Official Title: Cannabinoids for Pain Control during Medical Abortion

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1. **Protocol Title**
   Cannabinoid Analgesia for Medical Abortion: A Randomized Controlled Trial

2. **Objectives**
   Objective
   To compare the reported maximum pain score within 24 hours of induced medical abortion of women who receive cannabinoids and ibuprofen compared to ibuprofen and placebo using an 11-point numeric rating scale (NRS) (0-10). Pain levels will be collected prospectively via text message at hours 0 (misoprostol administration), 6, and 24 hours, and maximum pain score and timing during the preceding interval will be recorded.

   Hypothesis
   Women undergoing medical abortion up to 10 0/7 weeks who receive cannabinoid analgesia and ibuprofen will report lower maximum pain scores compared to ibuprofen alone.

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

   Secondary Outcomes
   1. Maximal pain score. (We have powered our study in order to have sufficient sample size for this secondary outcome).
   2. Pain level at time of participant-reported expulsion using NRS.
   3. Proportion of women reporting a maximum pain score $\geq$7.
   4. Number of capsules of study drug and ibuprofen tablets used during the 24 hours after administration of misoprostol.
   5. Use of additional medications.
   6. Presence of nausea/vomiting within 24 hours.
   7. Participant satisfaction with pain management.
   8. Need for additional pain medications between mifepristone ingestion and follow up appointment.
   9. Number of calls to the clinical advice line, as documented in the eletronic medical record.
   10. Adequacy of blinding: “Do you believe you took the study drug or a placebo?”
   11. Adverse events.

3. **Background**
   In 2011, nearly half (45% or 2.8 million) of the 6.1 million pregnancies in the United States were unintended [1], with an abortion rate of approximately 17 per 1,000 women [2]. Medical abortions account for approximately 31% of all abortions [3]. As a safe and efficacious alternative to surgical abortion, rates of medical abortion continue to rise relative to surgical abortion [4]. However, pain and anxiety during medical abortion continue to be significant issues and potential barriers to care. Abortion-related pain has not been systematically studied in clinical trials, limiting our ability to recommend appropriate analgesia [5]. Medical abortion has been described as painful in 36-86% of patients [6-8], with up to one-third of women reporting more pain than anticipated and unacceptable maximum pain scores [6].

Currently, nonsteroidal anti-inflammatory drugs (NSAIDs) are the cornerstone of analgesia regimens for abortion-related pain. However, NSAIDs do not provide sufficient pain relief for many women in the setting of medical abortion, with almost half of patients reporting maximum pain scores between 8-10 on an 11-point numeric rating scale [9]. To supplement ibuprofen, some providers offer opioids but no consensus exists regarding if opioids should be provided and if so, the dose, amount, and type to be given [10]. Additionally, a randomized controlled trial demonstrated that opioids did not improve pain with medical abortion but its results are limited, as it did not utilize an optimal dose or type of opioid [11]. Although further research is ongoing (Colwill, Fellowship Project) on the evaluation of opioid use for medical abortion related pain, opioids are increasingly under scrutiny due to the current U.S. opioid crisis and further restrictions may be put into place which may limit their use.

The use of medical cannabis is increasing, most commonly for pain, anxiety and depression [12]. Currently, 28 states and the District of Columbia enforce legalized medical cannabis laws, and 8 of these states have also legalized cannabis for recreational use [13]. A 2015 national survey showed cannabis use is increasing, with past-month use increasing from 5.8% in 2007 to 8.4% in 2014 [2]. A 2016 survey of 226 women found that 19% self-medicated with marijuana for pain during medical abortion, and all of these women reported some relief in pain [14].

Traditionally, ibuprofen are the mainstay of analgesia for abortion pain, with opioids commonly prescribed as an adjunct for pain control. Opioid pain medication use presents serious risks, including opioid-induced respiratory depression, overdose and opioid use disorder [15]. From 1999 to 2014, more than 165,000 people died from overdose related to opioid pain medication in the United States [16]. Even brief exposure to opioids can increase long term use. One study evaluated opioid-naïve patients who had undergone low-risk surgery, such as cataract surgery, and found that use of opioids within 7 days of surgery was associated with increased risk for use at 1 year [17]. A recent prospective study suggests that access to medical cannabis may decrease opioid use [18], thereby providing a safer alternative to opioid analgesia for some patients [19].

Marijuana is the common name for the Cannabis plant, from which at least 500 different compounds have been derived, including delta^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) [20]. The endocannabinoid system modulates neuronal and immune cell function, both crucial elements in the complex mechanism of pain perception, through two G protein-coupled cannabinoid receptors, CB_1 and CB_2. CB_1 receptors are found primarily in central and peripheral neurons, whereas CB_2 receptors are primarily expressed in immune cells [21]. Several studies have demonstrated the efficacy of cannabinoids in decreasing pain in chronic pain states such as multiple sclerosis and diabetic neuropathy [22]. However, less evidence exists for cannabinoids for treatment of acute pain.

Delta^9-tetrahydrocannabinol (THC) is a partial CB_1 receptor agonist responsible for producing psychotropic effects. Delta^9-tetrahydrocannabinol (THC) has been shown to reduce subject stress and anxiety [23]. Cannabidiol (CBD) is a non-euphoriant, anti-inflammatory analgesic with CB_1 and CB_2 receptor antagonist and endocannabinoid modulating effects [24] [25]. As combining CBD with THC has been shown to reduce the psychotropic effects while maintaining the analgesic and anxiolytic effects of THC, there

has been an emerging interest in blended cannabinoid products for various pain states [26]. A standardized, fixed 1:1 THC-CBD oromucosal spray has been approved to treated muscle spasticity in multiple sclerosis patients in 16 countries outside of the United States since 2012 and is currently in phase III trials within the United States [27]. At this time no FDA approved combined THC-CBD products exist, and significant regulatory hurdles prevent effective research on combined THC-CBD products.

In the United States, synthetic delta^9-tetrahydrocannabinol (THC) is available as Marinol (the generic is dronabinol) as an oral medication. This drug is approved by the FDA for two indications: chemotherapy-induced nausea and vomiting, and anorexia associated with weight loss in patients with AIDS. However, a number of studies has evaluated Marinol for chronic pain control, with mixed results [28]. The quality of evidence for pain relief in these studies were limited by the exclusion of participants with a history of substance abuse and other significant comorbidities, together with their small sample sizes. A small 2013 randomized control trial showed the Marinol reduced pain in the acute setting, with the effect being comparable to smoked marijuana, but showed a longer lasting effect on pain control [29] [30].

Combining the anxiolytic and anti-emetic effects of THC with the analgesic effects of ibuprofen is ideal for women undergoing abortion, as multiples studies have shown that women often report at least moderate levels of pain despite analgesia, and women who reports higher levels of anxiety experience significantly higher pain levels during abortion procedures [31] [32].

This study will be a randomized, double-blind, placebo controlled trial comparing pain levels in women undergoing medical abortion with one of two regimens: 1) ibuprofen 800mg and Marinol 5mg , and 2) ibuprofen 800mg and placebo pill at the time of misoprostol administration. Our primary objective will be to determine if a cannabinoid analgesic in addition to ibuprofen decreases maximum pain scores compared to ibuprofen and placebo when undergoing medical abortion. We plan to prospectively collect data via a text messaging system to evaluate pain scores, satisfaction, total analgesia use and adverse side effects. Results of this study will inform future providers who are counseling women undergoing medical abortion.

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 a cannabinoid analgesic and ibuprofen 800mg versus placebo and ibuprofen 800mg ingested 30 minutes prior to misoprostol administration. This study will be conducted at Planned Parenthood Columbia Willamette (PPCW) in Oregon. Potential participants will be approached by study staff after they have been fully consented for a medical abortion and been dispensed the abortion medications. Of note, the staff consenting subjects for the study will be different staff than those providing counseling about pregnancy options. Study procedures will be initiated following approval of the institutional review board at Oregon Health and Science University (OHSU), as well as approval from PPCW and Planned Parenthood Federation of America (PPFA). Study staff will thoroughly discuss the study with patients, assess for appropriate inclusion in the study, and consent the patients at the health center after completion of thorough counseling and consent for medical abortion.

All patients desiring medication abortion at PPCW will receive standard of care independent of study protocol. Per PPCW normal clinical standards, after being consented for a medical abortion patients will receive mifepristone to take either in the clinic or at home, and misoprostol and ondansetron to take at home. PPCW staff will instruct patients when and how to take standard of care medications. For example, PPCW staff will instruct patients when and how to self-administer mifepristone and misoprostol. As standard of care, over-the-counter ibuprofen is recommended for pain management. Patients do not receive an ibuprofen package insert, and ibuprofen is not dispensed by PPCW. Narcotics are not routinely prescribed for pain control at PPCW. However, if patients call the clinic requesting additional pain medication, a provider may prescribe narcotic medication if appropriate.

After consenting to medication abortion, OHSU study staff will approach PPCW patients about the study. Patients 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. If a patient desires study participation, informed consent will be obtained. The patient will then be randomized to either control or experimental arms of the study. The control arm receives 800mg ibuprofen and placebo and the experimental arm receives 800mg ibuprofen and 5mg Marinol. Because PPCW does not dispense ibuprofen, to standardize dose and timing, all patients will receive 800mg ibuprofen as part of their study regimen. For this reason, ibuprofen is considered a study medication. All patients will take these study medications 30 minutes before misoprostol administration. Misoprostol administration will occur as directed to patient by PPCW staff. Randomization will occur at the OHSU Research Pharmacy per Research Pharmacy protocol. Placebo and study drugs will be similar in appearance. Subject and study staff will remain blinded to study drug allocation and study medications will be given out in a consecutive fashion. For example, study medications will be labelled as follows: Subject #5.

After the patient enrolls, but at the time of the initial visit, study staff will initiate a test text message to ensure the participant has texting capabilities. TextIt Platform will be utilized to develop short messaging system (SMS) flow sheet scripts that will provide timed questionnaires to collect data. The patient will be given the study medications, including ibuprofen, and the study drug or placebo. The patient will be instructed to self-administer the ibuprofen, and study drug or placebo 30 minutes before PPCW instructed them to take their misoprostol medication. For example, if the patient was instructed by PPCW to self-administer misoprostol at 11:30am, they would be instructed to self-administer the study drugs at 11:00am.

Once the patient self-administers the misoprostol, the patient will trigger the text messaging script to begin and this will designate the start time of the study. Maximum pain scores using 11-point NRS (0-10) will be assessed at the time of misoprostol administration (“hour 0”), at 6 hours after administration of misoprostol and at 24 hours. If a patient has not triggered the text messaging script within 24 hours following in office mifepristone administration, they will receive one text message and two phone calls to ensure they have not missed initiating data collection. Patients will be asked what time they intend to take misoprostol. If the patient has not triggered the text messaging script within 2 hours of the

estimated time they reported they would be taking misoprostol, a text prompt will be sent reminding the patient to take misoprostol and report the time of self- administration. If a patient does not report the time of misoprostol administration within 48 hours of mifepristone administration, no additional pain scores will be collected. A satisfaction questionnaire will be completed via text message within 21 days of mifepristone administration.

Thorough chart review at the follow up visit will collect and analyze unanticipated phone calls and/or clinical contact between the initial clinic visit and the follow-up visit. If a participant is found to have an ongoing pregnancy, further data will be excluded from the final analysis. Subjects will timestamp administration of additional pain medications within the first 24 hours after misoprostol administration via text message. If subjects would like to contact the study coordinators, they can text “Help” at any point via text message and be provided with a phone number to reach a study coordinator or study investigator.

If a patient feels that their pain is not controlled with the prescribed study medications, they will be informed that they may call the advice line at the clinic or presents to clinic, and they may be prescribed additional pain medications at that time.

Subjects will be compensated at three points in this study: 1) during initial enrollment in the study, 2) after responding to text message surveys for up to 24 hours after misoprostol administration, and 3) after completion of the follow-up visit or final text questionnaire. Compensation will be distributed in debit card (Clincard) form and tracked by serial number. Clincard is a web-based reloadable debit card used to reimburse patients who are engaged in clinical research.

The primary outcome will evaluate the maximum pain score reported from the time of misoprostol administration to 24 hours after misoprostol administration. As less than 1% of women have ongoing pregnancies following the initial dose of misoprostol, we anticipate a very small number of women needing additional doses of misoprostol to complete their abortion and will not collect additional pain score data if additional misoprostol is administered [34]. If patients do not respond to text messaging at any point during data collection or do not complete a scheduled follow up appointment, we will attempt follow up with a maximum of one text and two phone calls. Study participation is considered complete following the follow-up visit survey or at 21 days following mifepristone administration. We will be following the SPIRIT guidelines for study design and the CONSORT guidelines for study reporting [35] [36].

Drug Dosing Guidelines for Pain

Initial dosing:

- Placebo Arm: Subjects will take ibuprofen 800mg and placebo 30 minutes prior to misoprostol administration.
- Study drug (Marinol) Arm: Subjects will take ibuprofen 800mg and one (1) 5mg pill of the study drug 30 minutes prior to misoprostol administration.

Re-dosing: Subjects will be able to re-dose ibuprofen 800mg every 8 hours as needed. If a patient calls the advice line or presents for an unscheduled encounter and requires additional medications, additional medication advice with be given.

Study drug information and dispensing policies/security (see sections 6. Procedures Involved and 13. Drugs) for more information.

Delta^9-tetrahydrocannabinol (THC) is a partial CB_1 receptor agonist, and is the component of cannabis best known for producing psychotropic effects. THC has analgesic, anxiolytic and anti-emetic effects. Marinol is a FDA approved synthetic form of THC which is why this drug was chosen for this study. Marinol is FDA approved to treat nausea in chemotherapy patients and poor appetite in AIDS patients. We will be using Marinol off-label to study the effects of THC on pain, anxiety and nausea during medical abortion.

The time of onset is approximately 30-60 minutes, with peak effect at 90 minutes, and a half-life of 240 minutes, with a terminal half-life of 25-36 hours.

In multiple reviews, Marinol is noted to have a favorable safety profile, with the most common side effects noted to be drowsiness, diarrhea and changes in appetite [37] [38]. There are no known fatalities from marijuana overdose in the United States [39].

Marinol is FDA approved for oral administration and is available in 2.5mg, 5mg and 10mg pills. Marinol will be studied for off label use in this protocol, and the study dosage was selected based on expert opinion after surveying medical professionals familiar with medicinal THC use.
Our proposed research use of Marinol meets criteria for exemption for an IND according to FDA guidance as:

1) The drug product, Marinol, is lawfully marketed in the United States.
2) Our investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug.
3) Our investigation is not intended to support a significant change in the advertising or use of Marinol.
4) Our investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 CFR 312.2(b)(1)(iii)). We have selected a 5 mg dose for this single treatment, the mid-range of the approved pills and will give this by the approved oral route.
5) Our investigation will be conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50).

Our investigation will be conducted in compliance with the requirements of § 312.7 (i.e., the investigation is not intended to promote or commercialize the drug product).

The placebo pill will be produced by the Oregon Health & Science University Research Pharmacy, and will be color and size matched.

5. Study Population

A. Number of Subjects

Recruitment will mainly be focused at PPCW Southeast Health Center in Oregon. As an estimation, 680 medical abortions were performed within the last calendar year at the

Planned Parenthood Beaverton clinic, which averages to 56 medical abortions per month. If recruitment is slower than anticipated, additional PPCW sites might be used.

After written consent has been obtained and text messaging capabilities have been confirmed, participants will be randomized in a 1:1 allocation to the study drug and placebo groups. Randomization and drug packaging will occur at the OHSU Research Pharmacy per Research Pharmacy protocol. Placebo and study drugs will be similar in appearance. Subject and study staff will remain blinded to study drug allocation and study medications will be given out in a consecutive fashion. For example, study medications will be labelled as follows: Subject #5.

We estimated our sample size to achieve 80% power to detect a 2 point reduction in the NRS for pain (standard deviation of 2.6 points) using a significance level of 0.05. Accounting for 20% participant withdrawal results in a minimum total sample of approximately 72 patients. We plan to enroll approximately 36 participants in each study arm.

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 OHSU 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.

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 21 years or older
- Consented for elective medical abortion
- Pregnancy to 10 0/7 weeks, dated by ultrasound
- Able and willing to receive SMS messages via phone, and signed consent for e-mail/text communications with OHSU healthcare providers
- English speaking
- 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:

- Desires to continue pregnancy or currently breastfeeding
- Lack of access to cell phone and texting capabilities

- Prior participation in this study
- Early pregnancy failure
- Contraindications to the study medications: Marinol or marijuana derivatives, sesame oil, Ibuprofen
- Contraindications to medical abortion with Mifepristone or Misoprostol
- History of methadone, buprenorphine or heroin use within the last year
- History of a seizure disorder
- Used marijuana 5 or more days in the last week
- History of any adverse effects associated with prior use of recreational or medical marijuana products, or sensitivity/allergy to Marinol.

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. The OHSU Research Pharmacy will prepare the study drug and the placebo pills and will prepare the randomized medication packets for distribution in the clinic. We are relying on the OHSU Institutional Review Board (IRB) to satisfy IRB review requirements.

Recruitment will occur at PPCW Southeast Health Center in Oregon. 680 medical abortions were performed within the 2016 calendar year at the Planned Parenthood Beaverton clinic, which averages to 56 medical abortions per month. If recruitment is slower than anticipated, additional PPCW sites might be used. 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. Patients interested in participating in this study 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 form with study staff and have the opportunity to ask questions. The OHSU IRB approved consent will be signed by the participant and study staff.

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 those who decline entry. Patient age, gestational age, and reason for exclusion or refusal will be documented.

Subjects will be contacted via phone using SMS text messaging.

Patients will be compensated up to $150 for participation in the study. Patients will be paid based on the number of study visits and text message responses completed, as outline below:

- $10 after signing consent
- $40 for completing all enrollment procedures (including randomization of study drug)
- $50 for completing all text message surveys after taking Misoprostol ($15 per survey. $50 for completing all three surveys)
- $50 for completion of follow-up appointment at PPCW or final follow up via text message survey

F. 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. Interested patients will undergo screening to determine eligibility in a private room at PPCW. Staff consenting subjects for the study will be different staff than those providing counseling about pregnancy options. If eligible, interested participants will have time to review the consent with study staff and have the opportunity to 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, six (6) 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 randomized in a 1:1 allocation to the study drug and placebo groups. Randomization will occur at the OHSU Research Pharmacy per Research Pharmacy protocol. 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. 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.

Each study arm will include 36 subjects for a total of 72 subjects.

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. Data will mainly be collected via SMS messaging using timed surveys at 6 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.

Delta^9-tetrahydrocannabinol (THC) is a partial CB_1 receptor agonist, and is the component of cannabis best known for producing psychotropic effects. We will be using Marinol, a synthetic form of THC, which is FDA approved for use for treating nausea in chemotherapy patients and low appetite in AIDS patients.

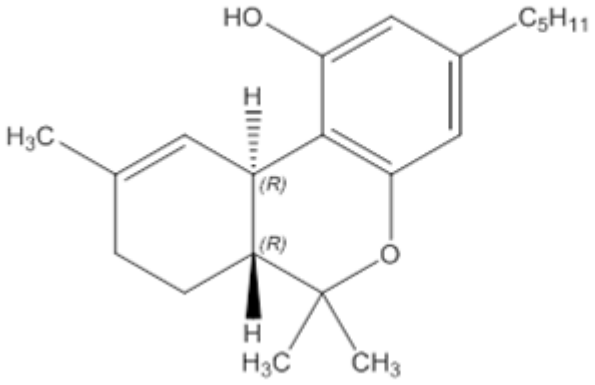
The time on onset is approximately 30-60 minutes, with peak effect at 90 minutes, and a half-life of 240 minutes.

In multiple reviews, cannabinoids are noted to have a favorable safety profile, with the most common side effects noted to be feeling “high”, drowsiness, diarrhea and changes in appetite [37] [38]. There are no known fatalities from marijuana overdose in the United States [39].

We will be using 5mg Marinol pills. The study drug dosage is based on expert opinion and market research, as there is a paucity of research on THC use in similar acute pain settings. In the absence of data to support a dose-effect for management of pain and anxiety for medical abortion, we selected 5 mg as an appropriate dose for initial study. We considered that 2.5 mg may be sufficient to improve appetite, but that most patients require dose escalation. Since the typical approved use requires dosing prior to each meal, with total daily doses of 7.5 – 20 mg, we feel our 5 mg dose represents an appropriate selection for an initial study.

The placebo pill will be produced by the Oregon Health & Science University Research Pharmacy, and will be color and size matched.

Marinol has the following structural formula:



Dronabinol, the active ingredient in MARINOL (dronabinol capsules, USP), is synthetic delta-9-tetrahydrocannabinol (THC).

Manufactured by: Patheon
Softgels Inc.
High Point, NC 27265

Manufactured for: AbbVie Inc.
North Chicago, IL 60064

Full prescribing information:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/018651s025s026lbl.pdf

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

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.

Sharing of Results with Subjects

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

Data and Specimen Banking
The data collected in this study will be stored per OHSU 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 [9], 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. 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 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 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 Marinol 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 Marinol 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. [42]
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 28 participants per group provided 80% probability of detecting the 2-point difference in the simulated data. To allow for up to 20% drop-out, we propose to enroll 36 participants per study arm (a total of 72 participants).

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.

Texting with Subjects: Information Privacy Security review was conducted and approval provided per email correspondence on 5/July/2018 contingent on having a signed BAA in place. Upon further review, the legal and security review team determined that due to the limited way that PHI is shared on this platform, neither a security review nor BAA are considered necessary. This is documented via email communication on

5/September/2018. When OHSU implements an enterprise security texting application the Women's Health Research Unit will agree to switch to using this for study data collection and communication with study subjects for all studies moving forward.

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

Please see Data Safety Monitoring Plan (DSMP).

11. Risks and Benefits

Risks to Subjects

A foreseeable risk to participants participating in this research would be a breach of confidentiality. Patients will be counseled on this risk and encouraged to take steps to protect confidentiality by password protecting their cell phone and keeping it on their person for the duration of the study. The list of questions that will be sent over text will be provided for review and patients will be asked to sign an additional consent to receive the questions via text message. 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 cannabis if a subject is in the study drug group.

As cannabis can be testing in urine drug screens, used by some employers, patients will be counseled before enrollment that if they receive the study drug, this may result in a positive drug test. They will be counseled that employers still reserve the right to terminate employment or enact other forms of discipline based on a positive urine drug screen despite the fact that cannabis is legal for medical and recreational purposes in the state of Oregon. If they choose to participate in the study, the study team is not responsible for any legal consequences of a positive urine drug screen.

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 cannabis products is category C. This means that animal studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. The use of 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. Patients will be counseled that risk of cannabis products to a developing fetus or a breastfeeding infant is not known, and as a result, the American Congress of Obstetrics and Gynecology recommend not using cannabis during pregnancy or while breastfeeding.

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

Marinol, the study drug, is FDA approved in the United States for the treatment of nausea in chemotherapy patients and low appetite in AIDS patients. However, it has not been studied to treat pain or nausea during medical abortion. We have included the Marinol Summary of Product Characteristics (Appendix B), which provides safety and pharmacokinetics information..

The study drug dosage is based on expert opinion and market research, as there is a paucity of research on THC use in similar acute pain settings. Medical professionals familiar with Marinol and medical marijuana, cannabis product producers and dispensary staff were surveyed on the most appropriate dosage for a marijuana naïve patient seeking relief from strong, acute cramping abdominal pain.

Marinol is a schedule III drug, and the OHSU Research Pharmacy will store the study drug. Packing of the study medications will also be handled by the OHSU Research Pharmacy for adequate blinding.

Subjects will return any unused medications at the end of study participation.

14. Multi-Site Coordination

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.

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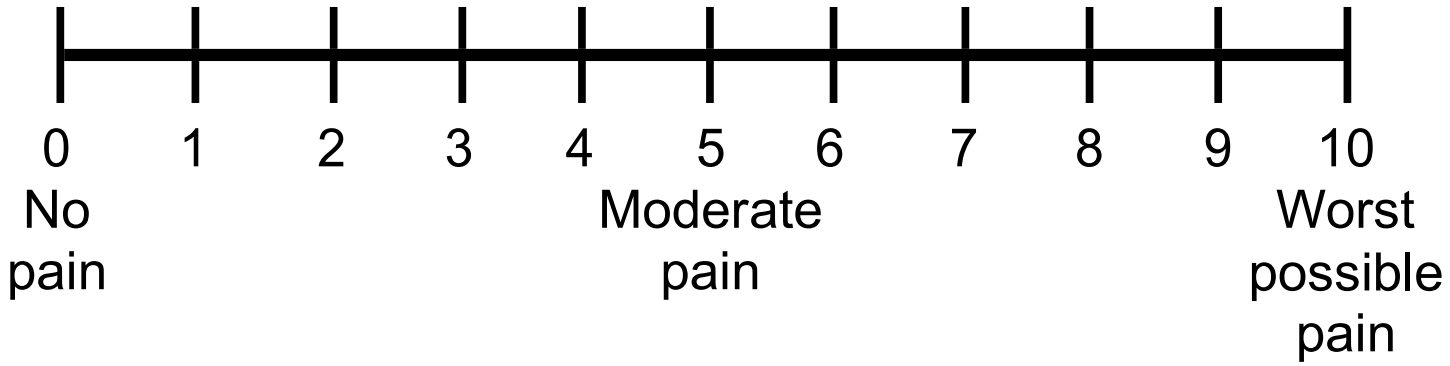
Appendix A

0–10 Numeric Pain Rating Scale



Appendix B Marinol Package Insert (see attachment)