Official Title:
Opioid Analgesia for Medical Abortion: A Randomized Controlled Trial

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Protocol Template

1. Protocol Title

Opioid Analgesia for Medical Abortion: A Randomized Controlled Trial

2. Objectives

Objective

Our primary objective will be to determine if a strong opioid, oxycodone, given at a dose recommended for severe pain in addition to ibuprofen decreases maximum pain scores compared to ibuprofen and placebo in women undergoing medical abortion. Results of this study will help future providers understand whether prescribing opioids are an important adjunct for pain control in women undergoing medical abortion.

Hypothesis

Women undergoing medical abortion up to 10 0/7 weeks who receive oxycodone and ibuprofen will report maximum pain scores at least 2 points lower on a numerical rating scale (NRS) compared to women receiving ibuprofen and placebo.

Primary Outcome

Maximum self-reported pain score on a NRS during the 24 hours after administration of misoprostol.

Secondary Outcomes

1. Maximal pain score stratified by gestational age (<7wks, 7-10 0/7wks). We have powered our study in order to have sufficient sample size for this outcome.
2. Pain level at time of participant-reported expulsion using 11 point NRS (Do you think you have passed the pregnancy? (yes/no). If yes: What was your worst pain at that time?
3. Proportion of women reporting a maximum pain score ≥7 pain score
    a. Oxycodone versus placebo arm
    b. Stratified by gestational age groups (oxycodone versus placebo arm)
4. Number of tablets of oxycodone and ibuprofen tablets used during the 24 hours after administration of misoprostol
5. Use of rescue medication (yes/no)
6. Number and chief complaints of subject initiated phone calls to the provider or clinic from time of mifepristone administration to scheduled follow-up appointment; for participants who do not show up to the follow-up visit, we will collect data on phone calls and complaints for 21 days following mifepristone administration. This information will be accessed through the Planned Parenthood of Columbia Willamette (PPCW) electronic medical record.
7. Presence of Nausea/Vomiting within 24 hours
8. Participant satisfaction with pain management (collected by text messaging survey: “Were you satisfied with the pain medications you received? (Yes/no)”
9. Need for additional pain medications (marijuana, opioids they had access to): “Did you use any additional pain medications or substances other than what was given to you through the study? (Yes/no)”; If yes: “What did you use? Freetext response)”

10. Adequacy of blinding: "Do you believe you took oxycodone or a placebo? (oxycodone/placebo)"
11. Adverse events

3. Background

Medical abortion is very common with over a quarter million performed in the United States in 2011.[1] Medical abortion, induced by the selective progesterone-receptor modulator, mifepristone, and prostaglandin analogue, misoprostol, has been widely researched to optimize dosing.[2] However, abortion-related pain has not been systematically studied in clinical trials, limiting our ability to recommend appropriate analgesia.[3] Medical abortion has been described as painful in 36-86% of patients.[4-6] Up to one-third of women reported more pain than anticipated and found the magnitude of pain unacceptable.[5,7]

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the cornerstone of analgesia regimens for abortion-related pain. NSAIDs inhibit the action of cyclooxygenase, an enzyme responsible for the formation of prostaglandins, which are known to cause cramping abdominal pain.[8] NSAIDs do not interfere with the action of misoprostol to induce uterine contractions and pregnancy expulsion in women undergoing medical abortion.[9] One randomized trial found that ibuprofen was more effective than acetaminophen for pain relief for medical abortion.[10] Another study using prophylactic versus treatment ibuprofen failed to show a difference in pain control for medical abortion.[11] However, NSAIDs do not provide sufficient pain relief for many women undergoing medical abortion with almost half still citing maximum pain scores between 8-10 on a 11-point numeric rating scale.[11]

Opioid analgesia is often prescribed as an adjunct to NSAIDs to aid in pain control for medical abortion, with up to 79% of patients using at least one dose *when* prescribed.[12] However, there is scant evidence to support using this treatment for reducing cramping experienced during medical abortion; only one randomized controlled trial exists, and it did not demonstrate an improvement in pain.[13] No provider consensus exists regarding the provision of opioids for medication abortion. If an opioid is provided, there is also substantial variation to the dose, amount, and type given. Further research is necessary to evaluate opioid use during medical abortion since it is a medication that is not without side effects and cost.

Immediate release oxycodone has a rapid onset with analgesia noted as early as 10 minutes, peaking at one hour, and lasting for 4 hours, and is prescribed for severe pain. In a randomized double blind control trial in patients with moderate to severe pain, oxycodone 5mg/ibuprofen 400mg provided significantly greater analgesia compared to oxycodone 5mg/acetaminophen 325mg and hydrocodone 7.5mg/acetaminophen 500mg.[14,15] The one prior study using an opioid for medical abortion used the less potent analgesic of acetaminophen with codeine, potentially under-utilizing the analgesic properties of opioids for the severe pain experienced by women undergoing medical abortion. By using a more potent opioid for severe pain, we may be more likely to detect a benefit of using opioids and decrease overall pain experienced during medical abortion.

Planned Parenthood of Columbia Willamette (PPCW) Beaverton Health Center has not been routinely prescribing opioids for medical abortion. An internal review revealed no changes in overall patient satisfaction and no increase in provider phone calls. They performed 680 medical abortions in the past year.

4. Study Design

This is a randomized, double-blind, placebo-controlled trial of women undergoing medical abortion through 10 0/7 weeks to compare maximum pain scores in women receiving oral oxycodone 10mg and ibuprofen 800mg compared to ibuprofen 800mg and placebo beginning at the time of misoprostol administration.

This study will be conducted at PPCW in Oregon. Potential participants will be approached by study staff after confirming the decision to proceed with medical abortion. Study procedures will be initiated following approval of the institutional review board (IRB) at Oregon Health and Science University (OHSU) as well as approval from Planned Parenthood Federation of America (PPFA).

Following written informed consent, women will be stratified based on gestational age of <7 weeks or 7-10 weeks and then randomized to either oxycodone or placebo arm. Randomization will occur using a predetermined computer-generated blocked randomization and will be allocated using sequentially numbered, opaque, sealed envelopes prepared and pre-packaged by the OSHU research pharmacy. Study staff, investigators, and participants will be blinded to study arm allocation. Placebo and study drugs will be similar in appearance due to over-encapsulation of study drugs by the OHSU research pharmacy. Study drug allocation and study medications will be given out in a consecutive fashion stratified by gestational age. For example, study medications will be labelled as follows: subject #5, <7 weeks. Study staff will dispense the study medications to each subject at PPCW.

Study staff will initiate a test text message while the subject is in the clinic to test her phone. Text messages through the TextIt platform will be utilized to send timed questions for data collection. The account will be linked to a dedicated study telephone and the number will be provided to study participants.

Drug Dosing Guidelines for Pain

Initial dosing:

- Placebo Arm: Subjects will take ibuprofen 800mg just prior to misoprostol administration. They will take placebo at the start of painful uterine contractions.
- Study drug (oxycodone) Arm: The oxycodone arm will take ibuprofen 800mg just prior to misoprostol administration. They will take oxycodone 10mg at the start of painful uterine contractions.

Re-dosing: Subjects will be able to re-dose ibuprofen 800mg every 8 hours as needed.

Rescue dosing: All subjects will be provided with a prescription for six tablets of oxycodone 5mg that they will be able to fill at their discretion. They will be able to take one tablet every 4 hours as needed.

Maximum pain scores using 11-point NRS (0-10) will be assessed 6-8 hours and 24 hours after misoprostol administration. A reminder text message and phone call will be sent out if a subject has not responded to text messages.

After the follow up visit or 21 days after mifepristone for subjects lost to follow up, review of the Planned Parenthood medical record charts will confirm completion of the medical abortion and review the number of unanticipated patient phone calls. If a participant is found to have an ongoing pregnancy, pain score data will not be collected beyond the 24 hours after the initial misoprostol administration. All unused study medication may be returned at the follow-up visit. Subjects will not be required to return study medication, as study staff may not be present at their follow up visit. However, if they choose to return study medication, this will be collected by Planned Parenthood or study staff.

In case of emergency, questions, or the need to take the rescue medication, subjects will be provided with the dedicated study telephone number.

Subjects will be compensated for their time and involvement in the study.

The primary outcome will be the difference in maximum pain score reported within 24 hours after the administration of misoprostol. We anticipate a very small number of women needing additional doses of misoprostol to complete their abortion, and as such, we will not collect pain data beyond the first 24 hours if additional dosing or a surgical intervention is needed. If participants do not respond to text messaging or do not complete their scheduled follow up appointment, we will attempt to text twice and call once. For all subjects, study participation is complete at the follow-up visit or 14 days following mifepristone administration. We will be following the SPIRIT guidelines for study design and CONSORT guidelines for reporting our trial.[16,17]

5. Study Population

a. Number of Subjects

Recruitment will occur at PPCW Beaverton Health Center in Oregon. 680 medical abortions were performed within the last calendar year at the Beaverton clinic which averages to 56 medical abortions per month. Two-thirds of these patients were <7 weeks and the remaining one-third was 7-10 weeks gestational age.

After written consent has been obtained and text messaging capabilities have been confirmed, participants will be stratified by gestational age group and then randomized in a 1:1 allocation to the oxycodone and placebo groups. Randomization will be assigned using two computer-generated randomization lists (one for each stratum). Each block cell will include 43 subjects for a total of 172 subjects. The study medication or placebo capsules will be placed in identical packets, labelled only with the study identification number and instructions for use so as to maintain

blinding in accordance with the allocation scheme. Investigators will assign each participant a study identification number in sequential order as they enroll, and they will receive the study medication packet with that same identification number, stratified by gestational age groups.

b. Inclusion and Exclusion Criteria

Subjects will be approached about this study after the decision to proceed with medical abortion has occurred. Study staff will approach women at PPCW. Women will be informed that they can participate in the study by their own free will, that their care will not change whether they choose to participate or not, and that they can be removed from the study at any time without penalty.

Subjects will receive detailed information regarding the study and an OSHU IRB approved consent form available in English will be reviewed and signed with interested participants. The patient's medical chart will be reviewed and demographic and medical history will be collected to ensure eligibility. The study coordinator will send out a test text message to ensure the subject has text messaging capabilities. A recruitment log will track subjects who are excluded at any point throughout the study, or who decline entry. Their age, gestational age, and reason for exclusion or refusal will be documented. Patients will not have access to other opioid prescription medications outside of the study.

Subjects in this RCT will be recruited from women who have consented for an elective medical termination of pregnancy up to 10 0/7 weeks gestation dated by ultrasound at PPCW.

Inclusion criteria:

-Aged 18 years or older
-Seeking elective medical abortion
-In good health and eligible for a medical abortion as defined by PPCW protocols
-Pregnancy with intrauterine gestational sac up to 10 0/7 weeks, dated by ultrasound; or otherwise deemed eligible for a Medical Abortion by PPCW standards and guidelines protocol
-Able and willing to receive SMS messages via phone
-Ability to speak and read English
-Able and willing to give informed consent and agree to the study terms
-Have assistance at home; no motor vehicle use while taking study medications

Exclusion criteria:

-Lack of access to cell phone and texting capabilities
-Early pregnancy failure
-Contraindications to the study medications: Oxycodone, Ibuprofen
-Contraindications to medical abortion with Mifepristone or Misoprostol
-History of methadone or heroin use
-Use of alcohol anytime from time of consent until completion of second text message questionnaire
-Used marijuana >4 times per week in the last week
-Any opioid in the past 30 days (ex: Vicodin, hydrocodone, hydromorphone, codeine, oxycodone, tramadol, fentanyl)
-Previously enrolled in this study

Confidentiality of personal health information will be maintained according to HIPAA requirements for research. All subjects will receive a study number to which all subsequent data will refer. Personal identifiers will not be

on questionnaires, data, abstract sheets, or in the main database. All data will be kept in locked files or a password protected computer.

The data collected for subjects who are unable to be randomized in this study will be kept until study completion and all data has been analyzed. All study charts will remain on-site at PPCW until participant has completed study or until completion of study. At that point, study charts will be brought to OHSU. Study charts will be kept in a locked cabinet in a locked office when not being used by study staff.

c. Vulnerable Populations

Pregnant women are the subjects of this study. Planned Parenthood requires women to be capable of giving voluntary informed consent in order to receive abortion services. Subjects will need to be able to provide voluntary informed consent to participate in this study. This study will not target decisionally-impaired adults, non-English speaking patients or prisoners.

d. Setting

Recruitment, consenting, study procedures, and data analysis will occur by OHSU personnel at PPCW. Data analysis will also occur at OHSU. OHSU Research Pharmacy Services will prepare, compound, and distribute our medications. We are relying on the OHSU Institutional Review Board (IRB) to satisfy IRB review requirements.

Recruitment will occur at PPCW Beaverton Health Center in Oregon. 680 medical abortions were performed within the last calendar year at the Beaverton clinic which averages to 56 medical abortions per month. Upon OHSU IRB approval, PPFA will review study prior to study initiation.

e. Recruitment Methods

When patient's check in for their medical abortion appointment at PPCW, they will receive handouts ("Study Fact Sheet" and "Flyer") informing them that they may be approached about a medical abortion study being conducted at PPCW through OHSU.

Study staff will approach patients at PPCW after they have confirmed their desire to have a medical abortion. Women will undergo the standard assessment and care for medical abortion at PPCW, which includes directly observed dosing of Mifepristone 200mg. Interested patients will undergo screening to determine eligibility. Screening will be conducted in the form of chart review by study staff. Screening information will be kept in a de-identified screening log (# of people qualified or not qualified). If eligible, interested participants will have time to review the consent and ask questions. The OHSU IRB approved consent will be signed by the participant and study staff.

A questionnaire will be given by study staff to determine if the participant is eligible for the study. Subjects will receive detailed information regarding the study and an OSHU IRB approved consent available in English will be signed with interested participants. The patient's medical chart will be reviewed and demographic and medical history will be collected. The study coordinator will send out a test text message to ensure the subject has text messaging capabilities. A recruitment log will track subjects who have signed consent and complete the study, as well as those who are excluded at any point throughout the study, or who decline entry. Their age, gestational age, and

reason for exclusion or refusal will be documented. Patients will not have access to other opioid prescription medications outside of the study.

Subjects will be contacted via phone using SMS text messaging.

We will collect the following data at 6-8 hours post-misoprostol use:

1. Did you take misoprostol? Text "Yes" or "No"
2. What is your current pain? Please respond with a number0-10? 0 = no pain and = 10 worst possible pain
3. What was your worst pain since taking misoprostol? (Reply 0-10)
4. How long did your worst pain last in hours and minutes? (Reply hh:mm)
5. Did you take the study medication for pain? Text YES or NO
    a. If yes, What time did you take the study medication? (Reply hh:mm)

We will collect the following data at 24 hours post-misoprostol use:

1. What is your current pain? Reply with a number 0-10? 0 = no pain and = 10 worst possible pain
2. What was your worst pain over the past 18 hours? (Reply 0-10)
3. How long did your worst pain last in number of hours and minutes? (Reply hh:mm)
4. How many ibuprofen tablets did you use? (Reply 0-9)
5. Did you require any oxycodone from the paper prescription for pain? (Reply YES or NO)
    a. If yes: How many tablets did you use? (Reply 0-6)
6. Did you experience nausea or vomiting over the past 24 hours? (Reply YES or NO)
7. Were you satisfied with the pain medications you received? (Reply YES or NO)
8. Did you take the study medication for pain? (Reply YES or NO)
    a. If yes, Do you believe you took oxycodone or a placebo? (Reply OXYCODONE or PLACEBO)
9. Did you use any additional pain medications or substances other that what was given to you through the study? (Reply YES or NO)
    a. If yes: What did you use?
10. Did you use any non-medical therapies for pain, such as heat or massage?
    a. If yes: What did you use?
11. Do you think you have passed the pregnancy? (Reply YES or NO)
    a. If yes: What was your worst pain at that time? (Reply 0-10)

Subjects will be compensated up to $100 for their participation in the study. Subjects will be paid based on the number of study visits and text message responses they complete.
Subjects will receive:

- $10 dollars after agreeing to participate and after signing consent
- $50 dollars for completing all text message surveys after taking Misoprostol ($25 per survey)
- $40 for completion of follow-up appointment at PPCW

Consent Process

Study staff will approach patients at PPCW after they have confirmed their desire to have a medical abortion. Women will undergo the standard assessment and care for medical abortion at PPCW, which includes directly observed dosing of Mifepristone 200mg. Interested patients will undergo screening to determine eligibility in a private room at PPCW. If eligible, interested participants will have time to review the consent and ask questions. The OHSU IRB approved consent will be signed by the participant and study staff.

Ongoing consent will be reviewed on a monthly basis. In order to meet our 12 month recruitment goal, thirteen subjects must be enrolled monthly. PPCW-Beaverton sees 56 subjects per month on average for medical abortion. The principal investigator will staff a medical abortion clinic in order to maximize recruitment potential and decrease burden on the PPCW clinic.

6. Procedures Involved

Subjects will be approached after the decision to proceed with medical abortion has occurred. Study staff will approach women at PPCW. Women will be informed that they can participate in the study by their own free will, that their care will not change whether they choose to participate or not, and that they can be removed from the study at any time.

Subjects will receive detailed information regarding the study and an OSHU IRB approved consent available in English will be signed with interested participants. The patient's medical chart will be reviewed and demographic and medical history will be collected. The study coordinator will send out a test text message to ensure the subject has text messaging capabilities. A recruitment log will track subjects who are excluded at any point throughout the study, or who decline entry. Their age, gestational age, and reason for exclusion or refusal will be documented. Patients will not have access to other opioid prescription medications outside of the study.

After written consent has been obtained and text messaging capabilities have been confirmed, participants will be stratified by gestational age group and then randomized in a 1:1 allocation to the oxycodone and placebo groups. Randomization will be assigned using two computer-generated randomization lists (one for each stratum). Each block cell will include 43 subjects for a total of 172 subjects. The study medication or placebo capsules will be placed in identical packets, labelled only with the study identification number and instructions for use so as to maintain blinding in accordance with the allocation scheme. Investigators will assign each participant a study identification number in sequential order as they enroll, and they will receive the study medication packet with that same identification number, stratified by gestational age groups.

At the time of randomization, subjects will be shown an 11-point Numeric Pain Rating Scale (NRS) handout (See Appendix A) and allow for any questions about responding to questions relating to reporting pain.[20] Data will mainly be collected via SMS messaging using timed surveys at 6-8 and 24 hours. Final data will be completed via chart review after the scheduled follow-up visit or 21 days after mifepristone administration.

If a participant does not respond to text messaging, we will attempt to contact the participant via text message twice, and call once. If a participant does not come to their follow up appointment, we will again attempt to contact by text message and phone call. If a participant receives care at another facility, we may request records from that facility for review.

Subjects have the right to withdraw from the study at any time. Once a participant indicates their request for withdrawal, no further data will be collected. Participants will be provided with contact information and their reason for discontinuation will be recorded.

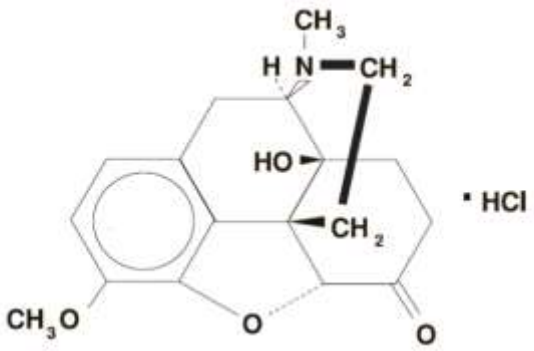
No laboratory evaluations will be conducted for this research study. Women will receive a follow-up ultrasound as standard of care to evaluate completion of the medical abortion per Planned Parenthood guidelines.

Data management will be managed by the PI. Baseline data will be collected at the initial visit by the study coordinator and PI. All data being collected after administration of misoprostol and study medications will be collected and stored on a secure server. Data regarding completion of medical abortion will be followed up via chart checking the electronic medical record of Planned Parenthood (NextGen).

All subject data will be kept confidential and locked in an office and on a password-protected computer. Each subject will be assigned a unique study identification number. A file linking subjects with their study ID and name will be kept in a locked file in the PI's office and stored separately from the data files. Only the study investigators will have access to this file. No subject names will be included in the study data during statistical analysis. The study coordinator and PI's telephones will be encrypted by OHSU and password protected.

Periodically, data will be pulled from the server and entered into REDCap and STATA. Random data entry checks will be performed to verify accuracy.

Oxycodone HCl (Roxicodone) 5mg and 10mg tablets- Immediate-release oral formulation of oxycodone HCl indicated for the management of acute and chronic moderate to severe pain. Oxycodone is a semi-synthetic opioid with multiple actions qualitatively similar to those of morphine; the most prominent of these involves the central nervous system and organs composed of smooth muscle. Chemically, oxycodone hydrochloride is 4, 5α-epoxy-14-hydroxy-3-methoxy-17methylmorphinan-6-one hydrochloride. It has the following structural formula:



The 10mg dose is manufactured by:
Zydus Pharma USA Inc
73 NJ-31, Pennington, NJ 08534
The 5mg dose is manufactured by:
Epic Pharma LLC
227-15 N Conduit Ave, Jamaica, NY 11413

Full prescribing information:
http://labeling.pfizer.com/showlabeling.aspx?id=620

Ibuprofen (Motrin) - Subjects will be taking 800mg tablets. Ibuprofen is a nonsteroidal anti-inflammatory drug. Its mode of action is not completely understood, but may be related to prostaglandin synthetase inhibition. Ibuprofen is (±) -2- (*p* – isobutylphenyl) propionic acid. Its chemical structure is:

Manufacturer:
Major Pharmaceuticals
17177 North Laurel Park Suite 233
Livonia, MI 48152
Full prescribing information:
http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/017463s105lbl.pdf

7. Data and Specimens

a. Handling of Data and Specimens

Data management will be managed by study staff. Baseline data will be collected at the initial visit by the study staff. All data being collected after administration of misoprostol and study medications will be collected and stored on a secure server. Data regarding completion of medical abortion will be followed up via chart checking the electronic medical record of Planned Parenthood (NextGen).

All subject data will be kept confidential and locked in an office and on a password-protected computer. Each subject will be assigned a unique study identification number. A file linking subjects with their study ID and name will be kept on a secure OHSU server and stored separately from the data files. Only the study staff will have access to this file. No subject names will be included in the study data during statistical analysis. The study staff's telephones will be encrypted by OHSU and password protected. Periodically, data will be pulled from the server and entered into REDCap and STATA. Random data entry checks will be performed to verify accuracy.

b. Sharing of Results with Subjects

Data results will not be shared with subjects or their providers.

c. Data and Specimen Banking

The data collected in this study will be stored per FDA guidelines after completion of all data analysis and publication. Study data will not be used for further research. We are not collecting any specimens for this study.

8. Data Analysis

We will use descriptive statistics to characterize the sample and test for differences in baseline demographic and clinical characteristics between treatment groups using Student's t-test, the Wilcoxon rank-sum test, Pearson's chi-squared test, or Fisher's exact test, as appropriate.

For the primary and secondary outcomes, we will follow the intention-to-treat principle, including all participants who provide pain scores. Based on previous medical abortion pain studies[11], we assume that maximum pain scores will not be normally distributed, so we will use a Wilcoxon rank-sum test to compare maximum NRS pain scores between the control and experimental groups. We will test for differences in NRS between the overall treatment groups and within gestational-age strata. For multivariable analysis of maximum pain scores, we will construct a proportional-odds cumulative logit model, a rank-based linear model, or a linear model on transformed data, depending on distribution of the data and model fit, with treatment group as the main predictor and adjusted for gestational age group and baseline demographic and clinical variables.

To make use of the repeated pain measures, we will use a generalized estimating equation (GEE) to model pain scores during the first 24 hours.

We will use logistic regression models to examine differences between groups in the following outcomes (all models will have treatment group as the main predictor and will be adjusted for gestational age group and baseline demographic and clinical characteristics):

- Proportion of women reporting a maximum pain score of 7 or higher.
- Use of rescue medication; this model will also adjust for the number of ibuprofen and oxycodone or placebo doses taken.
- Presence of nausea or vomiting
- Satisfaction with pain medication
- Need for additional (non-prescribed) pain medication

To examine differences between groups in the amount of ibuprofen and oxycodone or placebo used during the 24 hours after administration of misoprostol, we will use Poisson, negative binomial, or zero-inflated Poisson or negative binomial regression models, depending on the distribution of the data.

We will use descriptive statistics to characterize the number and chief complaints of patient-initiated phone calls to the provider or clinic. We will use Student's t-test or a Wilcoxon rank-sum test to test for differences between groups in the number of calls placed. We will group chief complaints into broad categories and test for differences across treatment groups using a chi-squared test. Similarly, we will group non-prescribed medications used for pain into broad categories and use descriptive statistics to characterize them.

Finally, we will use descriptive statistics to summarize adverse events.

Previous studies suggest that the 11-point numeric pain scale are as sensitive to changes in clinical pain as the visual analog scale.[18] We will administer numeric pain scales via text message that will prompt participants to rate their pain on a scale of 0-10. Significant difference in pain intensity for the numeric pain scale is a change in ≥ 2.[19] We will define a clinically significant change by a change in numeric pain of 2.

The sample size calculation was based on a simulation study using a Wilcoxon rank-sum test on data simulated from specified parameters (delta=2, sigma=2.6, alpha=0.05). It is difficult to simulate categorical data unless we assume a specific probability for each possible value of the NRS, which would be far too strong of a set of assumptions to make. For this reason, we treated the outcome as continuous and used a standard deviation as a measure of spread for the purpose of simulating data, and then used the more conservative rank-based test to calculate the sample. To calculate

sample size, we simulated pools of test and placebo ordinal NRS data whose means were 2 units apart and whose spreads were both 2.6 standard deviations. We selected these continuous and symmetric measures of center and spread in the absence of the availability of any other distributional assumptions of NRS data. The simulated pools of data were constrained to integer values ranging from 0 to 10. We repeatedly sampled from the simulated pools of data at sample sizes ranging from 10 to 100 per cell to calculate the probability of a significant (at alpha=0.05) Wilcoxon rank-sum test at each sample size. A sample size of 34 participants per group provided 80% probability of detecting the 2-point difference in the simulated data. Initially, we anticipated a 10% drop-out or study non-adherence and planned to enroll 38 participants per block cell (a total of 152 participants). After an interim analysis, 25% of participants are not using the study drug. While this is useful information for a secondary analysis, by increasing our sample size an additional 15%, we can allow for 25% drop-out or study non-adherence in order to analyze our primary outcome. This would increase our overall enrollment goal to 172 (43 participants per group).

9. Privacy, Confidentiality, and Data Security

Data collection and storage: Standard institutional practices will be followed as described in the OHSU Information Security and Research Data Resource Guide (http://ozone.ohsu.edu/cc/sec/isg/res_sec.pdf) to maintain the confidentiality and security of data collected in this study. Study staff will be trained with regard to these procedures. Paper files will be stored in locked filing cabinets in restricted access offices at PPCW and OHSU. Electronic data will be stored in the secure web-based data collection system, REDCap, and TextIt which is housed on an OHSU secure server. Access to data is restricted to study personnel.

Data coding: Upon enrollment, subjects will be assigned a code that will be used instead of their name, medical record number or other personally identifying information. Electronic files for data analysis will contain only the subject code. Codes will not contain any part of the 18 HIPAA identifiers (initials, DOB, MRN). The key associating the codes and the subjects' personally identifying information will be restricted to the PI and study staff. The key will be kept secure on a restricted OHSU network drive a in a limited access folder.

Final disposition of the data: The data collected in this study will be stored per FDA guidelines after completion of all data analysis and publication. Study data will not be used for further research. We are not collecting any specimens for this study.

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

Please see Data Safety Monitoring Plan (DSMP).

11. Risks and Benefits

a. Risks to Subjects

A foreseeable risk to participants participating in this research would be a breach of confidentiality. There are no anticipated inconveniences to study subjects related to participation in the research, as no additional procedures, tests or interventions will be performed apart from routine medical services provided to women seeking abortion care at Planned Parenthood.

Another risk to taking part in this study is that the study drug or the dose a participant receive may not be effective in helping to treat their pain. This means subjects may spend time in the study and experience side effects taking a drug that may not provide subjects with any health-related benefits. If a subject is not in the study, their treatment for pain during medical abortion

would be determined by PPCW which could include ibuprofen. By participating in the study, the only additional risk would be exposure to oxycodone if a subject is in the study drug group.

If a participant is nursing an infant or planning to continue a pregnancy, then a participant is not eligible for the study. In the rare possibility that a medical abortion fails and a subject has an ongoing pregnancy and decides to keep the pregnancy, then the use of opioids and ibuprofen in the first trimester of pregnancy are category B. This means that the medication is generally safe to use during the first trimester of pregnancy, and the risks to the developing fetus are low. Extended use of oxycodone can result in neonatal withdrawal syndrome. Oxycodone crosses the placenta and is excreted in breast milk. Sedation or respiratory depression may occur in the infant. Ibuprofen is excreted into breast milk. Based on the available data, adverse events have not been reported in nursing infants and milk production is not affected. This study may involve risks to an embryo, fetus, or nursing infant that are currently unknown.

b. Potential Benefits to Subjects

Subjects may or may not personally benefit from being in this study. However, subjects will help us learn how to benefit patients in the future.

12. Resources Available

Subjects will have access via phone to a Family Planning trained Obstetrics and Gynecology specialist available during the length of the study for any questions or concerns. Subjects will be given the contact number for the Women's Health Research Unit (WHRU) and the OHSU Paging Operator to ask to have on-call provider paged.

13. Drugs

The study drug (oxycodone) and ibuprofen used in this study have been approved by the Food and Drug Administration (FDA) for the treatment of pain. Study staff will follow the Research pharmacy policies and procedures. Study drugs will be prepared and handled by the pharmacy. Study staff will distribute the medications at PPCW. If not stored in the research pharmacy, medications will be maintained in a narcotic locker at the site. Subjects may return any unused medications at the end of study participation.

14. Multi-Site Coordination (delete if not applicable)

Planned Parenthood Federation of America (PPFA) will have the most current version of the protocol, consent and HIPAA authorization. PPFA will independently review the study. A research service agreement will be signed by OHSU and PPFA. All engaged participating sites will safeguard data as required by local information security policies. All local site investigators will conduct the study appropriately. All non-compliance with the study protocol will be reported in accordance with local policy. Communication of problems will be managed by the study PI. Interim results and study closure will be handled by the study PI.

References:

(1) Jones, R. K., Jerman J. "Abortion incidence and service availability in the United States, 2011." *Perspect Sex Reprod Health* 2014;46(1):3-14.
(2) Kulier R, GulmezogluAM, Hofmeyr GJ, et al. Medical methods for first trimester abortion. *Cochrane Database Syst Rev* 2004;(2).
(3) Fiala, C., et al. "Pain during medical abortion, the impact of the regimen: a neglected issue? A review." *Eur J Contracept Reprod Health Care* 2014;19(6):404-419.
(4) el-Refaey H, Templeton A. "Early abortion induction by a combination of mifepristone and oral misoprostol: a comparison between two dose regimens of misoprostol and their effect on blood pressure." *Br J Obstet Gynaecol* 1994;Sep;101(9):792-6.
(5) Raghavan S, Comendant R, Digol I, et al. "Two-pill regimens of misoprostol after mifepristone medical abortion through 63 days' gestational age: A randomized controlled trial of sublingual and oral misoprostol." *Contraception* 2009;79:84–90.
(6) World Health Organisation Task Force on Post-ovulatory Methods of Fertility Regulation. "Comparison of two doses of mifepristone in combination with misoprostol for early medical abortion: A randomized trial." *BJOG* 2000;107:524–30.
(7) Winikoff B, Dzuba IG, Creinin MD, et al. "Two distinct oral routes of misoprostol in mifepristone medical abortion: A randomized controlled trial." *Obstet Gynecol* 2008;112:1303–10.
(8) Marjoribanks, J., et al. "Nonsteroidal anti-inflammatory drugs for dysmenorrhoea." *Cochrane Database Syst Rev* 2015;(7):CD001751.
(9) Creinin MD, Shulman T. Effect of nonsteroidal anti-inflammatory drugs on the action of misoprostol in a regimen for early abortion. *Contraception* 1997;56:165–8.
(10) Livshits, A., et al. "Ibuprofen and paracetamol for pain relief during medical abortion: a double-blind randomized controlled study." *Fertil Steril* 2009;91(5):1877-1880.
(11) Raymond, E. G., et al. "Prophylactic compared with therapeutic ibuprofen analgesia in first-trimester medical abortion: a randomized controlled trial." *Obstet Gynecol* 2013;122(3):558-564.
(12) Westhoff C, Dasmahapatra, R, Schaff, E. "Analgesia during at-home use of misoprostol as part of a medical abortion regimen." *Contraception* 2000;62:311–314.

(13) Wiebe E. “Pain control in medical abortion.” *International Journal of Gynecology & Obstetrics* 2001;p74:275-280.
(14) Lugo, R. A. and S. E. Kern. "The Pharmacokinetics of Oxycodone." *Journal of Pain & Palliative Care Pharmacotherapy* 2009;18(4):17-30.
(15) Litkowski LJ, Christensen SE, Adamson DN, Van Dyke T, Han SH, Newman KB. Analgesic efficacy and tolerability of oxycodone 5 mg/ibuprofen 400 mg compared with those of oxycodone 5 mg/acetaminophen 325 mg and hydrocodone 7.5 mg/acetaminophen 500 mg in patients with moderate to severe postoperative pain: a randomized, double-blind, placebo-controlled, single-dose, parallel-group study in a dental pain model. *Clin Ther* 2005;27(4):418–29.
(16) Chan A., Tetzlaff J., Altman D., Laupacis A., Gøtzsche P., Krleža-Jerić K., Hróbjartsson A., Mann H., Dickersin K., Berlin J., Doré C., Parulekar W., Summerskill W., Groves T., Schulz K., Sox H., Rockhold F., Rennie D., Moher D.; SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials. *Ann Intern Med* 2013;158:200-207.
(17) Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332.
(18) Jensen M, Chen C, Brugger A. Interpretation of Visual Analog Scale Ratings and Change Scores: A Reanalysis of Two Clinical Trials of Postoperative Pain. *The Journal of Pain* 2003;4(7):407-14.
(19) Farrar J, Berlin J, Strom B. Clinically Important Changes in Acute Pain Outcome Measures: A Validation Study. J Pain Symptom Manage. 2003;25:406-11.
(20) 0–10 Numeric Pain Rating Scale: From McCaffery M, Pasero C. Pain: Clinical Manual, St. Louis, 1999, P. 16. Copyrighted by Mosby, Inc.

Appendix A

0–10 Numeric Pain Rating Scale