Title: Gabapentin as an adjunct to perioperative pain management regimens for uterine aspiration: a randomized controlled trial for a multicenter prospective meta-analysis.

Short title: Gabapentin as adjunct for blocking abortion pain (GABA)

NCT02725710

Site PI:
Beverly Gray, MD
Department of Gynecology and Obstetrics
246 Baker House
Durham, NC 27710
page: 919-970-3265
email: beverly.gray@duke.edu

Duke Collaborators:
Kara McElligott, MD, MPH
Liz Deans, MD

Research Objectives and Specific Aims

Pain control during and after abortion is a Society of Family Planning priority. Pain management regimens for surgical abortion can rely on local anesthetic, oral analgesics, moderate sedation, deep sedation, or a combination of approaches. While several recent studies have attempted to reduce pain with adding supplemental medications or therapies, such as nonsteroidal anti-inflammatory drugs, narcotics, anxiolytics, misoprostol, nitrous oxide, music, most studies have failed to improve pain scores. As optimal pain management has not been established, many women continuing to report moderate to severe pain during and after the procedure [1].

We propose a novel regimen of oral gabapentin administered prior to usual pain management regimens for surgical abortion. Gabapentin is used to treat neuropathic and chronic pain. Mechanism of action may include calcium channel blockade and modulation of nociceptive neurotransmitters. Clinical trials support use of perioperative gabapentin to reduce post-surgical pain in a variety of clinical settings[2]. Gabapentin is well-tolerated and inexpensive, with mild, if any, side effects. [3] In a systematic review of 22 randomized controlled trials (RCT) of multiple surgical procedures including ambulatory nasal surgery, orthopedic procedures and laparotomy, a single preoperative dose of gabapentin significantly reduced 24-hour opioid consumption[3]. Perioperative gabapentin before hysterectomy showed reduced pain scores, nausea and vomiting [4, 5] A randomized trial in the setting of cesarean showed improved pain scores and decreased pain requirements with a 600 mg dose of preoperative gabapentin [5]. Its use in the setting of abortion has never been evaluated.

We hypothesize that adding gabapentin preoperatively to current pain management regimens will reduce pain associated with surgical abortion. Additionally, *we hypothesize that preoperative gabapentin will reduce perioperative nausea, vomiting and anxiety with few adverse effects.*

Primary Aim: To evaluate the impact of adjunctive preoperative gabapentin on perioperative pain during uterine aspiration <15 weeks of gestation for abortion and pregnancy loss management compared to usual pain control regimens

Secondary Aims

- To evaluate the impact of preoperative gabapentin on:
    - perioperative nausea and vomiting
    - preoperative anxiety
    - use of pain medications and anti-emetics post-operatively
- To evaluate side effects or adverse events of gabapentin in this setting
- To identify subgroups where adjunctive gabapentin may be more effective at reducing perioperative pain such as gestational age ranges and patient characteristics (age, gravidity, substance abuse, preoperative anxiety level).

Background and Rationale:

Surgical abortions in North America are typically performed using either local anesthetic with oral analgesics or moderate sedation. A 2009 Cochrane review of evidence for pain control assessed that paracervical block in reducing abortion related pain is limited, while the addition of ibuprofen and naproxen can slightly reduce intraoperative and post operative pain [6]. Evidence supports the benefit of conscious sedation at reducing intraoperative and post-operative pain in abortions [7]. General anesthesia can be useful in some settings, however its use is limited due to cost, staffing and potential for additional risks. Further, studies have found, although better at reducing pain during the procedure, general anesthesia is not superior to moderate sedation for post-operative pain [8]. Other recently examined adjuncts to pain control have not proven to be beneficial in this setting [9-11].

Gabapentin is widely used to treat neuropathic and chronic pain. Mechanism of action may include calcium channel blockade and modulation of nociceptive neurotransmitters. Clinical trials support use of perioperative pregabalin and gabapentin to reduce perioperative and post-operative pain in a variety of clinical settings, for both major and minor surgical procedures [2, 12]. While pregabalin has a faster peak plasma concentration, gabapentin is a less expensive option with peak concentrations reached by 2 hours, with substantial evidence to support routine use and safety in reducing perioperative pain. In a systematic review of 22 randomized controlled trials (RCT), a single preoperative dose of gabapentin significantly reduced 24-hour

opioid consumption [3]. In the setting of obstetrics and gynecology, evidence supports perioperative gabapentin before hysterectomy to reduce pain scores, nausea, and vomiting [4, 5]. Preoperative gabapentin prior to cesarean section improved pain scores at 24 hours with less need for post-operative analgesia compared to placebo [5]. In an outpatient setting similar to abortion surgery, perioperative gabapentin have been shown to decrease post-operative opioid consumption and anxiety for minor orthopedic procedures and hemorrhoidectomy [13, 14].

Innovation in pain control and reduction of anxiety, nausea and vomiting using a low cost, well-tolerated intervention could impact hundreds of thousands of women each year with potential implications for other common outpatient gynecologic procedures. We propose a novel use of oral gabapentin administered in conjunction with usual pain management regimens for surgical abortion. *Use of gabapentin in the setting of uterine aspiration has never been evaluated; however it is used routinely and successfully in several similar surgical settings as an adjunct to pain management regimens.* It is generally well-tolerated and inexpensive, with minimal side effects and few contraindications [3]. If effective, this simple adjunct to current pain regimens could expand options for the management of women worldwide undergoing surgical abortions. Other secondary outcomes such as nausea, vomiting and anxiety influence a woman's ability to return to her normal baseline level of activity and her experience of abortion in general. Our prospective meta-analysis (PMA) design will allow us to simultaneously evaluate the impact of gabapentin among different gestational ages and combined with different anesthesia regimens to determine if there is utility of this easy to use, safe adjunct therapy in differing abortion care settings.

Study Design and Methodology

Study Design: This is a randomized controlled double-blind placebo-controlled trial evaluating the impact of gabapentin given preoperatively on perioperative pain scores for women receiving uterine aspiration between 6 and 14+6 weeks gestation. This study will be a trial included in a prospective meta-analysis evaluating the use of gabapentin on perioperative pain in the abortion setting.

Location: This study will take place at Duke Gynecology outpatient clinic, a hospital based clinic within the Duke system. This clinic operates 4 days per week (Tuesday through Friday) with a clinical volume of 1-4 procedures. Patients have their procedures with oral sedation and local anesthesia in the form of a paracervical block using lidocaine.

Approximately 220 women are have procedures under local anesthesia each year, with 2/3 of those patients being less than 8 weeks gestational age. Based on the patient volume, we do not anticipate any difficulty in recruiting patients to complete this study within the timeline presented. At this clinic, there are 3 providers whom have slightly different practices and protocols. Misoprostol for cervical preparation is used 2-3 hours prior starting procedures for cases at 12 to 14 weeks per provider preference.

Duke University School of Medicine, Department of Gynecology and Obstetrics at Duke University, where the study PI and coordination is based, has a strong clinical tradition, with its diverse patient population, the department have augmented expertise and experience across the discipline and provide a continuum of research opportunities in basic biomedical, translational, clinical and epidemiological research. This study will benefit from the existing research infrastructure at Duke for recruitment and enrollment.

Participant Selection:

A total of 96 women will be recruited and enrolled.

Inclusion and Exclusion Criteria

Inclusion criteria include:

- Women >=18 years-old
- Presenting for a surgical abortion
- No contraindication to outpatient abortion
- No contraindication to gabapentin
- Fluency in English and able to provide informed consent

Exclusion criteria include:

- Allergy, sensitivity or contraindication to gabapentin
- Severe renal disease, previously identified creatinine clearance of less than 30.
- Currently using gabapentin or pregabalin

Although patients on any chronic pain medications or with pre-existing pain conditions or history of alcohol or drug use may have a different metabolism or effect of the drugs, these women will not be excluded. Rather, data will be collected on these factors to evaluate the impact of these factors on study outcomes.

Description of the drugs and devices to be studied:
Gabapentin was originally approved by the U.S. Food and Drug Administration (FDA) in December 1993, for use as an adjuvant (effective when added to other antiseizure drugs) medication to control partial seizures in adults; that indication was extended to children in 2000[19] and later approved for treating postherpetic neuralgia (In December 2004 the FDA granted final approval to a generic equivalent to Neurontin made by the Israeli firm Teva.
It was originally synthesized to mimic the chemical structure of the neurotransmitter GABA. The mode of action of gabapentin is believed to be through its binds to the alpha 2 delta subunit of the DRN voltage dependent calcium channels. This causes decreased entry of calcium into the nerve endings, resulting in decreased release of nociceptive neurotransmitter (glutamate, substance p, noradrenaline). Other proposed mechanisms of action include the binding to NMDA receptors, sodium channel receptors, monoaminergic receptors, and opioid receptors

Overall, Gabapentin is an incredibly safe drug. The most common side effects of its use includes dizziness, somnolence, fatigue, ataxia, peripheral edema, nystagmus, nausea and vomiting, asthenia, headache, weight gain, amblyopia, however most of these are associated with chronic usage. Other extremely rare side effects include: DRESS (drug reaction with eosinophilia and systemic symptoms), multi-organ hypersensitivity, withdrawal seizures (if given for epilepsy), suicidal behavior and ideation, neuropsychiatric reactions in pediatric patients (3-12 yo), and sudden death.

Drug Interactions are rare and mild. Maalox or other aluminum or magnesium hydroxides decreases bioavailability of gabapentin by 20% if given at same time. Additionally, when used

with hydrocodone or morphine, gabapentin may decrease the AUC. Abuse and withdrawal potential is low. The drug is almost entirely metabolized through the renal metabolism where it is eliminated unchanged in the urine, thus dosage adjustments are needed for patients with renal impairment. The half-life for the medication is 5-7 hours with a 2 hour time to peak plasma concentration.

Study intervention groups:

Group 1/Placebo: Usual perioperative pain management protocol PLUS placebo orally 1-2 hour prior to procedure

Group 2/Gabapentin: Usual perioperative pain management protocol PLUS 600mg Gabapentin administered orally 1-2 hour prior to procedure.

600 mg of gabapentin was selected as a well-tolerated intermediate dosage with benefit proven in prior perioperative pain studies. The window of 1-2 hours is consistent with preoperative dosing in other studies and can allow for its co-administration with misoprostol, and allows for some variability that is practical with a busy clinic.

Study Procedures:

All recruitment, screening and enrollment questions will be asked by trained study staff in a private room.

Recruitment:

We will be recruiting a total of 96 women, with equal allocation to the invention group and placebo. The proposed research will take place at Duke Ryan Clinic, at the Duke gynecology outpatient clinic. Women who attend Duke for a uterine aspiration will have their preoperative evaluation and over the phone counseling. During this call, the clinical provider will introduce the study to the patient to determine interest in participating in the study. All patients are scheduled and given standardized pre-procedure counseling by our clinic coordinator. If the patient is interested in possible participation, study personnel will be notified. The study team will then contact the patient to provide them with information about the study. A standard recruitment script will be employed (Appendix A).

Screening and consent:

For individuals who are interested in participating, we will screen for eligibility using an eligibility checklist (Appendix A). Those eligible after screening will review the informed consent and sign consent forms prior to the final clinical preoperative review. Patient contact information will be collected at this time. After the nurse reviews the medical chart, randomization will occur and intervention will be received.

Randomization, Allocation Method and Blinding:

Women undergoing a procedure who meet study inclusion criteria and complete informed consent will be eligible for participation. *Randomization* will be done using computer-generated random numbers (randomization.com) in variable blocks of 8 and 10. *Allocation* concealment will be maintained by identically labeled sealed sequentially numbered opaque pill containers. Gabapentin and placebo tablets will be indistinguishable by appearance, thus maintaining blinding for participants and assessors. To maintain double *blinding* for both investigators and participants, an individual not associated with study conduct will create the randomization sequence and allocation containers. The randomization assignments will only be revealed at the point of data analysis or if an interim assessment is needed.

Enrollment:

After the final perioperative clearance, the individual will be randomized and receive their method allocated by the clinic nurse. The study staff will review the enrollment questionnaire that includes demographic questions. Following completion of the questionnaire, the participant will wait before moving to our procedure room (this will occur approximately 1-2 hour after nursing review and receipt of the study intervention). Prior to initiating the procedure, study staff will administer the preoperative questions. The physician will then complete the uterine aspiration while the study staff remains outside of the operative room. Immediately following the procedure, the study staff will then administer the immediate post-operative questions and follow the participant to the recovery room to complete the remaining questions assessed at 5 minutes, 10 minutes, 30 minutes and at discharge. When the discharge questions are complete, the

participant will receive a $20 gift card and instructed to expect a follow-up call the following day.

Follow-up:

On the day following the procedure (approximately 24 hours after the procedure), study staff will call the participant to complete the follow-up questions. On completion of the questions, an additional $10 will be transferred to the gift card.

Withdrawals, losses and deviations:

Randomization to study method will occur after completion of all intake forms and consent, immediately before the pill is to be taken, thus reducing the possibility of withdrawal after randomization. Primary outcome measures and most secondary outcome measures will be assessed immediately before, during or after the abortion procedure, thus any loss to follow-up will be limited to those who consent to, but change their mind while waiting for their procedure. Based on current clinical practice at this clinic, withdrawal after consent is extremely rare. Our secondary outcomes assessed post-operatively after discharge will be collected via the phone. We will maximize completion of these assessments through the following steps: participants will be told beforehand about the telephone contact following the procedure, a cellular telephone number will be collected and tested at the clinic, a secondary phone number and email will be collected as a backup, participants will be given a contact number for the study coordinator should they have any challenges with receiving a phone calls, and participants will receive an additional $10 sent to their gift-card following the completion of their phone assessment.

Data Collection/Outcome measurements:

Outcome measures and baseline variables are described in Table 1.

Primary study outcome

Our primary outcome measure will be pain score using an 100-mm visual analog scale (VAS) measured 5 minutes after removal of the speculum.

Secondary Outcomes:

We will also be measuring pain on the 100-mm VAS preoperatively immediately prior to the procedure, after the procedure, 10 minutes and 30 minutes following the procedure and at discharge. Nausea, using a VAS, and vomiting will be assessed preoperatively immediately prior to the procedure and post operatively at 10 minutes, 30 minutes and at discharge. Anxiety prior to the procedure will be measured using the preoperative state trait anxiety inventory. Side effects will be assessed using a checklist prior to discharge. We will also be contacting participants on post-operative day 1 to assess pain, nausea, vomiting, side effects and general satisfaction with the procedure (on a 5-point scale). The quantity and type of medications used perioperatively and post-operatively including medications used at home in the 24 hours post-operatively will be abstracted from the clinical record and assessed on the phone.

Baseline Characteristics and covariates:

We will collect baseline demographics, medical history (gravidity, parity, prior abortions (medical and surgical), gestational age, drug and alcohol use, psychiatric or sexual assault history), medications used at home and given at the clinic preoperatively, indication for procedure (personal/social, fetal or maternal health)).

Study Size and Power:

We will enroll a total of 96 women. Assuming a standard deviation of 26 mm on the 100-mm visual analog scale (VAS), based on prior studies, this will provide us with an 80% power, using a p-value of 0.05, to detect a 15 point difference in pain among all participants. A difference of 15-20 mm has been assessed to be clinically meaningful in prior studies. Given that our primary outcome will be measured immediately after the procedure, our loss to follow-up will be minimal. A 100-mm pain visual analog scale has been shown to be useful for the evaluation of pain in prior pain abortion research [5, 6] with a mean standard deviation in previous studies of approximately 26 mm [5]. We are assuming no loss-to-follow-up as our primary outcome will be measured at the time of the procedure.

Data Management and Analysis

Data Management:

Prior to study initiation, a database will be developed using a web-based password-protected relational database (REDCap). All data will be collected will be recorded on clinical research forms (CRFs) and entered into the database at the end of each day. All CRF source documents will be filed and stored for future reference. See monitoring and oversight section below for further details on procedures and protections.

Analytic Plan:

We will compare groups on the primary continuous outcome measure (pain score on 11-point VAS) using T-tests. Chi-square and T-tests will be used to evaluate secondary outcomes for categorical and continuous variables, respectively. Baseline characteristics will be evaluated for potential interaction or confounding with primary and secondary outcomes.

Upon study completion at each site for the prospective meta-analysis, data from each site will contribute to the final meta-analysis using criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions. Site RCT publications will mention contribution to this PMA. Subgroup analyses will address gabapentin adjunct to local anesthesia and moderate sedation, as well as by specified population characteristics and gestational age.

Ethical Concerns

The study will not commence until the study protocol has been reviewed and approved by the Duke University institutional review board (IRB).

Potential risks:

Risk of medication: Gabapentin has been used in several other clinical settings and is associated with few side effects, thus the risks associated with its use as an adjunct to abortion perioperative

pain regimens in minimal. As this is a low-cost intervention that has promise for improving pain, the potential for risk is balanced by the potential benefit. Side effects and adverse effects will be carefully tracked and monitored during the study. Documented side effects of gabapentin include: dizziness, somnolence, fatigue, ataxia, peripheral edema, nystagmus, nausea and vomiting, asthenia, headache, weight gain, amblyopia, however most of these are associated with chronic usage. Other rare side effects include: DRESS (drug reaction with eosinophilia and systemic symptoms), multi-organ hypersensitivity, withdrawal seizures (if given for epilepsy), suicidal behavior and ideation, neuropsychiatric reactions in pediatric patients (3-12 yo), and sudden death.

Sensitive information: The risks involved in study participation are those related to providing personal information about sensitive topics. Participants' privacy and the confidentiality of data will be protected through training of study staff, conducting all interviewing and physical examinations in private, storing study materials in a locked room, and securing computer files that include identifiers. Only the study identification number will identify participant research records. Linkages between the ID number and participants' identifying information will be maintained in a computer database that is password protected and only accessible to study staff. These linkages will be destroyed after completion of study activities. We will ensure that study staff is thoroughly trained to not to disclose any information about the study or the participant's attendance at the clinic to any individual other than the study participant. Breaches of confidentiality are possible, though safeguards are in place to protect the confidentiality of participants. Thus, the potential for experiencing an adverse event is minimal.

Protection against risks

In implementing this protocol, we will be following HHS guidelines for research practices outlined on 45 CFR 46 (also known as the common rule). The investigators will adhere to the basic principles of "Good Clinical Practice" as outlined in Code of Federal Regulations (CFR) 312, subpart D, "Responsibilities of Sponsors and Investigators," CFR 21, part 50, and CFR 21, part 56 and Section 4 of International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH**)** Harmonized Tripartite Guideline for Good Clinical Practice. Specifically, we will provide careful training of study staff who

interview or collect participant information. Training will include a component on careful patient counseling to enable the counselor to recognize complications, and when indicated, provide immediate referral for evaluation. A study participant will be informed of the voluntary nature of this study and that they may elect to not answer certain questions or to discontinue participation in the study at any time. Additionally prior to signing the informed consent form, study staff will assess comprehension of study procedures. Study staff will first review the informed consent document. After reviewing the consent document, the research staff member will ask the participant the comprehension questions. If a participant incorrectly responds to one of the comprehension questions, the staff member will further clarify study procedures. Those participants who incorrectly respond on a second attempt will be ineligible to participate in the study.

No clinical information will be released without written permission of the subject, except as necessary for monitoring by IRBs at participating institutions or the Office for Human Research Protection.

Inclusion of women, minorities, and children

Pursuant to HHS policy, women (females over the age of 21), members of minority groups, and children should be included in biomedical and behavioral clinical research projects involving human subjects. The proposed study conforms to this policy.

Benefits to participation

The benefits of this research extend to potentially leading to improvements in the pain management procedures provided at the facility. Moreover, the results could potentially impact individuals globally as we aim to better address pain management in the setting of outpatient abortions. Participants will receive a $30 compensation for study participation, $20 at the clinic and $10 following completion of the telephone follow-up.

Importance of the knowledge gained

The current study could help us to better manage perioperative pain during an abortion. Inclusion in the PMA, will provide robust information to address the inclusion of gabapentin in

different settings to further elucidate any benefit of this intervention. Study findings will be disseminated further via abstracts submitted to scientific meetings and manuscripts submitted to peer-reviewed journals in addition to a Cochrane Review. Benefit proven in the setting of outpatient abortion care would give precedence for exploring the use of gabapentin for other outpatient procedures.

Monitoring and Oversight

Site monitoring

Site monitoring may be performed by the Duke University's IRB and Office of Research Compliance, OHRP, FDA, or other government regulatory authorities. Clinical research site monitoring may include the review of the individual participant records, including consent forms, CRFs, supporting data, and medical records (physicians' progress notes, nurses' notes, individuals' hospital charts) to ensure protection of study participants, compliance with the protocol, and accuracy and completeness of records. The monitors may also inspect sites' regulatory files to ensure that regulatory requirements are being followed. The investigator will make study documents (e.g., consent forms, CRFs) and pertinent clinic records readily available for inspection.

Data quality assurance and protection

There will be study protocol and procedure training for all study staff prior to beginning of the study. A standard operations manual will be available to staff to refer to for operational details in running the study.

Each woman screened will be assigned a participant identification number (PIN) at the time of study entry. The PIN will be used on all data forms, specimens and communications related to the study. Clinical research forms (CRFs) will be used to collect all study related data. Subjects will be identified only by the PIN on the CRFs. To maintain subject confidentiality, only a coded number will identify all forms, reports and other records. All records will be kept in locked file cabinets, accessible only by local study staff. Electronic files will be password-protected, with access only by authorized study personnel. Clinical information will not be released without written permission of the

subject, except as necessary for monitoring from funding agencies and designees or except as mandated by law.

The study investigators will provide instructions concerning the recording of study data on CRFs. It will be the responsibility of the study investigator to assure the quality of computerized data. This role extends from protocol development to generation of the final study databases. Data from screening forms and study visit will be entered into RedCap. Electronic data will be secured in a password protected database that is accessible to members of the Duke investigative team. The Duke study investigators will maintain the link in a separate file that associates subjects with their PIN.

The data entry screens will be prepared with built-in quality control checks. To safeguard against loss of data, backups of the data will be made. Study staff will train the data entry staff in all data management procedures. We will conduct all statistical analyses using the SPSS System for Windows version 21.0 or similar analysis software program.

Protocol violation

A protocol violation is any intentional or unintentional change from the IRB-approved protocol that adversely affects (1) the risk/benefit ratio of the study, (2) the rights, safety, or welfare of the participants or others, or (3) the integrity of the study. Examples include breach of confidentiality, inclusion of ineligible participants, or initiation of study procedures before participant has signed the consent form. If a protocol violation were to occur, it would be documented on the appropriate protocol deviation report form, and if the violation were to meet reporting requirements, it would promptly be reported to the participating IRBs.

Adverse events

An adverse event (AE) is defined as any health-related reaction, effect, toxicity or abnormal laboratory result that a study participant experiences during the course of the study, irrespective of relationship to the study intervention. This includes changes in a participant's condition that have or could have a deleterious effect on a participant's health or well-being. A serious adverse event (SAE) is defined as any experience that is fatal or life-threatening, requires

in-patient hospitalization or prolongation of an existing hospitalization, or results in a persistent or significant disability or incapacity.

This study uses an additional medication for pain control in the setting of outpatient abortion. These activities are not anticipated to be associated with any deleterious impact on participants' health or well-being beyond the risks associated with the abortion procedure. AEs will be managed according to good clinical practice and the judgment of the on-site physician. All clinical and laboratory AEs will be followed-up closely by study staff. Any SAEs will be expeditiously reported to the principal investigators, via a designated SAE form. Notification and submission of SAE forms should occur within 48 hours of the site awareness of the SAE. The PI will then make the final independent judgment as to the severity, relatedness, and anticipated or unanticipated nature of the SAE and finalize the Human Subjects Adverse Event Report Form. If the event is determined to be serious, unanticipated, and the relationship is anything other than probably or definitely not related, then the PI will report the event within 48 hours and submit the required forms to the IRB at Duke. Thus, all anticipated SAEs that are at least possibly related to study intervention and all deaths that are at least possibly related to study intervention will be submitted to the Duke IRB.

The study may be discontinued at any time by an IRB at a participating institution or the Office for Human Research Protection. We will additionally have a medical monitor to review any adverse event and periodically review side effects to see if there are an increased number of events than anticipated by routine clinical care. If any suspicion for increased risk exists, study allocation may be revealed for a preliminary analysis and if related to the study intervention, the study could be prematurely ended.

Data Monitoring Committee/Study Termination

A Data Monitoring Committee (DMC) will be created to perform regular and timely review of data in order to identify early, significant benefit or harm for patients while the trial is in progress. On a regular basis (frequency as to be determined by the DMC based on the enrollment rate and potential risk to subjects), non-identified safety data will be communicated to the DMC who will then meet to review the data. The DMC will be composed of three faculty members within the Duke University Department of Gynecology and Obstetrics. Individuals who are investigators or co-investigators cannot be members. Members must have no financial,

scientific, or other conflicts of interest with the study. All investigators understand that the DMC serves as additional human subject's protection, but does not supplant reporting of significant adverse events to the Duke IRB. The DMC may devise its own stopping rules, and if there are significant numbers of adverse events, the DMC will recommend continuation, modification, or termination of the study after each meeting. This recommendation will be communicated to the Principle investigator who is responsible for reviewing the recommendation and forwarding it to the IRB. All investigators understand that the DMC may recommend their own "stopping rule" if other events occur which indicate a significant risk to study subjects.

Innovation

Gabapentin is a safe and inexpensive medication that has been employed as an adjunct to anesthesia with significant reductions in peri-operative pain and nausea. We aim to explore this novel medication as an adjunct to pain management strategies where other interventions have been less successful in improving pain scores. Further, we will employ the prospective meta-analysis design to increase the power, generalizability and capacity for evaluating sub-group interactions to gain a broader definitive understanding of the use of gabapentin in outpatient abortion care.

Strengths and Weaknesses, Limitations and Future directions

Strengths of this study include its linkage with 4 other sites to be included in a prospective meta-analysis. The PMA design can bypass some of the logistical challenges of a multisite RCT. The PMA design allows each site to operate independently, thus reducing impact of delays from one site. Sharing of resources, such as study drug and placebo, and patient gift cards, will save time and money. Limitations of this study is that we are only looking will only be able to evaluate the impact of gabapentin within the timeframe 1-2 hours preoperatively for surgical procedures. Future research may be useful in evaluating the utility of Gabapentin if given 1 day prior to the procedure, at time of laminaria placement for 2 day procedures, or if given prior to medication abortion.

Gabapentin is low-cost and effective in perioperative settings, and may be an effective adjunctive therapy for surgical abortion. PMA methodology will evaluate the potential effect of adding gabapentin to different pain control regimens and among different patient populations, maximizing external validity. We anticipate several publications and presentations from individual sites as well as from the combined in the PMA to allow for dissemination of our findings. Further, we aim to leverage the developed PMA infrastructure to apply for future large research studies in abortion care, providing an innovative and feasible approach for developing generalizable research and to target low prevalent groups.

Problems Anticipated

This study aims to recruit 96 women into a randomized controlled trial in an outpatient abortion setting. Given the patient volume at this clinic, coordination of the study may be challenging, however we anticipate that the patient volume is a factor that will increase the success in reaching recruitment targets quickly. To ensure that patient flow is not interrupted, we will have study staff dedicated to the study activities including consent and data collection, thus eliminating any dependence upon current clinical staff for study operation. We also anticipate that follow-up on post-operative day one may be challenging. To reduce the impact of loss to follow-up, our primary impact measure and most of our secondary measures are measured on the same day as the procedure. Further, to maximize retention, we will test a phone number at the time of enrollment, collect secondary contact information, give the patient a contact number for the study coordinator should they have difficulty receiving a call and provide reimbursement for completion via transferring funds to a gift-card following completion of the follow-up questionnaire.

We anticipate that some of the sites for the PMA may have difficulty in completing study activities. In contrast to a multisite randomized controlled trial, the PMA design allows for each site to have independent operations thus reducing delays from any individual site. Failure of one site to complete its study will not prevent our site from analyzing and publishing our study findings in a timely fashion. The benefit of the PMA is also that we can share certain resources, such as packaging for the study medication and formulation for the placebo, therefore saving time compared to each site operating independently.

Timeline

The study timeline is presented in table 3. We aim to start study operations within the first 3 months of study operations and plan to recruit for 1 year to 15 months with data analysis and drafting of manuscripts during the last 6 months of the study period.

Table 3: 2 year projected timeline for PMA of adjunctive gabapentin for perioperative pain management for surgical abortion

	Year 1 (7/12015-6/30/2016)				**Year 2** (7/2/2016-6/30/2017)			
Study Activity	Mo 1-3	Mo 4-7	Mo 8-9	Mo 10-12	Mo 13-15	Mo 16-18	Mo 19-21	Mo 22-24
Obtain IRB Approval and IND	■							
Hire & train staff	■	■						
Compounding study drug, randomization and allocation packaging, distribution to each site	■	■						
Database development	■	■						
Study Recruitment and Data collection		■	■	■	■	■		
Site data analysis and manuscript preparation						■	■	
PMA data analysis and manuscript preparation							■	■

[1] Raymond EG, Weaver MA, Louie KS, Dean G, Porsch L, Lichtenberg ES, et al. Prophylactic compared with therapeutic ibuprofen analgesia in first-trimester medical abortion: a randomized controlled trial. Obstetrics and gynecology. 2013;122:558-64.
[2] Schmidt PC, Ruchelli G, Mackey SC, Carroll IR. Perioperative gabapentinoids: choice of agent, dose, timing, and effects on chronic postsurgical pain. Anesthesiology. 2013;119:1215-21.
[3] Tiippana EM, Hamunen K, Kontinen VK, Kalso E. Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. Anesthesia and analgesia. 2007;104:1545-56, table of contents.
[4] Alayed N, Alghanaim N, Tan X, Tulandi T. Preemptive use of gabapentin in abdominal hysterectomy: a systematic review and meta-analysis. Obstetrics and gynecology. 2014;123:1221-9.
[5] Moore A, Costello J, Wieczorek P, Shah V, Taddio A, Carvalho JC. Gabapentin improves postcesarean delivery pain management: a randomized, placebo-controlled trial. Anesthesia and analgesia. 2011;112:167-73.
[6] Renner RM, Jensen JT, Nichols MD, Edelman A. Pain control in first trimester surgical abortion. Cochrane Database Syst Rev. 2009:CD006712.
[7] Allen RH, Fitzmaurice G, Lifford KL, Lasic M, Goldberg AB. Oral compared with intravenous sedation for first-trimester surgical abortion: a randomized controlled trial. Obstet Gynecol. 2009;113:276-83.
[8] Renner R, Jensen J, Nichols M, Edelman A. Pain control in first trimester abortion. The Cochrane database of systematic reviews. 2009.
[9] Jackson E, Kapp N. Pain control in first-trimester and second-trimester medical termination of pregnancy: a systematic review. Contraception. 2011;83:116-26.
[10] Braaten KP, Hurwitz S, Fortin J, Goldberg AB. Intramuscular ketorolac versus oral ibuprofen for pain relief in first-trimester surgical abortion: a randomized clinical trial. Contraception. 2014;89:116-21.
[11] Chor J, Hill B, Martins S, Mistretta S, Patel A, Gilliam M. Doula support during first-trimester surgical abortion: a randomized controlled trial. Am J Obstet Gynecol. 2015;212:45 e1-6.
[12] Clarke H, Bonin RP, Orser BA, Englesakis M, Wijeysundera DN, Katz J. The prevention of chronic postsurgical pain using gabapentin and pregabalin: a combined systematic review and meta-analysis. Anesth Analg. 2012;115:428-42.
[13] Mardani-Kivi M, Mobarakeh MK, Keyhani S, Motlagh KH, Ekhtiari KS. Is gabapentin effective on pain management after arthroscopic anterior cruciate ligament reconstruction? A triple blinded randomized controlled trial. Arch Bone Jt Surg. 2013;1:18-22.
[14] Poylin V, Quinn J, Messer K, Nagle D. Gabapentin significantly decreases posthemorrhoidectomy pain: a prospective study. Int J Colorectal Dis. 2014;29:1565-9.
[15] Lathrop E, Haddad L, McWhorter CP, Goedken P. Self-administration of misoprostol prior to intrauterine device insertion among nulliparous women: a randomized controlled trial. Contraception. 2013;88:725-9.

[16] Turok DK, Espey E, Edelman AB, Lotke PS, Lathrop EH, Teal SB, et al. The methodology for developing a prospective meta-analysis in the family planning community. Trials. 2011;12:104.
[17] Bednarek PH, Creinin MD, Reeves MF, Cwiak C, Espey E, Jensen JT. Immediate versus delayed IUD insertion after uterine aspiration. The New England journal of medicine. 2011;364:2208-17.
[18] Haddad LB, Cwiak C, Jamieson DJ, Feldacker C, Tweya H, Hosseinipour M, et al. Contraceptive adherence among HIV-infected women in Malawi: a randomized controlled trial of the copper intrauterine device and depot medroxyprogesterone acetate. Contraception. 2013;88:737-43.
[19] Mack A. Examination of the evidence for off-label use of gabapentin. Journal of managed care pharmacy : JMCP. 2003;9:559-68.
[20] Renner RM, Nichols MD, Jensen JT, Li H, Edelman AB. Paracervical block for pain control in first-trimester surgical abortion: a randomized controlled trial. Obstetrics and gynecology. 2012;119:1030-7.
[21] Jensen MP, Chen C, Brugger AM. Interpretation of visual analog scale ratings and change scores: a reanalysis of two clinical trials of postoperative pain. The journal of pain : official journal of the American Pain Society. 2003;4:407-14.
[22] Todd KH, Funk KG, Funk JP, Bonacci R. Clinical significance of reported changes in pain severity. Annals of emergency medicine. 1996;27:485-9.
[23] Rowbotham MC. What is a "clinically meaningful" reduction in pain? Pain. 2001;94:131-2.
[24] Knight RG, Waal-Manning HJ, Spears GF. Some norms and reliability data for the State--Trait Anxiety Inventory and the Zung Self-Rating Depression scale. The British journal of clinical psychology / the British Psychological Society. 1983;22 (Pt 4):245-9.
[25] Aldrete JA. The post-anesthesia recovery score revisited. J Clin Anesth. 1995;7:89-91.
[26] Stark PA, Myles PS, Burke JA. Development and psychometric evaluation of a postoperative quality of recovery score: the QoR-15. Anesthesiology. 2013;118:1332-40.

Appendix A

Clinic Recruitment Procedures

Recruitment script *"We would like to invite you to participate in a study that is looking at a medication called Gabapentin and how it may affect the pain you experience during your abortion procedure. This medication is very safe and has been used in many other surgical settings however has not been studied in the abortion setting. Your participation is completely voluntary and will not influence the care you receive at the clinic. During this study, you will be given the medication or a placebo, which is a pill that does not contain any medication, 1-2 hours prior to your procedure. Neither you nor the research or clinic staff will know whether you received the Gabapentin or not. We will be looking at your experience during and after the procedure, which will include your experience of discomfort, nausea, vomiting or any side effects. In addition to your visit today, we will contact you tomorrow to briefly ask you some questions. The study procedures today will be completed while you are waiting for your procedure and after your procedure. It should not delay your time at the clinic. You will be reimbursed $20 for your time today and receive an additional $10 after completing the phone call tomorrow. If you are interested in participating, we will give you a consent form to read and we can go through the study in detail with you. Again, whether or not you choose to be in the study will not affect your care at the Clinic. Are you interested in seeing if you are eligible?"*

Eligibility checklist:

1) What is your age? __ ___ (must be **18 years-old or older** to be eligible)
2) Are you here today for a surgical abortion or medication abortion or another procedure (must be **surgical abortion)**
    1) Medical
    2) Surgical abortion
    3) Other _____
3) Are you fluent in English and able to provide informed consent (must be **Yes**)
        1) Yes
        2) No
4) Do you have an allergy, sensitivity or other reason why you can not receive Gabapentin (must be **No**)
        1) Yes
        2) No
5) Do you have any renal disease (must be **No**)
        1) Yes
        2) No
6) Are you currently using gabapentin or pregabalin (must be **No**)
        1) Yes
        2) No

Duke Consent

You Are Being Asked to Be in a Research Study

What Is a Research Study?

The main purpose of research studies is to gain knowledge. This knowledge may be used to help others. Research studies are not intended to benefit you directly, though some might.

Do I Have to Do This?

No. Being in this study is entirely your choice. If you decide to join this study, you can change your mind later on and withdraw from the research study.

Taking part in a study is separate from medical care. The decision to join or not join the research study will not affect your status as a patient.

What Is This Document?

This form is an informed consent document. It will describe the study risks, procedures, and any costs to you.

This form is also a HIPAA Authorization document. It will describe how your health information will be used and by whom.

Signing this form indicates you are willing to take part in the study and allow your health information to be used.

What Should I Do Next?

1. Read this form, or have it read to you.
2. Make sure the study doctor or study staff explains the study to you.
3. Ask questions (e.g., time commitment, unfamiliar words, specific procedures, etc.)
4. If there will be medical treatment, know which parts are research and which are standard care.
5. Take time to consider this, and talk about it with your family and friends.

Duke University
Consent to be a Research Subject / HIPAA Authorization

Title: Gabapentin as an adjunct to perioperative pain management regimens for surgical abortion: a prospective meta-analysis

Principal Investigator: Beverly Gray, MD, FACOG Assistant Professor, Department of Gynecology and Obstetrics

Sponsor:

Introduction
You are being asked to be in a medical research study. This form is designed to tell you everything you need to think about before you decide if you want to be a part of the study. **It is entirely your choice. If you decide to take part, you can change your mind later on and withdraw from the research study.** The decision to join or not join the research study will not cause you to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat you.

Before making your decision:
- Please carefully read this form or have it read to you
- Please listen to the study doctor or study staff explain the study to you
- Please ask questions about anything that is not clear

You can take a copy of this consent form, to keep. Feel free to take your time thinking about whether you would like to participate. You may wish to discuss your decision with family or friends. Do not sign this consent form unless you have had a chance to ask questions and get answers that make sense to you. By signing this form you will not give up any legal rights.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This Web site will not include information that can identify you. At most the Web site will include a summary of the results. You may search this Web site at any time.

What is the purpose of this study?
The purpose of this study is to evaluate the use of a drug called **gabapentin** used in addition to the pain medication you are planning to receive at this clinic for pain with women who are receiving an abortion. We are doing this study to find out if the medication: **gabapentin** can reduce the pain experienced in women having abortion procedures. Previous research in other fields has shown that **gabapentin** can make a difference and reduce the need for other pain medications that can cause sedation and other side effects in women having abortion procedures. Other evidence has also suggested that gabapentin can reduce nausea and vomiting after the procedure as well.

What is **Gabapentin?** This is an anti-epileptic medication, but it has been used to treat various forms of chronic and acute pain. It affects chemicals and nerves in the body that are involved in the cause of seizures and some types of pain.

Why are we asking you to be in this study?
Any woman seeking abortion care in our clinic is being asked to participate in this study. We want to be able to involve as many women as possible to get enough information so that we can determine if this medication is helpful in women seeking abortions. If it is found to be effective, we may include gabapentin in the regular medications that we give to women who get an abortion.

What will I be asked to do?
If you agree to be in this study, after your counseling appointment, you will be taken to the nursing desk where you'll meet our nursing team. There, you will receive the normal preoperative medications that we give to all patients, plus either the gabapentin 600 mg tablet or a "placebo" tablet. Both of the medications look the same, which means that both you and none of your caregivers today will know if the medication or placebo was given. This process helps us to do the study without any bias.

You will then be given a short questionnaire and be taken into the operating room for your procedure. The questionnaire will take less than 5 minutes to complete. Before, during and after the procedure, you will be asked simple questions about how you feel (your anxiety, level of awareness, and any pain experienced). After the procedure, you will also be asked about pain and nausea. These questions will take less than 1 minute to answer. One day after the procedure, we will contact you by the method you've indicated (email, text, phone or skype) to ask a few short follow up questions. This should take about 1 minute to complete.

This will be the only difference between those choosing to participate in the study or not. The entire routine care for the abortion procedure will be the same as if you were not taking part in the study.

How long will you be in the study?
If you choose to participate, your involvement in the study will end the day after the procedure is completed, when you are contacted for the follow up questions.

Who owns my study information and samples?
If you join this study, you will be donating your study information. If you withdraw from the study, data that were already collected may be still be used for this study.

What are the possible risks and discomforts?
There may be side effects from the study drug that are not known at this time.
Gabapentin has been used in several other clinical settings and is associated with few side effects, thus the risks associated with its use with other medications used in abortion care is minimal.

The most common risks and discomforts expected in this study are: dizziness, fatigue, temporary problems with coordination of muscles and movement, nystagmus (eye twitching), nausea and vomiting, headache, or weight gain. These however are usually associated with chronic usage.

The less common risks and discomforts expected in this study are: limb swelling,

Rare but possible risks include: DRESS (drug reaction with eosinophilia and systemic symptoms), multi-organ hypersensitivity, withdrawal seizures (if given for epilepsy), suicidal behavior and ideation, and sudden death.

Some of the questions you will be asked may make you feel uncomfortable or upset. You may refuse to answer any question at any time. Counseling referrals are available if you need help at any time.

To protect against possible side effects of the study drug, women who are planning on continuing their pregnancy or nursing a child may not take part in this study. There may be risks to the embryo, or fetus. These risks are not yet known.

It is possible that the researchers will learn something new during the study about the risks of being in it. If this happens, they will tell you about it. Then you can decide if you want to continue to be in this study or not. You may be asked to sign a new consent form that includes the new information if you decide to stay in the study.

Will I benefit directly from the study?

This study is not designed to benefit you directly. Your pain, anxiety, nausea and vomiting during the abortion may improve while you are in this study but it may not, and it may even get worse. This study is designed to learn more about the use of gabapentin in the setting of abortion care. The study results may be used to help others in the future. Gabapentin, if effective, can be used for women seeking abortion procedures and lessen the need for other medications commonly used in abortion which can cause sedation, as well as other side effects (respiratory depression, hypotension, airway collapse).

Will I be compensated for my time and effort?

You will get $20 for completing the study visit today, to compensate you for your time and effort. Additionally, you will receive $10 for completing the follow-up tomorrow. If you do not finish the study, we will compensate you for the visits you have completed. You will get $30 total, if you complete all study activities.

What are my other options?

If you decide not to enter this study, there is care available to you outside of this research study. Nothing will happen if you decide not to be in this study. You will be cared for in exactly the same way as any of our other patients, according to your needs, to ensure that you have a safe procedure. The study doctor will discuss these with you. You do not have to be in this study to receive an abortion at this clinic.

How will you protect my private information that you collect in this study?

Duke will keep any research records that it creates private to the extent that this is required to do so by law. Whenever possible, a study number, rather than your name, will be used on study records. Your name and other identifying information will not appear when we present or publish the study results.

Certificate of Confidentiality

There is a Certificate of Confidentiality from the National Institutes of Health for this Study. The Certificate of Confidentiality helps us to keep others from learning that you participated in this study. Duke will rely on the

Certificate of Confidentiality to refuse to give out study information that identifies you. For example, if Duke received a subpoena for study records, it would not give out information that identifies you.

The Certificate of Confidentiality does not stop you or someone else, like a member of your family, from giving out information about your participation in this study. For example, if you let your insurance company know that you are in this study, and you agree to give the insurance company research information, then the investigator cannot use the Certificate to withhold this information. This means you and your family also need to protect your own privacy.

The Certificate does not stop Duke from making the following disclosures about you:

- Giving state public health officials information about certain infectious diseases,
- Giving law officials information about abuse of a child, elderly person or disabled person.
- Giving out information to prevent harm to you or others.
- Giving the study sponsor or funders information about the study, including information for an audit or evaluation.

Medical Record

A Duke medical record will be made for you for any clinical services you receive at this clinic. The results of some study tests and procedures will be used only for research purposes and will *not* be placed in your medical record. For this study, those items include: the study consent form and questionnaires you complete as part of the study.

If you decide to be in this study, it is up to you to let your other health providers know.

In Case of Injury

If you get ill or injured from being in the study, Duke will help you to get medical treatment. Duke and the sponsor have not, however, set aside any money to pay you or to pay for this medical treatment. The only exception is if it is proven that your injury or illness is directly caused by the negligence of a Duke or sponsor employee. "Negligence" is the failure to follow a standard duty of care.
If you become ill or injured from being in this study, your insurer will be billed for your treatment costs. If you do not have insurance, or if your insurer does not pay, then you will have to pay these costs.
If you believe you have become ill or injured from this research, you should contact Dr. Gray at 919-668-7888. You should also let any health care provider who treats you know that you are in a research study.

Costs

There are no additional costs for being in the study. The study sponsor will pay only for the study drug. You will have to pay for the items or services for which the study sponsor does not pay. The sponsor will not pay for your regular medical care including the services you plan to receive at Duke. If you have insurance, Duke will submit claims to your insurance for items and services that the sponsor does not cover. Duke will send in only those claims for items and services that it reasonably believes your insurance will pay and that the sponsor has not paid.

The actual amount that you have to pay depends on whether or not you have health insurance and whether or not that insurance will pay for any research study costs. Generally, insurance companies will not pay for items and services that are required just for a research study. Some insurance companies will not pay for regular medical treatment or treatment for complications if you are in a study. How much you will have to pay for any co-payments, deductibles or co-insurance depends on your plan. Duke and the sponsor will not pay for these costs.

It is a good idea to contact your insurance provider and tell them you want to be in this research study. Ask them what they will pay for and what they will not pay for. You can also ask the study team for help in figuring out what you will have to pay.

Withdrawal from the Study

You have the right to leave a study at any time without penalty.

The researchers also have the right to stop your participation in this study without your consent for any reason, especially if they believe it is in your best interest or if you were to object to any future changes that may be made in the study plan.

Authorization to Use and Disclose Protected Health Information

The privacy of your health information is important to us. We call your health information that identifies you, your "protected health information" or "PHI." To protect your PHI, we will follow federal and state privacy laws, including the Health Insurance Portability and Accountability Act and regulations (HIPAA). We refer to all of these laws as the "Privacy Rules." Here we let you know how we will use and disclose your PHI for the study

PHI that Will be Used/Disclosed:

The PHI that we will use or share for the main research study includes:

- Medical information about you including your medical history and present/past medications.
- Results of exams, procedures and tests you have before and during the study.

Purposes for Which Your PHI Will be Used/Disclosed:

We will use and share your PHI for the conduct and oversight of the research study. We will use and share your PHI to provide you with study related treatment and for payment for such treatment. We will also use and share your PHI to conduct normal business operations. We may share your PHI with other people and places that help us conduct or carry out the study, such as laboratories, data management centers, data monitors, contract research organizations, Institutional Review Boards (IRBs) and other study sites. If you leave the study, we may use your PHI to determine your health, vital status or contact information. We will use and disclose your PHI for the administration and payment of any costs relating to subject injury from the study.

Authorization to Use PHI is Required to Participate:

By signing this form, you give us permission to use and share your PHI as described in this document. You do not have to sign this form to authorize the use and disclosure of your PHI. If you do not sign this form, then you may not participate in the research study or receive research-related treatment. You may still receive non-research related treatment.

People Who will Use/Disclose Your PHI:
The following people and groups will use and disclose your PHI in connection with the research study:

- The Principal Investigator and the research staff will use and disclose your PHI to conduct the study and give you study related treatment.
- Duke may use and disclose your PHI to get payment for study related treatment and to run normal business operations.
- The Principal Investigator and research staff will share your PHI with other people and groups to help conduct the study or to provide oversight for the study.
- ___ is the Sponsor of the study. The Sponsor may use and disclose your PHI to make sure the research is done correctly and to collect and analyze the results of the research. The Sponsor may disclose your PHI to other people and groups like study monitors to help conduct the study or to provide oversight for the study.
- The research team and the Sponsor may use and disclose your PHI, including disclosure to insurance carriers to administer payment for subject injury.
- The following people and groups will use your PHI to make sure the research is done correctly and safely:
- Duke offices that are part of the Human Research Participant Protection Program and those that are involved in study administration and billing. These include the Duke IRB, the Duke Research and Healthcare Compliance Offices, and the Duke Office for Clinical Research.
- Government agencies that regulate the research including: Office for Human Research Protections; Food and Drug Administration.
- Public health agencies.
- Research monitors and reviewer.
- Accreditation agencies.

Expiration of Your Authorization
Your PHI will be used until this research study ends.

Revoking Your Authorization
If you sign this form, at any time later you may revoke (take back) your permission to use your information. If you want to do this, you must contact the study team at: 919-668-7888.

At that point, the researchers would not collect any more of your PHI. But they may use or disclose the information you already gave them so they can follow the law, protect your safety, or make sure that the study was done properly and the data is correct. If you revoke your authorization you will not be able to stay in the study.

Other Items You Should Know about Your Privacy

Not all people and entities are covered by the Privacy Rules. HIPAA only applies to health care providers, health care payers, and health care clearinghouses. If we disclose your information to people who are not covered by the Privacy Rules, including HIPAA, then your information won't be protected by the Privacy Rules. People who do not have to follow the Privacy rules can use or disclose your information with others without your permission if they are allowed to do so by the laws that cover them.

To maintain the integrity of this research study, you generally will not have access to your PHI related to this research until the study is complete. When the study ends, and at your request, you generally will have access to your PHI that we maintain in a designated record set. A designated record set is data that includes medical information or billing records that your health care providers use to make decisions about you. If it is necessary for your health care, your health information will be provided to your doctor.

We may remove identifying information from your PHI. Once we do this, the remaining information will not be subject to the Privacy Rules. Information without identifiers may be used or disclosed with other people or organizations for purposes besides this study.

Contact Information

Contact Dr. Gray at 919-668-7888

- if you have any questions about this study or your part in it,
- if you feel you have had a research-related injury or a bad reaction to the study drug, or
- if you have questions, concerns or complaints about the research

Contact the Duke Investigational Review Board @ (add phone # and email):

- if you have questions about your rights as a research participant.
- if you have questions, concerns or complaints about the research.

Consent and Authorization

Consent and HIPAA Authorization for Study:

Please print your name and sign below if you agree to be in this study. By signing this consent and authorization form, you will not give up any of your legal rights. We will give you a copy of the signed consent to keep.

_____
Name of Subject

_____
Signature of Subject Date Time

_____
Name of Person Conducting Informed Consent Discussion

_____
Signature of Person Conducting Informed Consent Discussion Date Time

_____
Signature of Legally Authorized Representative with authority for research decisions Date Time

_____
Authority of Legally Authorized Representative or Relationship to Subject

Draft Questionnaire

INTERVIEW DATE __ __ /__ __ /__ __ __ __ **TIME** __ __ : __ __ **INTERVIEWED BY** ___ ___

Interview Questions:

1. What is your birthdate? MM/DD/YYYY__ __/__ __ /__ __ __ __

2. Which of the following BEST describes your racial/ethnic background?
   - ☐1 American Indian/Alaskan Native
   - ☐2 Asian
   - ☐3 Black or African American
   - ☐4 Native Hawaiian/Pacific Islander
   - ☐5 White/Caucasian
   - ☐6 Mixed or Multi-racial
   - ☐7 Not Specified/Other
   - ☐9 Don't know/refused

3. Do you consider yourself to be Hispanic/Latina/Latino? ☐0 NO ☐1 YES

4. Is English your first language? ☐0 NO ☐1 YES

5. What is your marital status?
   - ☐0 Single/divorced/widowed
   - ☐1 Married
   - ☐2 Cohabitating
   - ☐3 Other

6. What is the highest level of education that you have completed?
   - ☐1 Less than high-school
   - ☐2 High-school diploma or GED
   - ☐3 Some college
   - ☐4 Associates degree or Technical Certification
   - ☐5 Bachelors degree
   - ☐6 Masters degree/Doctoral degree

7. What is your best estimate of the total income of all family members from all sources, before taxes, in [last calendar year in 4 digit format]? by "combined family income," I mean your income PLUS the income of all family members living in this household (including cohabitating partners, and armed forces members living at home).
   - ☐1 <10,000
   - ☐2 10-25,000
   - ☐3 25-50,000
   - ☐4 50-75,000
   - ☐5 75-100,000
   - ☐6 >100,000
   - ☐9 Don't know/refused

8. What is your insurance type
   - ☐1 medicaid
   - ☐2 medicare
   - ☐3 private insurance
   - ☐4 other, specify_____
   - ☐5 uninsured

Section 2: Substance Use or Medication use

9. Now I will ask you about smoking, alcohol and any substances you may have used.

	a. Ever	**b. Past 6 months**	**c. Frequency of use in past 6 months**			**d. In the past month, how many per day?**
			Daily	Weekly	Monthly	
1. Smoked cigarettes	☐$_0$NO ☐$_1$YES	☐$_0$NO ☐$_1$YES	☐$_1$	☐$_2$	☐$_3$	Cigarettes per day ☐$_0$ Have not smoked in last month ☐$_1$ < 1 ppd ☐$_2$ ≥ 1 ppd
2. Drank alcohol	☐$_0$NO ☐$_1$YES	☐$_0$NO ☐$_1$YES	☐$_1$	☐$_2$	☐$_3$	Drinks per day ☐$_1$ 1 or less ☐$_2$ 2 or more
3. Marijuana	☐$_0$NO ☐$_1$YES	☐$_0$NO ☐$_1$YES	☐$_1$	☐$_2$	☐$_3$	
4. Cocaine/Crack	☐$_0$NO ☐$_1$YES	☐$_0$NO ☐$_1$YES	☐$_1$	☐$_2$	☐$_3$	
5. Heroin	☐$_0$NO ☐$_1$YES	☐$_0$NO ☐$_1$YES	☐$_1$	☐$_2$	☐$_3$	
6. Methamphet-amine	☐$_0$NO ☐$_1$YES	☐$_0$NO ☐$_1$YES	☐$_1$	☐$_2$	☐$_3$	
7. Used any other illicit drugs to get high*	☐$_0$NO ☐$_1$YES	☐$_0$NO ☐$_1$YES	☐$_1$	☐$_2$	☐$_3$	
		e. Please list any other drugs used in the past year:				
* This may include hallucinogens (LSD, PCP, mushrooms, peyote), club drugs such as ecstasy, prescription drugs or any other drugs used to get high						

10. Do you take any of the following medications?

	a. Ever	**b. Past 6 months**	**c. Frequency of use in past 6 months**			
			Daily	Weekly	Monthly	
1. Ibuprofen	☐$_0$NO ☐$_1$YES	☐$_0$NO ☐$_1$YES	☐$_1$	☐$_2$	☐$_3$	
2. Opiate Pain medication (including oxycodone, Percocet, oxycontin)	☐$_0$NO ☐$_1$YES	☐$_0$NO ☐$_1$YES	☐$_1$	☐$_2$	☐$_3$	Type: _____
3. Other pain medication	☐$_0$NO ☐$_1$YES	☐$_0$NO ☐$_1$YES	☐$_1$	☐$_2$	☐$_3$	Type: _____

HEALTH HISTORY

11. Have you ever been pregnant before (prompt: regardless of outcome)?
☐$_0$ NO ☐$_1$ YES → Answer questions a-e below

a) How many times? _____
b) Number of miscarriages or ectopic pregnancies_____
c) Number of C-sections? _____
d) Number of vaginal deliveries? _____
e) Number of abortions? ____ (if 0→ 12)
f) Number of medical abortions: ____
g) Number of surgical abortions: ____
h) Number under local anesthesia: ____

12. Now I will ask you a couple questions about your medical history

Do you have any of the following conditions			**Follow-up questions if YES**
1	**Anxiety**	☐$_0$ NO ☐$_1$YES	b. Do you take medication for it? ☐$_0$ NO ☐$_1$ YES c. Type of medication
2	**Depression**	☐$_0$ NO ☐$_1$YES	b. Do you take medication for it? ☐$_0$ NO ☐$_1$ YES c. Type of medication
3	**Other psychiatric condition (such as bipolar, schitophrenia, PTSD)**	☐$_0$ NO ☐$_1$YES	b. Other condition _____ c. Do you take medication for it? ☐$_0$ NO ☐$_1$ YES d. Type of medication

13. Have you ever been sexually or physically assaulted?

☐$_0$ NO
☐$_1$YES, Sexually Assualted
☐$_2$YES, Physically Assaulted
☐$_3$YES, Both sexually and physically assaulted

From Chart Abstraction:

Gestational Age: _____

Height: _____

Weight: _____

Anesthestic Regimen: ☐$_1$ LOCAL ☐$_2$ IV Moderate Sedation ☐$_3$ Deep Sedation

Medications Used:

Type: (include antibiotics, misoprostol or other uterotonics, pain and nausea medication)	Mode (Oral/IV/Rectal/ Vaginal/Paracervical)	Dose	Timing in relation to surgery (pre-op/intraop/postop)	Time	Notes

Time of speculum placement: ___ ___: ___ ___ AM/PM

Time of speculum removal: ___ ___: ___ ___ AM/PM

Procedural Complications?
☐$_0$ NO ☐$_1$YES: Description:
_____
_____

Preop Assessment
Time: ___ ___: ___ ___ AM/PM

For these questions we are going to ask you to make a hash mark on a line.

For example, let's say you are asked how much you like Oreo cookies:
How much do you like Oreo cookies? (make a hash mark on the line)

very little _____ very much

You answer the question by making a hash mark on the line according to how much you like or dislike Oreo cookies.

If you liked Oreo cookies a lot, then you might make a hash mark on the line like so:

very little _____|_____ very much

If you liked Oreo cookies more than life itself(!), then you might make a hash mark on the line like so:

very little _____|_ very much

If you hated Oreo cookies, then you might make a hash mark like so:

very little _|_____ very much

If you thought Oreo cookies were just "OK," then you might make a hash mark like so:

very little _____|_____ very much

The idea is that if you like Oreo cookies, you make a hash mark on the line closer to the phrase "very much;" the closer you make the hash mark, the more you are saying you like Oreo cookies. If you don't like Oreo cookies, you make a hash mark on the line closer to the phrase "very little;" the closer you make the hash mark, the more you are saying you don't like Oreo cookies.

1. Make a hash mark on the line to indicate how nervous you feel about the surgery you are about to have.

NOT NERVOUS _____ VERY NERVOUS

2. Make a hash mark on the line to indicate how nervous you feel about the pain you will experience during your procedure.

NOT NERVOUS _____ VERY NERVOUS

3. Make a hash mark on the line to indicate how much pain you expect to have during your abortion procedure.

NO PAIN _____ WORST PAIN IN MY LIFE

4. Make a hash mark on the line to indicate how much pain you have waiting for your procedure to start.

NO PAIN _____ WORST PAIN IN MY LIFE

5. Make a hash mark on the line to indicate how much nausea you currently have

NO NAUSEA _____ WORST NAUSEA I HAVE EVER HAD

Have you vomitted since you received your study medication? ☐$_0$ NO ☐$_1$YES

State Trait Anxiety Inventory[1]

Read each statement and select the appropriate response to indicate how you feel right now, that is, at this very moment. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

		Not at all	**A little**	**Somewhat**	**Very much so**
1	I feel calm	1	2	3	4
2	I feel secure	1	2	3	4
3	I feel tense	1	2	3	4
4	I feel strained	1	2	3	4
5	I feel at ease	1	2	3	4
6	I feel upset	1	2	3	4
7	I am presently worrying over possible misfortunes				
8	I feel satisfied	1	2	3	4
9	I feel frightened	1	2	3	4
10	I feel uncomfortable	1	2	3	4
11	I feel self confident	1	2	3	4
12	I feel nervous	1	2	3	4
13	I feel jittery	1	2	3	4
14	I feel indecisive	1	2	3	4

15	I am relaxed	1	2	3	4
16	I feel content	1	2	3	4
17	I am worried	1	2	3	4
18	I feel confused	1	2	3	4
19	I feel steady	1	2	3	4
20	I feel pleasant	1	2	3	4

Intraoperative – FOR LOCAL ONLY

1. Make a hash mark on the line to indicate how much pain you had with the speculum insertion.

NO PAIN ——————————————————— WORST PAIN IN MY LIFE

ACTUAL TIME OF ASSESMENT _____ **: _____**

2. Make a hash mark on the line to indicate how much pain you had while the numbing medicine was injected into your cervix.

NO PAIN ——————————————————— WORST PAIN IN MY LIFE

[Study staff: END OF PCB (Duration since speculum insertion) ___ MINUTES ___ SECONDS]

3. Make a hash mark on the line to indicate how much pain you had while your cervix was opened to prepare for the suction procedure.

NO PAIN ——————————————————— WORST PAIN IN MY LIFE

[Study staff: END OF CERVICAL DILATION (Duration since speculum insertion) ___ MINUTES ___ SECONDS]

4. Make a hash mark on the line to indicate how much pain you had during the suction procedure.

NO PAIN ——————————————————— WORST PAIN IN MY LIFE

[Study staff: END OF SUCTION PROCEDURE (Duration since speculum insertion)___ MINUTES ___ SECONDS]

Immediate Post Op Assessment (on removal of speculum)
Time: ___ ___: ___ ___ AM/PM

5. Make a hash mark on the line to indicate how much pain you are currently in after removing the speculum.

NO PAIN _____ WORST PAIN IN MY LIFE

5-Minute Post Op Assessment
Time: ___ ___: ___ ___ AM/PM

1. Make a hash mark on the line to indicate the worst pain you have felt up to this point today.

NO PAIN _____ WORST PAIN IN MY LIFE

2. Make a hash mark on the line to indicate how much pain you are currently in.

NO PAIN _____ WORST PAIN IN MY LIFE

3.
Make a hash mark on the line to indicate how much anxiety you are currently experiencing.

NO ANXIETY _____ EXTREMELY ANXIOUS

4. **Make a hash mark on the line to indicate how much nausea you are currently experiencing.**

NO NAUSEA _____ WORST NAUSEA I HAVE EVER HAD

5. Have you vomitted since you had your procedure? ☐$_0$ NO ☐$_1$YES

10-Minute Post Op Assessment
Time: ___ ___: ___ ___ AM/PM

1. Make a hash mark on the line to indicate the worst pain you have felt up to this point today.

NO PAIN ——————————————— WORST PAIN IN MY LIFE

2. Make a hash mark on the line to indicate how much pain you are currently in.

NO PAIN ——————————————— WORST PAIN IN MY LIFE

3. Make a hash mark on the line to indicate how much anxiety you are currently experiencing.

NO ANXIETY ——————————————— EXTREMELY ANXIOUS

4. **Make a hash mark on the line to indicate how much nausea you are currently experiencing.**

NO NAUSEA ——————————————— WORST NAUSEA I HAVE EVER HAD

5. Have you vomitted since you had your procedure? ☐$_0$ NO ☐$_1$YES

SIDE EFFECTS: Do you have any of the following?

Dizziness	☐$_0$ NO ☐$_1$YES, mild ☐$_2$YES, moderate ☐$_3$YES, severe
Ataxia (lack of muscle control)	☐$_0$ NO ☐$_1$YES, mild ☐$_2$YES, moderate ☐$_3$YES, severe
Somnolence (sleepiness or drowsiness)	☐$_0$ NO ☐$_1$YES, mild ☐$_2$YES, moderate ☐$_3$YES, severe
Asthenia (weakness, lack of energy)	☐$_0$ NO ☐$_1$YES, mild ☐$_2$YES, moderate ☐$_3$YES, severe
Headache	☐$_0$ NO ☐$_1$YES, mild ☐$_2$YES, moderate ☐$_3$YES, severe
Amblyopia (vision in one eye reduced/lazy eye)	☐$_0$ NO ☐$_1$YES, mild ☐$_2$YES, moderate ☐$_3$YES, severe

Post- anesthetic aldrete recovery score : modified Criteria	Points
Oxygenation	
SpO2 > 92% on room air	2
SpO2 > 90% on oxygen	1
SpO2 < 90% on oxygen	0
Respiration	
Breathes deeply and coughs freely	2
Dyspneic, shallow or limited breathing	1
Apnea	0
Circulation	
BP +/- 20% of normal	2
BP +/- 20-50% of normal	1
BP > 50% of normal	0
Consciousness	
Fully awake	2
Arousable on calling	1
Not responsive	0
Activity	
Moves all extremities	2
Moves two extremities	1
No movement	0

30-Minute Post Op Assessment
Time: ___ ___: ___ ___ AM/PM

1. Make a hash mark on the line to indicate the worst pain you have felt up to this point today.

NO PAIN _____ WORST PAIN IN MY LIFE

2. Make a hash mark on the line to indicate how much pain you are currently in.

NO PAIN _____ WORST PAIN IN MY LIFE

3. Make a hash mark on the line to indicate how much anxiety you are currently experiencing.

NO ANXIETY _____ EXTREMELY ANXIOUS

4. **Make a hash mark on the line to indicate how much nausea you are currently experiencing.**

NO NAUSEA _____ WORST NAUSEA I HAVE EVER HAD

4. Have you vomitted since you had your procedure? ☐$_0$ NO ☐$_1$YES

Discharge Assessment
Time: ___ ___: ___ ___ AM/PM

1. Make a hash mark on the line to indicate the worst pain you have felt up to this point today.

NO PAIN ——————————————— WORST PAIN IN MY LIFE

2. Make a hash mark on the line to indicate how much pain you are currently in.

NO PAIN ——————————————— WORST PAIN IN MY LIFE

3. Make a hash mark on the line to indicate how much anxiety you are currently experiencing.

NO ANXIETY ——————————————— EXTREMELY ANXIOUS

4. **Make a hash mark on the line to indicate how much nausea you are currently experiencing.**

NO NAUSEA ——————————————— WORST NAUSEA I HAVE EVER HAD

5. Have you vomitted since you had your procedure? ☐$_0$ NO ☐$_1$YES

Post- anesthetic Aldrete recovery score Modified Criteria [2]	**Points**
Oxygenation	
SpO2 > 92% on room air	2
SpO2 > 90% on oxygen	1
SpO2 < 90% on oxygen	0
Respiration	
Breathes deeply and coughs freely	2
Dyspneic, shallow or limited breathing	1
Apnea	0
Circulation	
BP +/- 20% of normal	2
BP +/- 20-50% of normal	1
BP > 50% of normal	0
Consciousness	
Fully awake	2
Arousable on calling	1
Not responsive	0
Activity	
Moves all extremities	2
Moves two extremities	1
No movement	0

24 hours post-procedure measures
Time: ___ ___: ___ ___ AM/PM

Did you fill any pain medication prescription? ☐$_0$ NO ☐$_1$YES

Have you taken any medication since you left the clinic for pain, nausea, vomiting or any other medication

Medication type	Dose	Number of doses	Time of last dose	Notes

Have you vomited since you left the clinic? ☐$_0$ NO ☐$_1$YES, number of times _____

Overall satisfaction with experience 0-10 scale (0 = very dissatisfied; 10 = very satisfied): _____

Quality of Recovery Survey[3]

Part A

	How have you been feeling in the last 24 hours? (0 to 10, where 0 = none of the time [poor] and 10 = all of the time [excellent])	0-10
1	Able to breathe easily	
2	Been able to enjoy food	
3	Feeling rested	
4	Have had a good sleep	
5	Able to look after personal toilet and hygiene unaided	
6	Able to communicate with family and friends	
7	Getting support from hospital doctors and nurses	
8	Able to return to work or usual home activities	
9	Feeling comfortable and in control	
10	Having a feeling of general well-being	

Part B

	Have you had any of the following in the last 24 hours? (0 to 10, where 10= none of the time [excellent] and 0 = all of the time [poor])	0-10
1	Moderate pain	
2	Severe pain	
3	Nausea or vomiting	

4	Feeling worried or anxious	
5	Feeling sad or depressed	

[1] Knight RG, Waal-Manning HJ, Spears GF. Some norms and reliability data for the State--Trait Anxiety Inventory and the Zung Self-Rating Depression scale. The British journal of clinical psychology / the British Psychological Society. 1983;22 (Pt 4):245-9.
[2] Aldrete JA. The post-anesthesia recovery score revisited. J Clin Anesth. 1995;7:89-91.
[3] Stark PA, Myles PS, Burke JA. Development and psychometric evaluation of a postoperative quality of recovery score: the QoR-15. Anesthesiology. 2013;118:1332-40.