Methadone for pain relief in first trimester medication abortion

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1 List of Abbreviations

Abbreviation	Abbreviation definition
NSAIDs	Non-steroidal anti-inflammatory drugs
WHO	World Health Organization
NMDAr	N-methyl-D-aspartate receptor
FDA	Food and drug administration
NRS	numeric rating scale
AE	Adverse Event

2 Protocol Summary

Title:	Methadone for pain relief in first trimester medication abortion
Population:	Women who have consented to medical abortion at ≥10 weeks gestation, who report willingness to participate in this study. Inclusion criteria will be pregnant women, age 18 and older, gestational age 10 weeks or less, English speaking, able to receive and send text messages, opioid naïve, and healthy. Exclusion criteria will be daily drug and alcohol use; opioid use in last 30 days; chronic use of pain medications; chronic use of benzodiazepines; any chronic disease including renal, liver, respiratory or cardiac disease; and any known allergies to nonsteroidal anti-inflammatory drugs (such as ibuprofen) and methadone.
Intervention:	Methadone 5mg tablet taken orally – to be taken with misoprostol in addition to standard ibuprofen dose
Objectives:	The primary objective is to determine the feasibility of enrolling 25 participants in a study within 6 months of study approval that requires the consumption of methadone for acute pain control in early medication abortion. Secondary objectives will be to evaluate pain scores at 0-, 4-, 8- and 24-hours post-misoprostol and methadone, use of supplementary analgesia, reported adverse effects (up to 48 hours post methadone), and patient satisfaction evaluated 1 week post methadone consumption
Design/Methodology:	We propose a non-randomized pilot study where we expect to be able to feasibly study between 15 – 25 women (recruited within a time period of 6 months from study approval) who will be given a prophylactic analgesic (methadone) while undergoing medical abortion at $\leq$10 weeks gestation with mifepristone and misoprostol.
Total Study Duration:	August 2021-May 2022
Subject Participation Duration:	1 week

3 Background/Rationale & Purpose

3.1 Background Information

Pain has been recognized as the most common and predictable side effect of medication abortion causing significant distress associated with the process. Yet there is little known about the optimal management of pain during this process, with no current evidence-based recommendations for the optimal analgesic regimen during the first trimester. The pain associated with medication abortion has been linked to the consumption of prostaglandin analogues, with women reporting high peak pain scores occurring 2.5 to 4 hours after the consumption of misoprostol (1). The lack of standardization in pain management, conflicting study results on the efficacy of currently used analgesics (2, 3) and the described inadequate pain control during this process warrants the need to identify an effective analgesic regimen.

Currently, non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen are routinely recommended for pain management for early medication abortion, including by the World Health Organization (5*).* Study results on the efficacy of ibuprofen when given prophylactically versus therapeutically have been conflicting. A study reported no observed difference in mean maximum pain scores with the comparison of prophylactic versus therapeutic ibuprofen, while others reported that pre-emptive ibuprofen use showed statistically significant benefit for pain management (Raymond et al. 2, 4 Avraham et al.).

In addition to NSAIDs, the WHO analgesic ladder for the management of acute and chronic non-cancer pain recommends the use of weak opioids with or without non-opioid analgesics for moderate pain and potent opioids (i.e. oxycodone, hydromorphone, or methadone) for severe and persistent pain with or without non-opioid analgesics (6). Various studies conducted to evaluate different regimens for pain control with early medication abortions have demonstrated an average mean pain score range of 6.2 to 8 out of 10 on a 11 point numerical rating scale (**NRS**) from 0 (no pain) to 10 (worst pain) (1,7). Consequently, the pain experienced in early medication abortion is significant and needs more research to investigate regimen options for pain reduction.

The female reproductive organs are dually innervated by the hypogastric nerve branch of the lumbar splanchnic nerve and the pelvic nerves (9, 10), which are part of the visceral pain pathway. Pharmacological modulation of visceral afferents target receptors to control visceral pain is the subject of continued research. Of the many target receptors available, modulation of the N-methyl-D-aspartate receptor (NMDAr) has moderating effects on the response of sensory afferents and spinal processing of visceral pain (10). Tramadol is a synthetic opioid which binds to mu-opioid receptors and has some inhibitory effects on NMDAr. A multicontinental randomized controlled trial comparing the prophylactic administration of tramadol versus ibuprofen and metoclopramide versus placebo for pain control during early medication abortion did not elicit a statistically significant difference (Dragoman et al). Although they hypothesized that women receiving prophylactic analgesia would report lower maximal pain scores in the first 8 hours following misoprostol, the results showed no difference in pain trajectories in either study arm (11).

Methadone is a synthetic opioid with multiple actions qualitatively like morphine. The primary therapeutic uses of methadone are for analgesia and maintenance therapy in opioid use disorder (12). Methadone is included on the third step of the WHO analgesic ladder as an opioid analgesic that can be used for persistent or severe pain (6). Although methadone is a potent opioid agonist with similar mu-receptor affinity to morphine, it also contributes to analgesia via non-opioid actions: inhibition of the reuptake of serotonin and norepinephrine and antagonism of the NMDAr. Methadone is well absorbed following oral administration with levels detectable within 30 minutes and peak concentrations within 4

hours (13). Consequently, analgesic duration of action typically ranges 4-8hours (12). Methadone has been studied extensively as a suitable therapy for cancer pain and chronic pain. It is considered an acceptable alternate opioid when pain remains inadequately controlled with other opioids. Multiple studies evaluating the reported improvement in pain control following the transition to methadone in patients with cancer pain reflected single dose or short-term use administration as opposed to longer term use, which is more relevant in clinical practice (15).

We seek to investigate whether the administration of methadone, in addition to a standard dose of ibuprofen, will be effective in reducing pain associated with early medication abortion. The current standard of care is administration of ibuprofen. Our hypothesis is that this combination of analgesics would serve as a viable regimen for improved pain control during early medication abortion in an outpatient setting. This is the first study proposed to investigate the use of methadone as part of the analgesic regimen for early medication abortion. Although opioids are sometimes used for pain during early medication abortion, their efficacy has not been established. Several small, randomized studies demonstrated no difference in pain scores in patients undergoing early medication abortion when opioids including codeine were added to ibuprofen or acetaminophen when compared to placebo (7), oxycodone versus placebo (1) or the use of hydrocodone-acetaminophen (8).

This study will be conducted in compliance with the protocol, applicable regulatory requirements, and BMC/BU Medical Campus Human Research Protection policies and procedures.

3.2 Rationale and Purpose

Pain is an expected consequence of medication abortion. Reviews of multiple studies evaluating the experience of women undergoing medical abortion during the first trimester concluded that approximately 75% of women experience intense pain of a severity requiring narcotic analgesia (16). In addition, neither an assessment of pain nor analgesic options are consistently reported in clinical trials of medical abortion (17). This reflects oversight on the importance of pain as a significant side effect of medication abortion. It is important that new analgesic strategies be evaluated to help reduce pain experienced during medical abortion to improve the quality of patients' experiences and satisfaction with the process.

4 Objectives

4.1 Study Objectives

The primary objective is to determine the feasibility of enrolling 25 patients within a span of 6 months in a study that requires the consumption of methadone for acute analgesia experienced during early medication abortion. The secondary objectives include evaluation of pain scores at 0, 4, 8 and 24 hours, use of supplementary analgesia, reported adverse effects, and participant satisfaction.

4.2 Study Outcome Measures

4.2.1 Primary Outcome Measures

The primary outcome will be the feasibility of the recruitment process in enrolling 25 study participants in 6 months into a study involving the administration of methadone for pain control during early medication abortion. Feasibility would be determined by the ease of the recruitment process by evaluating the number of participants eligible for screening and recruitment, and actual number of participants recruited.

4.2.2 Secondary Outcome Measures

The principal secondary outcome of this study is a participant reported pain score measured 4 hours after administration of misoprostol, on a clinically validated 11 point Numerical Rating Scale of pain (NRS). Several small randomized studies performed in the United States and Canada evaluating pain control with medication abortion while analyzing different pain regimens have reported an average maximum mean pain score of 7, ranging from 6.2 - 8 (2,11) measured with an 11-point NRS; (0-10) where 0 is equivalent to no pain and 10 is the worst pain. We hypothesisze that a change of at least 2 points on the NRS within the first 4 hours after misoprosol administration would indicate a clinically significant reduction in average mean pain scores in our study patients in comparison to these studies. We also hypothesize a decrease in pain scores within 24 hours following misoprostol with the study intervention using the same NRS scale, a decrease in the use of supplementary analgesia and increase in patient satisfaction measured by developed surveys which would be administered at 0,4,8, 24, 48 hours and 1 week post the consumption of misoprostol and study intervention.

We will also use descriptive statistics to report on use of supplementary analgesia (medications, dosages, and frequencies), reported adverse effects, and patient satisfaction utilizing a patient satisfaction survey.

5 Study Design

We propose a non-randomized pilot study of women who will be given a preemptive analgesic (methadone) in addition to a standard dose of ibuprofen while undergoing early medication abortion with mifepristone and misoprostol at ≤10 weeks gestation. This is an open-label, single-arm study that will assess the feasibility of recruiting and enrolling 25 study participants into this study in a time period of 6 months from study approval. All participants will also be provided with a prescription of supplementary ibuprofen to be used at their own discretion during the process. The current standard of care is administration of ibuprofen alone.

Women presenting to the clinic with a request for early medication abortion will be screened for inclusion into the study **(Appendix: Screening Form)**. The eligible participants will be provided with an informed and voluntary consent for enrollment into the study only after the consent for the abortion procedure has been obtained separately. Copy of signed consent can be provided to patient if they choose to have one but study team will retain a signed copy for our records regardless of their choice to take the copy of signed consent. Participants will be given time to ask questions and talk to their family or friends, if desired, about the study.

After study staff answers all questions and obtains written informed consent, participants will receive the standard medication abortion procedures #'s 1-3 and the research intervention (#4):

1) They will take mifepristone orally in the clinic
2) They will be dispensed 800 mcg of misoprostol, with standard instructions to self-administer buccally approximately 24-48hours after taking mifepristone
3) They will be prescribed ibuprofen 600 or 800 mg (per their preference)
4) In addition to these standard abortion medications, a single dose of the study medication, methadone 5mg, will be prescribed (both medications can be dispensed at the Yawkey outpatient pharmacy).
Participants will be instructed to take methadone at the same time as their misoprostol. Participants will be provided with a telephone number to which they will be required to text study staff indicating that misoprostol and methadone have been consumed.

Study staff will phone the participants at 0, 4, 8, and 24 hours post-misoprostol dosing. These phone calls, lasting approximately 5 minutes, will include a survey asking the patients to indicate their maximum pain scores on a 0-10 NRS scale, their compliance with study medications, and any adverse effects experienced including dizziness, difficulty breathing, nausea or vomiting. Participants will also be contacted via phone at 48 hours after their methadone dose for further evaluation of any reported adverse events, and again at 1 week after misoprostol to assess ease of study design and instructions, pain experience, personal view on consumption of specific study medication (methadone) and patient satisfaction.

6 Potential Risks and Benefits

6.1 Risks

Package insert of methadone from FDA (**Attached**).

While there are no known interactions between misoprostol, ibuprofen, or mifepristone and methadone, methadone has been associated with respiratory depression. Respiratory depression has been observed, particularly in the early dosing period and is associated with high initial dosing (12). Methadone has also been associated with cases of QT interval prolongation and serious arrhythmias (torsades de pointes), with most cases involving patients being treated with multiple, large daily doses of methadone (12). In our study, participants will receive only **ONE** dose of methadone (5mg), mitigating the risks of these occurrences.

The common side effects associated with methadone, similar to other opioids, are sedation, dizziness, nausea, vomiting, lightheadedness, sweating, constipation, and dry mouth. Methadone has been associated with respiratory depression, QT interval prolongation and serious arrhythmias (torsades de pointes) in patients receiving very high initial doses and doses commonly used for maintenance and treatment of opioid addiction, respectively (12).

Participants will be informed about the low/ unlikely risk of opioid addiction.

The Massachusetts prescription monitoring program will be used to confirm any prescriptions participants may have received using the online Massachusetts Prescription Awareness Tool, per standard prescribing policy.

We will ensure that the study drug, methadone, is dispensed by the Yawkey pharmacy in a child-proof, tamper proof container.

Participants will be advised not to operate heavy machinery, operate a vehicle, or drink alcohol for 24 hours following methadone dose.

Participants may become tired of doing the surveys or they may be tired or in pain when we call. We will do our best to conduct the surveys with these possibilities in mind and always be guided by the subject in regards to whether the survey can be completed at that time.

The interviewers will be research assistants and physicians. Study principal investigators (PIs) will be available 24/7. If interviewers who are not physicians detect any adverse events, they will immediately contact the study PIs, who will be available 24/7. The study PIs will then contact the patient directly to obtain further information and make informed, shared decisions about triaging the adverse events.

As per the family planning policy that is in place for routine medication abortions, the research team will be able to contact the family planning physician on call (there is 24/7 call coverage). If a participant expresses any emotional distress, study staff will assess for any suicidal ideation, which would prompt an urgent referral to the emergency department for evaluation. If the participant is not expressing any thoughts of harm to self or others, study staff will offer an urgent consult with social work, referral to behavior health, and give information about abortion hotlines.

There is always a risk associated with breach of confidentiality; however, procedures are in place to make such breaches unlikely. All participant information will be deidentified using a master code unrelated to the PHI. The review of subjects' medical records is for limited information, and all data will be securely stored and deidentified behind BMC firewalls.

6.2 Potential Benefits

Participants may or may not receive a direct benefit with study participation. They may experience less pain during their medication abortion. Their experiences will provide valuable information that may help identify a potential analgesic strategy that would aid in the prevention and reduction of pain associated with medication abortion, improving the quality of the experience and satisfaction with the process for future patients.

6.3 Analysis of Risks in Relation to Benefits

As described previously, literature in the field of pain management for medication abortions is scarce and its potential importance in reducing distress amongst women who undergo this procedure is significant. This study can provide evidence to guide clinicians, reduce the incidence of post-procedure pain, and improve patient satisfaction and outcomes. While there are adverse events associated with the use of high doses and repeated doses of methadone, we will only administer **one single** dose tablet of methadone: 5mg. The risk of addiction to opioids is minimal in these healthy, opioid naïve patients who are provided one dose. Our hypothesis is that therapeutic benefit of providing a single, small dose of methadone for pain relief would show preliminary signals of efficacy in providing pain relief for women undergoing medication abortion, outweighing the potential risks associated with its administration.

7 Study Subject Selection

7.1 Subject Inclusion Criteria

To be eligible to participate in this study, an individual must meet all the following criteria:

1. Women who have consented to undergoing medication abortion at or under 10 weeks gestation
2. Age 18 years and older
3. Fluent English speaking and reading
4. Able and willing to receive and send text messages and receive phone calls

(Appendix: Screening Form)

7.2 Subject Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Prior history of opioid abuse or opioid use disorder
2. Reluctance or resistance to the use of opioids
3. Participants who have any history of daily drug or alcohol use
4. Participants with any significant medical illness, including renal, liver, neurologic, gastrointestinal, respiratory, or cardiac disease
5. Opioid use in last 30 days
6. Chronic use of pain medications, benzodiazepines, or on opioid-maintenance therapies (i.e. naloxone, naltrexone, buprenorphine, or combinations thereof)
7. Chronic use of medications that may interact with methadone: antiretrovirals (i.e. abacavir, atazanavir, darunavir, indinavir, efavirenz, nevlfinavir, nevirapine, ritonavir, lopinavir, didanosine, stavudine, zidovudine), antibiotics (erythromycin, rifampicin), antifungals (fluconazole, ketoconazole), anticonvulsants (carbamazepine, phenobarbital), monoamine oxidase inhibitors (phenelzine), tricyclic antidepressants (desipramine), St. John's Wort
8. Any known allergies to ibuprofen or methadone.
9. Patients with known history of QT prolongation (**Appendix: Screening Form)**

8 Study Intervention

The study intervention, a single dose of methadone 5mg, will be self-administered orally by the participant at the same time as buccal misoprostol and within the context of a medical abortion. All participants will be provided with instructions about the study intervention, methadone, including timing of administration, administration route, and possible side effects.

Although methadone is not a common first-line opioid, its use may be beneficial in opioid-naïve patients due to its slow onset and long duration of effect. Guidelines published in 2000 by the College of Physicians and Surgeons of Ontario provided suggestions for starting doses in opioid naïve patients: 2.5mg orally every 8 hours (14). Per the Food and Drug Administration (FDA), initiation of therapy with

methadone in opioid non-tolerant patients may range from 2.5- 10 mg every 8-12 h (12). These recommendations pertain to the use of methadone for the management of analgesia extending beyond one day. We propose the use of one 5mg dose of methadone to be administered **ONCE** to study participants for the management of acute pain associated with medication abortion.

9 Study Procedures

See the **Appendix 1** for the schedule of events.

- As part of screening process, the electronic medical records of patients scheduled for medication abortion will be reviewed for eligibility.
- After a patient who has been determined to be potentially eligible for the study per chart review has provided informed consent for a medication abortion, and has begun the medication abortion process by taking the first medication required for medication abortion (mifepristone) their clinician will ask if they want to hear about the study. If yes, the clinician will provide a warm hand-off to the study staff.
- Researchers will review the study, including information about the study drug, clear instructions for use, and a review of the study contact points. No additional in-person visits are required for study participation.
- The patients will have the opportunity to ask questions to the study staff, as well as talk to family and friends about the study.
- If a patient is interested in participation, the study staff will review the eligibility criteria. If the patient is eligible, study staff will obtain written informed consent.
- After informed consent has been obtained, study staff will review with participants their basic demographic information, medical and pregnancy history, history of prior medication abortions, and estimated gestational age.
- Copy of signed consent can be provided to patient if they choose to have one but study team will retain a signed copy for our records regardless of their choice to take the copy of signed consent.
- Study staff will also review other informational handouts that participants will be provided with including a detailed medication pamphlet explaining in detail the side effects of mifepristone, misoprostol, ibuprofen and the study drug methadone.
- Participants will be counseled on the expectation of the presence of pain with cramping and bleeding that may be caused by misoprostol, and which may last up to several hours. This pain has been described as mild, moderate and even severe but the intensity of pain is different for every individual.
- Participants will also be counseled on the expectation of dizziness, diarrhea and mild fever. Mild cramping for a few days after the abortion process may also be expected but is normally not enough to prevent them from going back to school or work. The only restriction will be on the operation of heavy machinery, operating a vehicle or drinking alcohol for 24 hours following their methadone dose.
- The participant will then receive a prescription of misoprostol to be taken 24-48hours later per standard of care.

- The participant will also receive a prescription for the study drug and standard of care, ibuprofen, with written instructions about dosing of the medications and points of contact with study staff.
- Participants will be instructed to send a text message to study staff indicating that they have self-administered misoprostol and the study medication, by texting the word “DONE” and their initials. After the receipt of the text message by participants, study staff will then generate a telephone call to participants to conduct a survey at 0, 4, 8 and 24hours following misoprostol/methadone administration.
- Study team will utilize a Google Voice number (857-217-4995) for contact with participants since this will enable PIs as well as other members of study team such as research assistant/ manager to have access to participants call or texts in case of adverse events or any emergencies in addition to regular follow-up texts. A reminder that no PHI will be transmitted over Google Voice.
- Study team member will send the participant a text message after they sign the informed consent. This text message will state "TEST". This will ensure participants have the study team’s contact information (without needing to keep physical paperwork, if desired).
- Study team will also suggest participant saves the team’s contact number as "BU Study Team". This will only be done IF the participant agrees.
- Study staff will be provided a standardized script that will be constant for every phone interaction with a participant. This script will not include the term “abortion” when calling participants to conduct the surveys.
- These scripts will state: “Hi. We are calling from the BU team. Can you please confirm your name?”
- These telephone conducted surveys will include questions on maximum pain scores using the NRS (0-10) pain scale, when and whether methadone was consumed, when and whether ibuprofen was consumed, whether any side effects were experienced, and whether supplementary NSAIDs or acetaminophen were used.
- Study staff will send a text message OR call study participants once every 24hrs after mifepristone administered in clinic to remind them about sending a text message when misoprostol and study medication are administered.
- If we reach the participant by phone we confirm identity and then ask the participant if they've taken their misoprostol (second medication) yet. If they say no, we thank them and remind them of their next follow-up. If they say yes, that starts our "time 0". If we're unable to reach them by phone, we send a text message stating "Reminder to call BU Study Team" at the 24 AND 48 hour mark post-mifepristone (if the participant responds before 48 hour mark then call or message will not be sent).
- No health information will ever be exchanged through text.
- All participants will be contacted via telephone again at 48hours after consumption of misoprostol for evaluation of any side effects or reported adverse events, and again at 1 week following consumption of misoprostol to assess patient satisfaction.
- If unable to reach study participants, three (3) attempted telephone contacts will be made and documented before considering the participant lost to follow-up.
- Partial data will be stored for all participants who report pain scores up to 8 hours after consumption of methadone, but are unable to be reached for further assessment at the 24, 48 hours and 1 week timeframe. 3 attempted telephone contacts will be made and documented before considering the patient lost to follow-up

- Standard of care after medication abortion is a follow-up appointment in 1-2 weeks to confirm abortion completion.
- Participants will have been counseled by their family planning clinician that not taking the misoprostol will increase the risk of incomplete abortion, and that they are encouraged to follow-up with the clinician as scheduled whether or not they take the misoprostol.
- During the study, we are asking participants to text us when they have taken the misoprostol; if they do not reach out to us or do not take the misoprostol, but do take the methadone, they are not at any higher risk from study involvement. We think it is highly unlikely that a participant will stay in contact with the study team but not take their misoprostol.

10 Assessment of Safety and Data Safety Monitoring Plan (DSMP)

10.1 Definitions

The following definitions will be used in the assessment of safety:

Adverse Event (AE) is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. In our study, the following routine study measurements are considered AEs but are not necessarily related to the subject's participation in the research as they may be commonly associated with the medication abortion procedure, (though assessments on relatedness will be made for each occurrence): pain, vaginal bleeding, nausea, vomiting, fever, chills and diarrhea. The following routine study measurement will not be considered an AE because it is defined as a study endpoint: abortion.

Serious Adverse Event (SAE) is any adverse event that

(1) results in death;
(2) is life-threatening;
(3) results in inpatient hospitalization or prolongation of existing hospitalization;
(4) results in a persistent or significant disability/incapacity;
(5) results in a congenital anomaly/birth defect; or
(6) based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Life-threatening means that the event places the subject at immediate risk of death from the event as it occurred.

Unanticipated Problem is defined as an event, experience or outcome that meets **all three** of the following criteria:

- <u>is unexpected</u>; AND
- <u>is related or possibly related</u> to participation in the research; AND

- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research

Unexpected means the nature, severity, or frequency of the event is not consistent with either:

- the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol–related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or
- The expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

10.2 Safety Review

Both the risks listed in Section 6.1 and unknown risks will be monitored as follows: subjects will be contacted via phone call at 0, 4, 8, 24, and 48 hours following administration of methadone and misoprostol. Subjects will be asked to report pain scores as well any side effects or adverse events. The PI and sub-investigator (physicians) will monitor and review the survey answers promptly. If the PI determines that any adverse events need further assessment, the subject will be contacted directly for further information and assessment. Participants will be provided with information on when, how, and where to seek medical attention.

Details about each AE will be recorded on an Adverse Event Form, and about SAE on a Serious Adverse Event Form. These forms will require information to be collected on the AE, onset date/time, date/time study staff aware, resolution date, action taken and comments. These forms will be completed by study staff and Principal Investigator informed as soon as possible.

10.3 Reporting Plans

The Principal Investigator at BMC will report Unanticipated Problems, and Adverse Events to the BMC IRB in accordance with IRB policies:

- Unanticipated Problems occurring at BMC/BU Medical Campus will be reported to the IRB within 7 days of the investigator learning of the event.
- Any reports with recommended changes will be reported to the IRB within 7 days of the investigator receiving the report.
- Adverse Events (including Serious Adverse Events) will be reported in summary at the time of continuing review, along with a statement that the pattern of adverse events, in total, does not suggest that the research places subjects or others at a greater risk of harm than was previously known.
- Any reports with no recommended changes will be reported to the IRB at the time of continuing review.

10.4 Stopping Rules

The study will be stopped if two or more patients have a SAE. A subject will be withdrawn from the study if they have adverse reactions associated with methadone use including: respiratory depression, signs and symptoms of arrhythmia and any other unaccounted event. A subject can choose to no longer participate in the study at any time.

11 Data Handling and Record Keeping

11.1 Confidentiality

Study staff will implement procedures to protect the confidentiality of patient and participant information.

- When patients are screened for eligibility, we will record the responses in a way that does not identify the individual. For those that choose to participate and sign the informed consent/HIPAA authorization, we will then write the study ID on the screening responses and keep these in the study files. For those who are not eligible or who don't want to participate, we will record the reasons for not taking part but we will not link this to the individual.
- When a patient has enrolled in the study, we will collect participant contact information including phone numbers, medical record number, and email address. This information will be stored in a password-protected Excel file and kept on a secure hospital server. Only study staff will have access to this file.
- We will create a single master key; all participants will be given a study number beginning with 101. Study numbers will be recorded on the Excel file, which will be the only location where participant identifiers are connected to their study ID.
- Study staff will record baseline information on demographics and medical history into a REDCap survey, using only the participant study ID.
- All follow-up surveys obtained by telephone will be entered into REDCap, again using only the participant study ID.
- Study staff will be provided a standardized script that will be constant for every phone interaction with a participant. This script will not include the term "abortion" when calling participants to conduct the surveys.
- This scripts will state: "Hi. We are calling from the BU team. Can you please confirm your name?"
- Once a participant has completed study activities, their information will be stored securely for 7 years, then will be deleted from the master Excel file. All remaining information in the REDCap surveys will thus remain deidentified.

All data containing patient identifiers, including patient phone numbers and text message data, will be stored on virtual drives behind the BMC firewall. The master code will contain the patient identifiers connected to a unique Study ID. Data will be coded and stored separately from the master code. All statistical analyses, as well as distribution, will only be performed on a final coded dataset in which subjects are identified only by a unique study-specific code assigned for the sole purpose of this research project. The master code, which connects study ID and identifiers, will be stored securely for 7 years then will be destroyed. This study is registered on ClinicalTrials.gov.

11.2 Source Documents

Source data includes EPIC hospital records, clinical and office charts, anesthesia records, surgical report, participant text messages and laboratory notes.

Data generated by the methods described in the protocol will be recorded in the subjects' medical records and/or study progress notes. Data will be transcribed directly into REDcap and will be deidentified. As described above, patients will be given a unique study identification code upon acceptance into the study. This unique study ID code will be used in REDcap and will have no link to PHI.

11.3 Case Report Forms

A REDcap database will be the primary data collection instrument for the study. All data requested will be transcribed into REDcap. All missing data will be explained. If a data set on REDcap is left blank because the procedure was not done or the question was not asked, the code “9999” will be entered. If the item is not applicable to the individual case, “N/A” will be written. All entries will be entered directly into REDcap.

See the Appendix for the following CRFs: REDcap

11.4 Study Records Retention

Study records, including participant consents, will be retained for at least seven years after completion of the study as is required by the BUSM/BMC IRB. These records will be retained in a locked file cabinet in the PI’s office within the Department of Anesthesiology.

12 Statistical Plan

12.1

Study Hypotheses

This is a feasibility study on the recruitment process of study participants in utilizing a study intervention drug, 5mg of oral methadone, along with a standard dose of ibuprofen, following medication abortion with misoprostol. We hypothesize that it will be feasible to recruit and enroll 25 eligible women per mentioned screening criteria into this pilot study in the time period of 6 months post study approval. The feasibility of this study will aid in the planning of a larger sufficiently powered efficacy trial which would determine that there is a reduction in pain scores after the administration of misoprostol in medication abortion when the study intervention drug is consumed concomitantly

12.2 Sample Size Determination and Statistical Methods

In this planned pilot study of methadone as a one-time treatment for pain, we can expect to be able to feasibly study between 15-25 women within 6 months of study approval. From the literature we know

that previous studies have found a mean maximum pain score of 7 (range across studies 6.2-8) and most of these studies sued a standard deviation of 2 – 2.5. We are hoping to power to see reduction in maximum pain scores by 2 points; meaning, we expect our intervention group will have a mean pain score of 5, compared to the historical mean of 7. We thus can compute the upper bound of a two-sided 95% confidence interval for an expected mean pain score of 5 and determine if this limit excludes the mean score from other studies (treated here as a target population mean). We assume a standard deviation of 2.25 for these computations. With a sample of 15 participants, the upper bound of the 95% confidence interval is 6.25. For 20 participants, the upper bound is 6.05 and for 25 participants it is 5.93. Thus, with even the smallest anticipated sample, we expect that the pain scores of women treated with methadone will statistically exclude in its upper confidence bound the population mean level of 7. We will analyze these data using a mixed linear model that will account for the correlated nature of the observations per patient.

13 Ethics/Protection of Human Subjects

This study is to be conducted according to applicable US federal regulations and institutional policies (which are based in federal regulations, guidance, and ICH Good Clinical Practice guidelines).

This protocol and any amendments will be submitted to the Boston Medical Center and Boston University Medical Campus IRB for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator.

All subjects for this study will be given a consent form, if they choose to have one, describing the study and providing sufficient information for subjects to make an informed decision about their participation in the study. The consent form will be submitted with the protocol for review and approval by the IRB. The consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. Consent will be documented as required by the IRB.

14 Literature References

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15 Appendix

Schedule of Events, Screening Form, Surveys at 0, 4, 8, 24, 48 hours and 1 week.