and proficiency will be judged uniformly by successful completion of a test.

9.2. Nurses or physicians will be responsible for administering sedation and for monitoring for signs of adequate or over sedation and will have no other concurrent responsibilities. Additionally, nurses at both locations are well versed in outpatient moderate sedation. At the Center for Reproductive Health, nurses are trained in intravenous sedation and moderate sedation, maintain Advanced Cardiac Life Support (ACLS) certification and participate in quarterly safety drills. In order to provide nitrous oxide for this study, nursing staff and providers will also be responsible for reading material on the provision of nitrous oxide, attending a didactic course and successfully completing a test to establish proficiency. Clinic sites will be equipped for management of over sedation including reversal drugs, crash cart inclusive of bagmaskvalve device and nasal and oral airways as well as availability to transfer to higher level care as needed. Providers will also maintain ACLS certification.

Moderate sedation will be administered according to standardized study protocols which are the same at both sites. All participants must have observed fasting recommendations of two hours for clear liquids and six hours for solids. All participants will require an escort home in order to receive sedation. During the procedure, all participants will have noninvasive blood pressure and pulse oximetry monitoring.

9.3. Based on prior studies and chart review, investigators estimate that the University of New Mexico clinic performs approximately ten abortion procedures between 12 and 16 weeks gestational age a month. Additionally, The University of Colorado clinic performs approximately 15 procedures per month in this gestational age range. Investigators

assume 80% enrollment based on prior abortion studies at the University of New Mexico utilizing nitrous oxide(6). Using this information, we approximate that recruitment would be complete in 8 months. We anticipate another month of data cleaning following end of recruitment and three months of data analysis.

Research Staff and/or coordinators will provide study support by assisting with collecting data and adhering to study protocol. Staff have undergone the required training to manage and collect patient information. Data will be entered into RedCap on date of procedure by research staff at each respective site. Research staff will have completed institutional training in RedCap prior to initiation of study.

10. Prior Approvals

10.1. This protocol is also being reviewed by the University of Colorado IRB and a copy of that protocol is attached.

11. Multi-Site Research

11.1. This study is proposed as a multi-site randomized clinical trial design. All sites have the most current version of the protocol, consent document, and HIPAA authorization. Additionally, data will be shared across sites for quarterly reporting to the DSMB as well as for final data analysis and reporting. There may be times when we are required by law to share information. However, protected health information (PHI) will not be used in any published reports about this study.

Information collected as part of the study will be labeled with a study number. De-identified information will be entered into a computer database/locked file cabinet in the Principal Investigator's office. Dr. Singh, Dr. Teal and their associates will have access to this study information.

All engaged participating sites will safeguard data as required by law.

12. Study Procedures

12.1. Following enrollment, participants will be instructed in the use of the face mask and be instructed on completion of the VAS score. The participant will fill out baseline demographic information as well as baseline and anticipated VAS pain scores prior to the procedure. The patient will then either proceed to the procedure or cervical preparation as determined by the clinician. Cervical preparation and timing of

procedure (i.e. whether or not the patient requires a two day procedure) will be recorded in study documents.

Study randomization will occur just prior to initiation of the abortion procedure to nitrous oxide or IV sedation. The research coordinator, participant and providers will be masked to the treatment allocation. The only unmasked member of the team will be the nurse administering the medications. Investigators will utilize a centralized stratified block randomization with allocation listed as “study drug 1” and “study drug 2”. Study coordinators will determine allocation and discuss this with clinic nurses. The meanings of these labels will be separately revealed to clinical nursing staff responsible for administration.

Within the IV sedation group, women will receive 100mcg fentanyl and 2mg midazolam at least two minutes prior to initiation of the procedure. IV sedation with midazolam and fentanyl was chosen as the comparison group as it is the most frequently used method of pain control for outpatient second trimester procedures (2), as well as the current standard of care for both clinical recruitment sites. This group will also receive 100% oxygen by scented face mask. Women in the nitrous oxide group will receive an identical scented face mask through which nitrous oxide will be administered. The nitrous content of the gas will be titrated up by 20% every 5 breaths with a goal of 70% N_2O/ 30% O_2 as tolerated by the patient. If the participant is noted to have signs of over sedation or other uncomfortable side effects, the ratio will be titrated down to a lower concentration until side-effects or over sedation has resolved. If there is concern for over sedation, the nurse will provide initial management by decreasing nitrous in the nitrous group or providing 100% oxygen in the IV sedation group. If these initial interventions do not rapidly resolve over-sedation, the abortion provider will be unmasked to treatment allocation in order to appropriately participate in management. The nurse will be instructed to seek the help of the physician at any point to ensure patient safety. If the physician is at any point concerned about participant health or safety, treatment allocation will be revealed so optimal management can be provided. If allocation is unmasked to the treatment team, this will be recorded. Nitrous oxide will be administered for at least 2 minutes before the procedure is initiated. Maximum ratio will be recorded in study documents.

The abortion procedure will proceed in the usual fashion with the following standardized procedures:

- All providers will be family planning fellows or attendings.

- All patients will receive 600 mg of ibuprofen prior to the procedure.

- Participants will receive a bimanual exam at beginning of procedure. This will define the beginning of the procedure and this time will be recorded.

- Osmotic dilators, if present, will either be removed at this time or following insertion of the speculum.

- Following insertion of the speculum and surgical site preparation with betadine, or alternative for those allergic to iodine, a cervical block will be performed. This will be done with 2cc 1% buffered lidocaine injected intracervically at the tenaculum site, followed by 18cc 1% buffered lidocaine injected paracervically at the 4 and 8 o'clock positions.

- Rigid cervical dilation will be performed using Pratt or Denniston dilators to a cervical dilation which facilitates placement of the appropriately sized suction curette.

- Cervical preparation and dilation will not be standardized, but number and type of osmotic dilators as well as maximal diameter and type of rigid dilators used will be recorded.

The only laboratory and diagnostic procedures involved in this study are those that are part of standard care for second trimester abortion and are unrelated to study participation. For example, physicians will continue to perform preoperative ultrasound to establish gestational age by measurement of either crown rump length or biparietal diameter and femur length as well as establish placentation and position. Additionally, all participants will receive standard labs including preoperative hemoglobin as well as blood type.

If a participant verbalizes inadequate pain control, the physician will evaluate whether or not additional pain medications are needed based on clinical judgment and request additional anesthesia accordingly. If there is no risk of excessive bleeding or other procedural risk, the procedure will be halted for three minutes while the participant receives 100% oxygen. This waiting period allows time for participants in the nitrous oxide group to clear the gas prior to conversion to IV sedation. Following three minutes, participants in the IV sedation group will be given another 50 mcg of fentanyl. If pain control remains inadequate as

determined by the physician, the participant will be given another 50mcg of fentanyl. If pain control is still inadequate, procedure again will halt and additional midazolam will be given, to a maximum dosing of 200mcg fentanyl and 4mg midazolam. In the nitrous oxide group, following three minutes of 100% oxygen, the participant will be converted to IV sedation, at an initial dose of 100mg Fentanyl and 2 mg Midazolam. The physician will wait two minutes prior to resumption of procedure. All medications received will be recorded.

The D&E procedure will not be standardized between clinic and providers but procedure data including vacuum source, use of forceps and training of the provider will be collected. We will also collect information on any patients receiving intrauterine contraception. Timing of completion of the procedure will be defined by removal of the speculum. Successful procedure completion will be confirmed by each clinic's standard practices including uterine cri, ultrasound with thin endometrial complex, and/or tissue examination.

Immediately after procedure completion, participants in both groups will receive a VAS of maximum procedural pain. After completion of the VAS no further IV meds will be given and those in the nitrous oxide group will be converted to 100% oxygen. All participants will receive 100% oxygen for a minimum of three minutes.

Women will be monitored in the clinic for a minimum of 30 minutes following procedure. Discharge criteria will include a minimum Aldrete Scale score of 8 and receipt and verbalized understanding of discharge instructions. At this point, the participant will receive and complete an ISAS and VAS again recalling maximum procedural pain as well as current pain.

We will assess pain using the VAS at baseline (T0), immediately following removal of the speculum (which defines completion of the procedure [T1]), and at least thirty minutes following procedure (T2). Our first outcome is maximum pain experienced during the procedure; this will be obtained at T1. At T2, we will also assess satisfaction as measured using the ISAS.

Pain will be assessed using an unmarked 100mm VAS scale, with anchors at 0mm (left) being "no pain" and 100mm (right) being "pain as bad as it could be". Providers will also rate their perception of the amount of pain the participant experienced during the procedure using the same VAS scale.

Satisfaction will be assessed using the ISAS, a validated patient satisfaction measurement tool. This survey was specifically designed to assess participant satisfaction with anesthetic care itself. It consists of 11 questions, related to anesthetic care, each assessed on a Likert type scale ranging from “Disagree very much” to “Agree very much.” These items are then scored from -3 to +3 and an average score obtained. This instrument has been validated in multiple studies involving monitored anesthesia care, including multi-site studies(9).

All study end points will be collected on the date of the procedure. Participants will be followed up clinically as per each clinic's standards for follow up after D&E.

13. Data Analysis

13.1 Immediate post procedure VAS pain scores and ISAS scores will be analyzed using a 1-sided, 2-group test of non-inferiority with 80% power and a type I error of 5%. Randomization will be stratified according to gestational age by week as we suspect pain scores will be higher among women at later gestational ages. We set a non-inferiority margin of 15mm on the VAS scale based on clinical experience. The non-inferiority margin for the ISAS was set at 0.6U based on prior literature. Data will be analyzed according to intent to treat analysis followed by per protocol analysis. Only data obtained from patients following randomized treatment allocation will be analyzed among intent to treat analysis and all deviations from protocol including premature discontinuation or missing data excluded. If non inferiority is evident, we will assess for superiority of nitrous oxide using a two-group one-sided ttest of means.

14. Provisions to Monitor the Data to Ensure the Safety of Subjects

14.1. This study will utilize a data safety monitoring board (DSMB) with pre-determined stopping rules. A committee of external reviewers knowledgeable in Family Planning and abortion care, not involved in the study, will be recruited to review the data every 38 patients recruited. Review of clinic data from the past year at the University of Colorado’s clinic reveals that among women undergoing abortion in our target gestational age, 24+/-7% (CI 95%) received additional IV pain medication (dosing greater than 100mcg fentanyl or greater than 2mg midazolam) during their procedures. On quarterly enrollment review, if

greater than 35% of women in either group are requiring additional pain medications, the study will be halted and a full review triggered. Adverse event reporting will follow guidelines as proposed by Good Clinical Practice and collected as they occur or are reported by patients. These reports will be compiled for review by the DSMB quarterly; except for serious adverse events which will be reported to the IRB and DSMB within 24 hours of the occurrence. All subjects will have access to clinical care which is not dependent on study participation and will be notified of the availability of that care. Additionally, data will be shared across sites for quarterly reporting to the DSMB as well as for final data analysis and reporting. There may be times when we are required by law to share information. However, protected health information (PHI) will not be used in any published reports about this study.

15. Withdrawal of Subjects

15. 1.The research team will provide thorough screening to see if the patient will meet inclusion and exclusion criteria. Staff does not anticipate any circumstances which subjects may be withdrawn from the study without their consent.

15.2. Participants that require unmasking of study allocation or conversion to IV sedation will continue to be enrolled in the study and data will be analyzed according to intention to treat analysis.

15.3.There will be no collection of data bio specimens – N/A

15.4.Participants may withdraw from study involvement at any point in time and this will not affect their ability to obtain standard clinical care that day. All data points will be collected on the date of the procedure and therefore we anticipate loss to follow up and withdrawal rates will be low. Participants will be given the information on how to withdraw in the study consent.

16. Data Management/Confidentiality

16. 1.Only IRB-approved study team members will have access to RedCap and participant materials.

16.2.A study identification number will be assigned to each participant in lieu of using their personal information for identification (e.g., name). All participant data will be de-identified.

Participant data will be stored separately from any identifiers to protect patient privacy.

We will use de-identified cover sheets for document packets containing PHI.

16.3. This study will not be collecting information considered extremely sensitive or require additional protections such as HIV, genetic test results, mental health information, substance abuse information, and/or criminal records.

16.4. Data will be entered into RedCap on date of procedure by research staff at each respective site. Research staff will have completed institutional training in RedCap prior to initiation of study.

16. 5. Study packets will be stored in a secure file cabinet located in the clinics at each respective site. These cabinets will be kept locked at all times. In a separately locked file cabinet, stored in the same room, the study consents will be stored. This second file cabinet is locked with a second, separate key from all other study materials.

16.6. DSMB members will be given remote access to RedCap in order to review quarterly. The list that links participant information to the study identification number will be destroyed after data analysis is complete. Data will be stored for five years, and then will be destroyed.

16.7. As mentioned above, data will be entered into RedCap on date of procedure by research staff at each respective site.

16.8. The study will not be collecting photographs of patients – N/A

16.9. To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. The researchers can use this Certificate to legally refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you,

The Certificate cannot be used to resist a demand for information from personnel of the United States federal or state government agency sponsoring the project and that will be used for auditing or program evaluation of agency funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, medical care provider, or other person obtains your written consent to receive

research information, then the researchers will not use the Certificate to withhold that information.

17. Data and Specimen Banking – N/A

18. Risks to Subjects

18.1. Nitrous oxide and the IV pain medications have been associated with mild side effects including headache, dizziness, lightheadedness, or nausea and vomiting. Oxygen will be administered with either treatment to prevent any problems with a decrease in oxygenation. Everyone taking part in the study will be followed carefully for any side effects.

18.1.1. The UNM Center for Reproductive Health and the University of Colorado Comprehensive Women's Health Center are both staffed by providers specialized in reproductive health and family planning. Additionally, nurses at both locations are well versed in outpatient moderate sedation. At the Center for Reproductive Health, nurses are trained in intravenous sedation and moderate sedation, maintain Advanced Cardiac Life Support (ACLS) certification and participate in quarterly safety drills.

18.1.2. Moderate sedation will be administered according to standardized study protocols which are the same at both sites. All participants must have observed fasting recommendations of two hours for clear liquids and six hours for solids. All participants will require an escort home in order to receive sedation. During the procedure, all participants will have noninvasive blood pressure and pulse oximetry monitoring. Nurses or physicians will be responsible for administering sedation and for monitoring for signs of adequate or over sedation and will have no other concurrent responsibilities. Clinic sites will be equipped for management of over sedation including reversal drugs, crash cart inclusive of bag-mask-valve device and nasal and oral airways as well as availability to transfer to higher level care as needed. Providers will also maintain ACLS certification.

18.2. We will take measures to protect the security of all personal information, but we cannot guarantee confidentiality of all study data.

18.2.1. To minimize the privacy risk, the research team will do the following: Information contained in study records is used by study staff alone. The University of New Mexico and the University of Colorado Institutional Review Board (IRB) that oversee human subject research and/or other entities may be permitted to access records. Additionally, data will be shared across sites for quarterly reporting to the DSMB as well as for final data analysis and reporting. There may be times when we are required by law to share information. However, protected health information (PHI) will not be used in any published reports about this study.

Information collected as part of the study will be labeled with a study number. De-identified information will be entered into a computer database/locked file cabinet in the Principal Investigator's office. Dr. Singh, Dr. Teal and their associates will have access to this study information. Data will be stored for five years, and then will be destroyed.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law.

18.2.2. A study participant's privacy interests will be protected through the following measures:

The study will be thoroughly explained to the potential participant using the HRPO-approved consent form. As part of the informed consent process, the recruiting co-investigator or research assistant will provide as much time as needed for the potential participant to consider study participation. If any privacy interests are expressed by the patient, they will be addressed immediately by the research team member and if necessary, the issue will also be considered by the principal investigator.

A study identification number will be assigned to each participant in lieu of using their personal information for identification (e.g., name). All participant data will be de-identified.

Participant data will be stored separately from any identifiers to protect patient privacy.

We will use de-identified cover sheets for document packets containing PHI.

19. Potential Benefits to Subjects

19.1. The completion of this pain score and satisfaction analysis will show whether women randomized to nitrous oxide will report noninferior pain and satisfaction compared to women randomized to receive standard IV sedation. The contribution of the proposed research is to determine if nitrous oxide is a safe and effective alternative to intravenous sedation for second trimester abortion. This contribution to the literature is significant because current anesthetic options are limited and insufficient and there is a need for more patient-centered options.

19.2. Participants will receive no direct benefit by participating in the study, which will also be verbalized to the patient by trained research staff.

20. Recruitment Methods

20.1. This study will be conducted at two separate clinics, both of which provide pregnancy termination services up to 22 weeks gestational age. In New Mexico, participants will be recruited from the University of New Mexico Center for Reproductive Health (CRH) clinic and in Colorado, participants will be recruited from the Comprehensive Women's Health Center (CWHC). These are both outpatient clinics where Family Planning fellows, faculty and Ob/Gyn residents perform second trimester procedures. Only Attendings and Fellows will perform procedures for study participants.

20.2. Eligibility for participation will be determined by clinic staff at initial encounter. In order to recruit efficiently, all women seeking pregnancy termination between 12w0d and 16w0d gestational age will be approached about possible study participation. Women presenting for abortion will be screened by clinic providers for eligibility. If determined to be eligible for participation and interested, women will meet with trained research staff in a private clinic room.

20.3. Recruitment materials in the form of flyers/brochures (in both English and Spanish) will be posted at UNM's CRH clinic. These materials will summarize the study and include a phone number for participants to contact research staff to inquire for more details about the study. Should the participant contact research staff prior to their appointment at CRH,

the research coordinators will consult with the patient's provider to ensure eligibility.

OB/GYN healthcare providers at UNM will also be provided with a flyer describing the study. The flyer will list eligibility criteria and will allow the providers to discuss the study with their patients should they show interest and meet criteria.

21. Provisions to Protect the Privacy Interests of Subjects

21.1. We will take measures to protect the security of all personal information, but we cannot guarantee confidentiality of all study data.

To minimize the privacy risk, the research team will reassure the patient of the following: Information contained in study records is used by study staff alone. The University of New Mexico and the University of Colorado Institutional Review Board (IRB) that oversee human subject research and/or other entities may be permitted to access records. Additionally, data will be shared across sites for quarterly reporting to the DSMB as well as for final data analysis and reporting. There may be times when we are required by law to share information. However, protected health information (PHI) will not be used in any published reports about this study.

Information collected as part of the study will be labeled with a study number. De-identified information will be entered into a computer database/locked file cabinet in the Principal Investigator's office. Dr. Singh, Dr. Teal and their associates will have access to this study information. Data will be stored for five years, and then will be destroyed.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law.

21.2. A study participant's privacy interests during recruitment and data collection will be protected through the following measures:

The study will be thoroughly explained to the potential participant using the HRPO-approved consent form. As part of the informed consent process, the recruiting co-investigator or research assistant will provide as much time as needed for the potential participant to consider study participation. If any privacy interests are expressed by the patient, they will be addressed immediately by the research team member and if

necessary, the issue will also be considered by the principal investigator.

21.2.1. Participants will be recruited and consented in a private clinic setting. This will also include the recruitment and screening process as well as the data collection procedures.

22. Economic Burden to Subjects

22.1. Patients will not be billed for the cost of tests and procedures directly associated with this study. They will be informed that their third party payer (i.e. insurance company) is responsible for all other costs related to clinical treatment. This would be the case regardless of study involvement. There is no additional cost for the nitrous oxide over and above the cost of the procedure. Please see the table below.

Research Procedures	Number of Samples/Procedures	Responsible Party	
		Study	3rd Party Payer or Participant
Nitrous Oxide gas	75	☒	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
Standard of Care Procedures	**Number of Samples/Procedures**	**Responsible Party**	
		Study	**3rd Party Payer or Participant**
Termination Procedure	75	☐	☒
IV anesthesia	75	☐	☒
Diagnostics & Exam	75	☐	☒
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐

22.2. Participants will not be charged additionally for the nitrous oxide over and above the cost of the procedure.

22. 3. Patients will be informed during the consent process that if they become sick as a result of this study, the University of Colorado Hospital (UCH) or University of New Mexico Health Sciences Center (UNMHSC) will provide emergency treatment at their cost.

No commitment is made by UCH or UNMHSC to provide free medical care or money for injuries to participants in this study.

22.4. In the event that the patient has an injury or illness that is caused by participation in this study, patients will be reminded of the following: reimbursement for all related costs of care will be sought from the patient's insurer, managed care plan, or other benefits program. If they do not have insurance, they may be responsible for these costs. Patients will also be responsible for any associated co-payments or deductibles required by your insurance.

23. Compensation

23.1. Each participant will receive a $35 gift card as compensation for completing surveys in clinic.

24. Compensation for Research-Related Injury

24.1. In the event that the patient has an injury or illness that is caused by participation in this study, patients will be verbally reminded of the following during the consent process: reimbursement for all related costs of care will be sought from the patient's insurer, managed care plan, or other benefits program. If they do not have insurance, they may be responsible for these costs. Patients will also be responsible for any associated co-payments or deductibles required by your insurance.

25. Consent Process

25.1. In summary, patients presenting for abortion between 12 weeks 0 days and 16 weeks 0 days gestation will be screened by the abortion provider for eligibility criteria, only after participant has signed appropriate clinical consent forms for the abortion procedure. Enrollment in this study will in no way affect the patient decision to proceed with an abortion as patients will only be approached about the study after they have met eligibility criteria, ie desire to have a surgical abortion. If eligible, the woman will be approached for possible participation by a research assistant in a private clinic room. She will again be screened for eligibility and undergo informed consent for study enrollment if eligible and willing to participate. All participants determined eligible and approached will be documented per CONSORT guidelines.

25.1.1. The inclusion and exclusion criteria for study participation will be reviewed by a member of the research team to confirm eligibility. Prior to consent, the study will be described verbally to women, and potential subjects will receive a copy of the consent

form to read. If patients are comfortable enrolling in the study at that point, they may do so. All potential participants will be reassured that declining study participation will have no effect on the care that they receive. If patients choose not to participate, they will not be approached again unless they broach the subject. Women who elect to participate will be informed about the standard risks, benefits and alternatives of the procedure per standard of care. Co-investigators or trained research staff will follow HRPO regulations for written documentation of consent.

25.1.2. The consent discussion will take approximately 5-10 minutes after the consent has been read by the potential participant. Research staff will review the consent with the potential participant and provide ample opportunity for the subject to ask questions in a private setting.

25.1.3. Steps that will be taken to minimize the possibility of coercion or undue influence include providing ample opportunity for the subject to ask questions they may have about research and providing privacy for subjects.

25.1.4. Research staff will confirm the participant's interest and allow more opportunity for questions before the consent form is finally signed by the patient.

25.1.5. Steps that will be taken to ensure understanding include providing ample time for the potential participant to read the consent. The recruiting co-investigator or trained research assistant will speak directly to potential subjects about the aims of the study and participant involvement in this study. Potential subjects will be asked if they understand the study and its importance, and side effects will also be emphasized as well as the voluntary nature of participation.

25.1.6. Spanish-speaking patients will be recruited using a UNMH certified Spanish interpreter service or a fluent Spanishspeaking research team member. Spanish-speaking patients will be provided with a hard copy of the Spanish consent form.

25.1.7. This study will not be recruiting women who are cognitively impaired and/or unable to consent.

25.1.8. This study will not be recruiting women under the age of 18.

25.2. **HIPAA Authorization**

This study will obtain HIPAA authorization prior to enrollment. HIPAA authorization is imbedded within the study consent form which will be reviewed with all participants by the research coordinator. Specific information that will be obtained includes prior medical history, surgical history, reproductive health history including child bearing,

and drug allergies. This information will obtained by health care providers, not research coordinators, as deemed necessary for a more complete and accurate medical history of the patient.

26. Documentation of Consent

26.1. Patients presenting for abortion between 12 weeks 0 days and 16 weeks 0 days gestation will be screened by the abortion provider for eligibility criteria, only after participant has signed appropriate clinical consent forms for the abortion procedure.

26.2. This study will not be collecting tissue samples.

26.3. Consent will be obtained in-person. The patient will be provided with a hard copy of the consent form and will read and discuss the study with trained research staff. Before signing the consent form, staff will confirm the patient's interests in participating as well as answer any remaining questions. After signing the consent form, the patient will receive a copy for their own personal records.

27. Study Test Results/Incidental Findings

27.1. Since the patient's participation in this study is limited to the day of their procedure, no new information will be known before the participation in this study concludes.

28. Sharing Study Progress or Results with Subjects

28.1. The patient's participation in this study is limited to the day of their procedure, and it is a double-blind study. The participants will be blinded to their study arm and this information will not be disclosed during the length of the study to guard against bias. Women that are interested in study results will have contact information of the study staff and may inquire about overall study results only once the study is complete. Study results for individual participants will not be shared.

29. Inclusion of Vulnerable Populations

29.1. This research involves women over the age of 18 who are seeking termination of their pregnancy. Research staff and providers will be unable to approach these participants outside of this study site. Research staff will not have permission to approach these women

unless they 1) show interest and 2) meet eligibility criteria as determined by staff and their provider. Should they show interest, to reduce coercion, research staff will conduct a thorough consent process and reiterate that their participating is completely voluntary

29.1.1. This research will not include vulnerable individuals who have contraindications to outpatient abortion, such as patients with a major medical illness. This study will also exclude patients with contraindications to nitrous oxide. This includes pernicious anemia, chemotherapy, active upper respiratory illness, COPD, intrauterine fetal demise, and chronic narcotic use.

29.1.2. Please refer to the Pregnant Women checklist included below.

29.1.3. This study will not include women who are incarcerated.

29.1.4. This study will not include women under the age of 18.

29.1.5. This study will not include women with cognitive impairments and/or are unable to understand the consent process.

30. Community-Based Participatory Research – N/A

30.1. This is not a Community-Based Participatory Research study.

31. Research Involving American Indian/Native Populations – N/A

31. 1.This research study focuses on women seeking abortion and pain management options. This study is inclusive to all women of varying ethnic backgrounds so long as they are English or Spanish –speaking. This study does not focus solely on women of American Indian heritage.

32. Transnational Research

32.1.This study will not be conducted outside of Colorado and New Mexico.

33.Drugs or Devices

33.1. This study will involve the use of nitrous oxide. The nitrous oxide equipment will be stored in the clinic and maintained by clinic personnel meeting appropriate training requirements. Nitrous oxide will be similarly

delivered by physicians and nurses who have completed training in the administration of the gas and possess appropriate training certification.

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Checklist Section

This section contains checklists to provide information on a variety of topics that require special determinations by the IRB. Please complete all checklists relevant to your research.

I. Waivers or Alterations of Consent, Assent, and HIPAA Authorization – NOT APPLICABLE

A. Partial Waiver of Consent for Screening/Recruitment

Complete this checklist if you are requesting a partial waiver of consent so that you can review private information to identify potential subjects and/or determine eligibility prior to approaching potential subjects for consent or parental permission.

1. Describe the data source that you need to review (e.g., medical records):
2. Describe the purpose for the review (e.g., screening):
3. Describe who will conducting the reviews (e.g., investigators, research staff):
4. Do all persons who will be conducting the reviews already have permitted access to the data source? Yes
   ☐ No. Explain:
   ☐
5. Verify that each of the following are true or provide an alternate justification for the underlined regulatory criteria:
   a) The activity involves no more than minimal risk to the subjects because the records review itself is non-invasive and the results of the records review will not be used for any purposes other than those described above. True
      ☐ Other justification:
      ☐
   b) The waiver or alteration will not adversely affect the rights and welfare of the subjects because eligible subjects will be approached for consent to participate in the research and are free to decline. Further, the information accessed during the records review will not be disclosed to anyone without a legitimate purpose (e.g., verification of eligibility). True
      ☐ Other justification:
      ☐
   c) The research could not practicably be carried out without the waiver or alteration because there is no other reasonably
      ☐
      ☐

efficient and effective way to identify who to approach for possible participation in the research. True

Other justification:

d) Whenever appropriate, potentially eligible subjects will be presented with information about the research and asked to consider participation. *(Regulatory criteria: Whenever appropriate, the subjects will be provided with additional pertinent information after participation.)* True

☐ Other justification:

☐

Partial Waiver of HIPAA Authorization for Screening/Recruitment

Complete the following additional questions/attestations if the records you will review to identify potential subjects and/or determine eligibility include Protected Health Information (PHI).

6. Will you be recording any PHI when conducting the records review to identify potential subjects and/or determine eligibility?

   ☐

   ☐ Yes. Describe: No

7. If you answered "Yes" to question 6 above, please describe when you will destroy identifiers (must be the earliest opportunity consistent with the conduct of the research) or provide justification for why they must be retained:

8. The PHI accessed or recorded for identification/screening purposes will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.

   ☐ True

   ☐ False

B. Waiver of Documentation of Consent

Complete this checklist if you intend to obtain consent verbally but will not be obtaining signatures from subjects on a consent form to document consent. Waivers of documentation of consent are commonly requested when using scripts, information sheets, or email or survey introductions to present the elements of consent instead of using a traditional consent form.

1. Are you requesting a waiver of documentation of consent for some or all subjects?
   - ☐ All
   - ☐ Some. Explain:

2. Provide justification for <u>one</u> of the following:

   a) 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. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern.

   b) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

3. Do you intend to provide subjects with a written statement regarding the research in lieu of a traditional consent form?
   - ☐ Yes. Please attach a copy to your submission in Click.
   - ☐ No

C. Alteration of Consent

Complete this checklist if you intend to obtain consent but will be eliminating or altering one or more of the required elements of consent. Alterations of consent are commonly requested for research involving deception or for minimal risk research when an abbreviated consent is desired and one or more of the required element are not relevant to the research.

<u>Note: FDA-regulated research is not eligible for an alteration of consent.</u>

1. Which element(s) of consent do you wish to eliminate <u>and</u> why?

2. Which element(s) of consent do you wish to alter <u>and</u> why?

3. Provide justification for each of the following regulatory criteria:
   a) The research involves no more than minimal risk to the subjects:

b) The waiver or alteration will not adversely affect the rights and welfare of the subjects:

c) The research could not practicably be carried out without the waiver or alteration:

d) Whenever appropriate, the subjects will be provided with additional pertinent information after participation:

D. Full Waiver of Consent/Parental Permission

Complete this checklist if you are requesting a full waiver of consent for all subjects or certain subject groups (e.g., retrospective cohort). Full waivers of consent are commonly requested when the research does not include any opportunity for interaction with subjects (e.g., chart review).

Note: FDA-regulated research is not eligible for a full waiver of consent using these criteria. If you believe that your FDA-regulated research may be eligible for a waiver under another mechanism, such as planned emergency research, contact the HRPO for assistance in determining what information to provide to the HRRC.

1. Are you requesting a waiver for some or all subjects?
   - ☐ All
   - ☐ Some. Explain:

2. Provide justification for each of the following regulatory criteria:
   a) The research involves no more than minimal risk to the subjects:

   b) The waiver or alteration will not adversely affect the rights and welfare of the subjects:

   c) The research could not practicably be carried out without the waiver or alteration:

   d) Whenever appropriate, the subjects will be provided with additional pertinent information after participation:

E. Full Waiver of Consent/Parental Permission (Public Benefit or Service Programs) *Complete this checklist if you are requesting a full waiver of consent for all subjects or certain subject groups (e.g., retrospective cohort) and the research involves the evaluation of a public benefit or service program.*

1. Are you requesting a waiver for some or all subjects?
   - ☐ All
   - ☐ Some. Explain:

2. Provide justification for each of the following regulatory criteria:

   a) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs:

   b) The research could not practicably be carried out without the waiver or alteration.

F. Full Waiver of HIPAA Authorization

Complete this checklist if you are requesting a full waiver of the requirement to obtain HIPAA authorization for all subjects or certain subject groups (e.g., retrospective cohort). Full waivers of HIPAA authorization are commonly requested when the research does not include any opportunity for interaction with subjects (e.g., chart review).

1. Are you requesting a waiver of authorization for some or all subjects?
   - ☐ All
   - ☐ Some. Explain:

2. Describe your plan to protect health information identifiers from improper use and disclosure:

3. Describe your plan to destroy identifiers at the earliest opportunity consistent with conduct of the research (absent a health or research justification for retaining them or a legal requirement to do so):

4. Describe why the research could not practicably be conducted without the waiver or alteration:

5. The PHI accessed or recorded for identification/screening purposes will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.
   ☐ True
   ☐ False

G. Other Waiver Types

If you are seeking another waiver type (e.g., Planned Emergency Research, Waiver of Parental Permission to Protect Child Participants, Enforcement Discretion for In Vitro Diagnostics, etc. contact the HRPO office for assistance in determining what information to submit for the HRRC's consideration.

II. Vulnerable Populations

A. Adults with Cognitive Impairments – NOT APPLICABLE

Complete this checklist if the subject population will include adults with cognitive impairments.

<u>This checklist does not need to be completed if the research doesn't involve interactions or interventions with subjects and will be conducted under a waiver of consent.</u>

1. Describe why the objectives of the study cannot be met without inclusion of adults with cognitive impairments.

2. Describe how capacity to consent will be evaluated.

3. If subjects may regain capacity to consent, or if subjects may have fluctuating capacity to consent, describe your plans to evaluate capacity to consent throughout the research and to obtain consent to continue participation if capacity is regained.

4. Describe your plans, if any, to provide information about the research to subjects and the steps you will take to assess understanding.

5. Describe your plans to obtain assent, including whether assent will be obtained from none, some, or all subjects.

6. Describe why risks to subjects are reasonable in relation to anticipated benefits to the subjects.

7. If this study involves a health or behavioral intervention, describe why the relation of the anticipated benefit to the risk of the research is at least as favorable to the subjects as that presented by alternative procedures.

8. Describe your plans for monitoring the well-being of subjects including any plans to withdraw subjects from the research if they appear to be unduly distressed.

B. Children – NOT APPLICABLE

Complete this checklist if the subject population will include children.

1. Select the category of research that you believe this research falls within and provide justification for any associated criteria. If there are different assessments for different groups of children or arms (e.g., placebo vs. drug), include a memo to provide an assessment for each group.

   ☐ Research not involving greater than minimal risk. *(Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.)*

   ☐ Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

   Provide justification for each of the following criteria:

(1) The risk is justified by the anticipated benefit to the subjects:

(2) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches:

☐ Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

Provide justification for each of the following criteria:

(1) The risk represents a minor increase over minimal risk:

(2) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations:

(3) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition

C. Pregnant Women and Fetuses

Complete this checklist if the subject population will include pregnant women and fetuses.

This checklist does not need to be completed if the research is both minimal risk and is not conducted, funded, or otherwise subject to regulation by DHHS, DOD, or EPA.

Provide justification for each of the following:

1. Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses.

Nitrous oxide is an inhaled gas which can be titrated in conjunction with oxygen. It has been shown to be safe an effective for sedation in a number of other clinical settings including emergency departments, labor and delivery and dentistry. It has also been used in prior abortion studies within the first trimester with benign safety profile. This study

will collect adverse events which will be reported and monitored by the DSMB.

2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; ***or***, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.

   There is no direct benefit to the woman for participating in this research, as outlined in the benefits section of this protocol. This will also be explained to the participant. In order to participate, the patient must voluntarily elect to seek an abortion. Patients will not be approached about study participation until they have expressed desire for abortion to eliminate coercion.

3. Any risk is the least possible for achieving the objectives of the research.

   The clinical sites wherein recruitment will take place are both well equipped to manage adverse events including over sedation or other risks of the procedure. Notably, these are risks inherent to the procedure and unrelated to study involvement. If adverse events are felt to be disproportionately represented in a single group, this will prompt review by the DSMB and possible early cessation of the study.

D. Neonates of Uncertain Viability or Nonviable Neonates – NOT APPLICABLE

Complete this checklist if the subject population will include neonates of uncertain viability.

Provide justification for each of the following:

1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.

2. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.

3. Individuals engaged in the research will have no part in determining the viability of a neonate.

4. The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for

achieving that objective, ***or***, the purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research

E. Nonviable Neonates- NOT APPLICABLE

Complete this checklist if the subject population will include nonviable neonates.

Provide justification for each of the following:

1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.

2. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.

3. Individuals engaged in the research will have no part in determining the viability of a neonate.

4. The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means.

Verify each of the following:

5. Vital functions of the neonate will not be artificially maintained
   - ☐ True
   - ☐ False

6. The research will not terminate the heartbeat or respiration of the neonate
   - ☐ True
   - ☐ False

7. There will be no added risk to the neonate resulting from the research
   - ☐ True
   - ☐ False

F. Biomedical and Behavioral Research Involving Prisoners – NOT APPLICABLE

Complete this checklist if the subject population will include prisoners.

Note: Minimal risk for research involving prisoners is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

1. Select and justify which allowable category of research involving prisoners this research falls within:

☐ Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects

☐ Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects

☐ Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults)

☐ Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject

☐ Epidemiologic studies in which the sole purpose is to describe the prevalence or incidence of a disease by identifying all cases or to study potential risk factor associations for a disease, the research presents no more than Minimal Risk and no more than inconvenience to the subjects, and Prisoners are not a particular focus of the research.

2. Provide justification for each of the following regulatory criteria:

a) Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired

b) The risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers

c) Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless justification is provided, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project

d) The information is presented in language which is understandable to the subject population

e) Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole

f) When appropriate, adequate provision has been made for follow up examination or care after research participation, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact

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III.Medical Devices – NOT APPLICABLE

Complete this checklist if the research evaluates the safety or effectiveness of a medical device.

If more than one medical device is being evaluated, provide the requested information for each.

A. Device Name: B. Manufacturer:

C. Does the research involve a Significant Risk Device under an IDE?
☐ Yes. Include documentation of the FDA approval of the IDE with your submission. *Acceptable methods of documentation include: (1) FDA letter noting IDE number and approval status; (2) Industry sponsor letter noting IDE number and FDA approval status; or (3) FDA-approved industry sponsor protocol with IDE number noted*
☐ No

D. Is the research IDE-exempt?
☐

Yes. Include a FDA letter with your submission noting the determination that the research is IDE-exempt or a letter from the sponsor (or sponsor-investigator) justifying why they believe the research is IDE-exempt*. ☐ No

E. Does the research involve a Non-Significant Risk (NSR) Device?

☐ Yes. Include a FDA letter with your submission noting the determination that the research is NSR or a letter from the sponsor (or sponsor-investigator) justifying why they believe the research is NSR**.

☐ No

* This FDA guidance includes a description for when a device study is exempt from the IDE requirements:
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127067.pdf

**This FDA guidance includes information on how to differentiate between Significant Risk and Non-Significant Risk device studies:
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf