A randomized controlled trial of transcutaneous electrical nerve stimulation for pain control during
intrauterine device insertion
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A randomized controlled trial of transcutaneous electrical nerve stimulation for pain control during intrauterine device insertion

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Principal Investigator: Ariella Goldman

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
3.6	Added history of heart disease to exclusion criteria	Patients with a history of heart disease have a potential risk of cardiac rhythm problems with TENS use so they will be excluded from the study
1.1, 3.1	Added new study site and updated randomization method	Our division will be relocated to a new site in the upcoming weeks. New randomization method incorporates REDCap and will be more effective for multi-site use.
3.6	Added another exclusion criteria for planned and/or pre-procedure pain interventions	The planned and/or pre-procedure pain interventions are pharmacologic methods. The use of these interventions would confound our results since we are studying a non-pharmacologic pain intervention.
1.3, 3.1	Added PROMIS 10 questionnaire as a data collection tool, explained timing of	PROMIS 10 is a validated survey developed by researchers at multiple academic institutions and the National

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	PROMIS 10 and purpose of use in the study population	**Institutes of Health that measures self-reported physical, mental, and social health. The PROMIS 10 responses will provide us with knowledge about how our study participants view their health.**
1.1, 3.1, 3.5	**Added Yale School of Medicine as a new study site, updated item 4 of inclusion criteria to include new site**	**Fellow Family Planning colleagues at Yale reached out and expressed interest in the study and being added as a site. Adding Yale as an additional site will help our study team reach our recruitment goal.**
3.1, 3.6	**Added history of epilepsy to exclusion criteria**	**Patients with a history of epilepsy are advised against TENS use due to concerns that the stimulation from the device can potentially trigger seizures for patients with epilepsy.**
5.1.5	**Updated Principal Investigator for study**	**Dr. Lauren Kus has completed her fellowship at Mount Sinai.**
5.1.11	**Explained what data will be shared through Data Use Agreement with NYU Langone**	**Previous Principal Investigator, Dr. Lauren Kus, is now working at NYU Langone. This project was her fellowship project while she was a Family Planning fellow at Mount Sinai. The data use agreement will facilitate collaboration between our institution and NYU Langone and allow Dr. Kus to publish the results of this project.**

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.]

PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	A randomized controlled trial of transcutaneous electrical nerve stimulation for pain control during intrauterine device insertion
Study Description:	We propose a randomized controlled trial to assess the utility of transcutaneous electrical nerve stimulation (TENS) to reduce pain with IUD insertion. We will compare pain scores on a 100 mm visual analogue scale (VAS) recorded at the time of IUD (LNG 52 mg or copper T380A) insertion among individuals exposed to active or placebo treatment to determine if use imparts a clinically meaningful reduction in pain.
Objectives:	Primary Objective: Assess pain at time of IUD insertion with and without TENS Secondary Objectives: Identify factors that may be associated with higher pain scores during IUD insertion including pre-procedure anxiety and anticipated procedural pain
Endpoints:	Primary Endpoints: Pain as measured by visual analogue scale at time of IUD insertion Secondary Endpoints: Factors associated with increased pain during IUD insertion; Acceptability of hfTENS device
Study Population:	We will enroll 98 patients (49 in each arm) to detect a clinically significant difference in VAS scores of 20 mm with a power of 80%, accounting for protocol deviation and non-parametric distribution. Eligible participants will include patients aged 18 years or older undergoing IUD insertion with

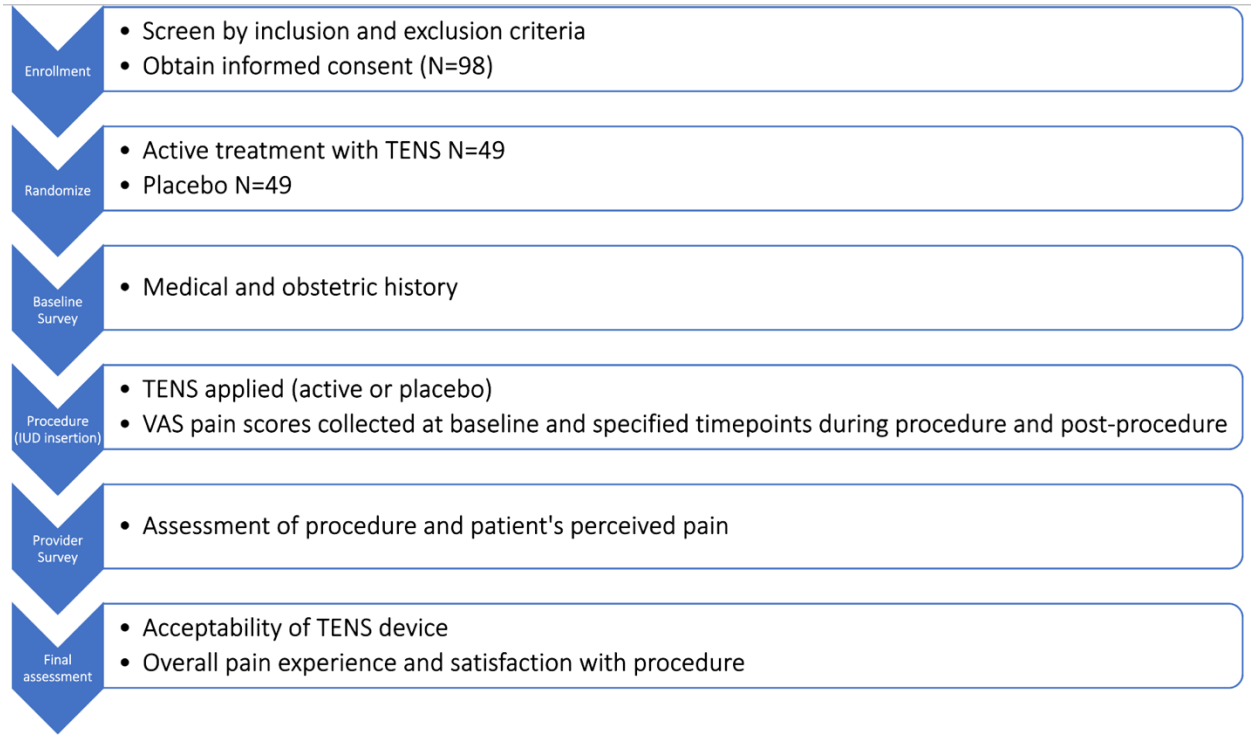
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	either 52mg LNG-IUD or Paragard IUD without contraindication to TENS use.
Phase:	N/A
Description of Sites/Facilities Enrolling Participants:	Participants will be enrolled from 5 sites within the Mount Sinai Health System including Mount Sinai Hospital, Mount Sinai Beth Israel, Mount Sinai Union Square, Mount Sinai West, and Mount Sinai Morningside. Participants will also be enrolled from 2 sites within the Yale School of Medicine: the Center for Women's Health and Midwifery and the Yale Family Planning Clinic.
Description of Study Intervention:	We will use a TENS 7000 digital TENS unit (see Appendix), a low cost, over the counter, battery operated device with high consumer ratings. The handheld device works by transmitting an electronically generated topical stimulus to a specified area on the body to alter response to pain signals and promote endogenous endorphin release for pain reduction. High frequency TENS (>50 Hz; "hfTENS") significantly reduces pain associated with dysmenorrhea and other outpatient gynecologic procedures. The same device will be used for both active and placebo treatment. A research staff member will apply TENS pads to specified areas on the lower abdomen and lower back corresponding to T10-11 and S2-4 dermatomes. For the active treatment group, the device will be set to 80 Hz (hfTENS)and device intensity (0-8) will be titrated to patient comfort, as is the standard protocol for TENS use. For the placebo group, setup will be identical, but the device will not be turned on.
Study Duration:	18 months
Participant Duration:	All study procedures will take place on the day of IUD insertion (one day)

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1.2 SCHEMA



1.3 SCHEDULE OF ACTIVITIES (SOA)

	Day 0 Day of IUD insertion
Recruitment	X
Informed consent	X
Demographics	X
Medical history	X
Randomization	X
Baseline Survey	X
PROMIS 10 Global Health Questionnaire	X
Administer study intervention	X
Intraprocedural survey and pain scores	X
Provider post procedure survey	X
Participant post procedure survey	X

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INTRODUCTION

1.4 STUDY RATIONALE

Intrauterine device (IUD) insertion is a common ambulatory gynecologic procedure. Between 2017 and 2019, 8.4% of contraceptive users in the United States reported use of an IUD.[1] Pain associated with IUD insertion is variably described, and evidence suggests that physicians underestimate the severity of pain patients experience with this procedure.[2] In one study of young nulliparous patients, nearly 80% reported moderate or severe pain associated with IUD insertion.[3] Other studies have also demonstrated moderate insertional pain ranging from 5 to 7 out of 10 cm (equivalent to 50-70 out of 100 mm) on VAS.[4-6] Trivializing or failing to address pain associated with IUD insertion undermines the physician-patient relationship at best and can traumatize patients at worst.[7] Recent public discourse emphasizes negative pain experiences associated with IUD insertion and demand for a meaningful response to this pain from the healthcare community.[8,9] In a 2023 study of the social media platform TikTok, 96.8% of the top videos about patient experiences with IUDs focused on pain.[10] In addition, fear of pain associated with insertion is frequently cited as a barrier to IUD initiation. While a small study suggested that this fear may not be a major deterrent to choosing the method, it certainly is a consideration during contraceptive decision-making.[11]

1.5 BACKGROUND

CDC Selected Practice Recommendations for Contraceptive Use from 2016 acknowledge that paracervical block with lidocaine might reduce pain during IUD insertion;[12] however, the risk-benefit profile of this intervention likely precludes routine use.[4] A subsequent 2020 systematic review summarizing available evidence about interventions to ease IUD insertion pain noted conflicting outcomes. Use of tramadol and some lidocaine formulations successfully reduced pain, but results are challenging to interpret given varied study quality and inconsistent reporting of co-interventions.[13] Without investigation of new pain management approaches and better data to guide service delivery, clinical practice varies, and patients will continue to be at risk for moderate to severe pain.

Transcutaneous electrical nerve stimulation (TENS) is a relatively low-cost, low-risk, non-pharmacologic intervention for pain management that warrants high quality investigation for the indication of IUD insertion pain. The handheld device works by transmitting an electronically generated topical stimulus to a specified area on the body to alter response to pain signals and promote endogenous endorphin release for pain reduction.[14,15] High frequency TENS (>50 Hz; “hfTENS”) significantly reduces pain associated with dysmenorrhea[14,16-18] and other outpatient gynecologic procedures, including medication abortion,[19] hysteroscopy,[20,21] and uterine aspiration.[22] To the best of our knowledge, this is the first study to evaluate the application of this technology for pain management with IUD insertion.

1.6 RISK/BENEFIT ASSESSMENT

1.6.1 KNOWN POTENTIAL RISKS

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There is minimal risk associated with the study intervention. According to the TENS 7000™ package insert[23], skin irritation and electrode burns are potential adverse reactions. Additionally, the device is contraindicated in the presence of cardiac pacemakers or heart disease without consulting a physician.

1.6.2 KNOWN POTENTIAL BENEFITS

There is a potential benefit to participants of reduced pain during IUD insertion. The TENS device is indicated for temporary relief of pain associated with sore and aching muscles in the shoulder, waist, back, upper extremities and lower extremities. According to the device insert, pain relief varies by individual patient and type of pain but in most patients, it is effective in reducing or eliminating pain. For many patients, pain reduction lasts even longer than the period of transcutaneous electrical nerve stimulation.[23]

1.6.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

There is minimal risk associated with the TENS device, which is available over the counter, without a prescription. Patients with a contraindication to TENS use will be excluded. Since there is standardized pain management intervention for IUD insertion, the potential benefit of pain control with the TENS device outweighs the minimal risk associated with its use.

2 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To determine whether use of high-frequency transcutaneous electrical nerve stimulation (hfTENS) is superior to use of placebo TENS, measured by reduced reported pain at the time of IUD insertion	Pain score as measured on visual analogue scale at time of IUD insertion	Pain at IUD insertion tends to be the most painful part of the procedure based on prior literature,[4] and therefore the most important endpoint to examine for potential benefit
Secondary		
To identify covariates other than exposure to hfTENS associated with higher reported pain	Demographic, medical history factors, and other personal characteristics will be examined in relation to reported pain throughout procedure	To further examine risk factors for pain during IUD insertion
To describe acceptability of hfTENS for use in this context	Survey data from post-procedure survey	To be able to comment on patient acceptability of the proposed intervention

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3 STUDY DESIGN

3.1 OVERALL DESIGN

We propose a double-blind, randomized, placebo-controlled trial to evaluate the use of high frequency TENS for pain control during IUD insertion. Participants will be randomized in a 1:1 ratio to either active treatment or placebo (placebo TENS) and we will compare self-recorded pain scores using a 100 mm visual analog scale (VAS) at the time of insertion.

We will recruit eligible participants from patients who opt for IUD initiation during ambulatory care visits to the Mount Sinai Complex Family Planning service at up to 5 sites. Eligible participants will also be recruited at two sites within the Yale School of Medicine, the Center for Women's Health and Midwifery and the Yale Family Planning Clinic. English-speaking individuals, 18 years of age or older, interested in initiation of either a LNG 52 mg or copper T380A IUD and who provide voluntary informed consent will be included. Anyone with a contraindication to IUD initiation (i.e. pregnancy, current pelvic infection, distorted uterine anatomy), contraindication or allergy to ibuprofen, history of a chronic pain disorder, recent opioid use in the previous 30 days, history of a cardiac arrhythmia or presence of an implantable device with an electrical discharge (i.e. pacemaker), history of heart disease (i.e. atrial fibrillation, congestive heart failure), history of epilepsy will not be eligible for participation. History of epilepsy is an exclusion criterion due to concerns that the stimulation from the TENS device can potentially cause seizures for patients with epilepsy. Patients who have used a TENS device in the past will be excluded because of inability to blind participants who are familiar with TENS. Patients with a BMI greater than 50 (class 4 obesity) will not be eligible, as a very large pannus could impede appropriate pad placement. Patients with a planned pain intervention outside standard of care (i.e. paracervical block, misoprotol etc.) or who use a non-standard pain medication (i.e. benzodiazepines, marijuana, muscle relaxers, gabapentin, Benadryl) pre procedure also will not be eligible. These planned and/or pre-procedure interventions are pharmacologic methods. Their use would confound our results since we are studying a non-pharmacologic pain intervention.

Following the decision to initiate an eligible IUD (LNG 52 mg or copper T380A), medical assessment, and completion of the informed consent process for the insertion procedure, participants will be notified of the possibility to participate in this study. Research staff will complete study screening and subsequent enrollment of eligible individuals who consent to participation.

Allocation to treatment will be based on a 1:1 blocked randomization scheme stratified by parity. The randomization scheme will be created by the statistician and uploaded into REDCap. In order to maintain blinding, a member of the research team who is not involved in study implementation will randomize each patient using the REDCap randomization module. A member of the research/clinical team other than the person performing IUD insertion will call the team member who isn't involved in study implementation to identify the treatment allocation assigned to the corresponding subject ID. Then, the team member will set up the TENS unit accordingly by applying pads to the participant and initiating treatment with the correct settings. When setup is complete (<5 minutes), the person performing the IUD insertion and other clinical staff assisting with the procedure will enter the exam room with no knowledge of TENS treatment assignment to insert the IUD.

We will use a TENS 7000 digital TENS unit (see Study Intervention), a low cost, over the counter, battery operated device with high consumer ratings. This device has previously demonstrated success



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with pain control during aspiration abortion.[22] The same device will be used for both active and placebo treatment. A research staff member will apply TENS pads to specified areas on the lower abdomen and lower back corresponding to T10-11 and S2-4 dermatomes (see Appendix). For the active treatment group, the device will be set to 80 Hz (hfTENS)[19,21] and device intensity (0-8) will be titrated to patient comfort, as is the standard protocol for TENS use.[21,22] For the placebo group, setup will be identical, but the device will not be turned on.

All participants will receive a standard analgesia regimen of ibuprofen 800 mg orally prior to the start of the procedure. Disposable hot packs are also available on demand for application to the lower abdomen following the procedure.

Participants will complete a baseline electronic survey prior to the procedure. We will collect demographics, clinical information such as medical, obstetric, and gynecologic history along with other characteristics, and will use a VAS score to assess the patient's anticipated pain and level of pre-procedure anxiety. We will also collect data via the PROMIS 10 Global Health Questionnaire. Responses to the PROMIS 10 will be collected after demographics and VAS anticipated pain and pre-procedure anxiety scores. PROMIS 10 is a validated survey developed by researchers at multiple academic institutions and the National Institutes of Health that measures self-reported physical, mental, and social health. It has been used to assess health and well being in adults in the general population as well as those living with chronic conditions. By including this questionnaire in our study, we will be able to gain more knowledge about how our study participants view their health. The PROMIS 10 questionnaire will also be completed prior to the procedure. REDCap™, a HIPAA-compliant, secure web application used for building and managing online surveys and databases, will be used for data collection in this study. The Yale study team will be added as external collaborators to our institutional REDCap via SailPoint requests. Since collaborator accounts are temporary and expire every 120 days, the ISMMS team will ensure that these accounts are renewed prior to the expiration date(s). The data shared between ISMMS and Yale via REDCap will not be de-identified as we are collecting date of birth and e-mail address on the Demographics data collection form. Date of birth is necessary to confirm that patient meets the minimum age requirement for study participation. Collecting e-mail addresses is necessary so the research coordinator can send study patients their Amazon gift card via e-mail for study participation.

IUD insertion will be performed by complex family planning faculty and fellows, as well as OB/GYN residents on their family planning rotation. A research staff member will be within reach of the study participant during the procedure to collect pain scores using a visual analog scale (VAS) presented on an iPad. Existing data validates this method of digital VAS pain scoring.[24] The participant will be asked to rate their pain at multiple timepoints during the procedure just by moving a digital slider to a value between 0 and 100 using the touch screen. These include:

1. Baseline
2. Immediately after bimanual exam
3. Immediately after speculum insertion
4. Immediately after tenaculum placement
5. Immediately after uterine sounding
6. Immediately after IUD insertion
7. 5 minutes after speculum removal

After the last pain score is collected, participants will be asked to fill out a final survey requesting reflections on their experience with IUD insertion and acceptability of the TENS device.

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Providers will also be asked to provide information on their assessment of patient pain and ease of the insertion procedure. Participants will receive a $15 amazon gift card for study participation that will be delivered via e-mail within 2 weeks of study completion.

To achieve 80% power to detect a 20 mm difference in pain scores reported at IUD insertion, assuming a 30 mm standard deviation and 15% inflation to account for nonparametric distribution, we need 49 participants in each treatment arm. Previous studies note that a reduction in pain scores by 20 mm on VAS is clinically significant for various conditions, guiding our choice of effect size.[25-28]

We will present our data using descriptive statistics (means and standard deviation or medians and interquartile ranges for continuous data, as appropriate, and frequencies and percentages for categorical data). We will perform t-tests or Wilcoxon rank sum tests as appropriate to compare mean or median pain scores at time of IUD insertion as measured by VAS scores between TENS and placebo groups. We will use a multivariable regression model to adjust for potential confounders of the association between the intervention and pain scores. We will report descriptive statistics reflecting on the acceptability of TENS to participants.

3.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The current standard of practice (pre-procedure ibuprofen alone) will serve as the control group. This study addresses a gap in knowledge about a routine, frequently painful ambulatory gynecologic procedure and may propose a practical and feasible intervention for routine pain management in this context.

3.3 JUSTIFICATION FOR DOSE

The TENS 7000 settings chosen for this study (80 Hz hfTENS) have previously demonstrated use in other gynecologic contexts.[19,21] Device intensity (0-8) will be titrated to patient comfort, as is the standard protocol for TENS use.[21,22]

3.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if they have completed all phases of the study including the final survey on the day of their scheduled procedure. The end of the study is defined as completion of the last visit and procedure shown in the SoA in the trial.

STUDY POPULATION

3.5 INCLUSION CRITERIA

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

1. Provision of signed and dated informed consent form for IUD Insertion
2. Stated willingness to comply with all study procedures
3. English speaking individuals aged 18 years or older

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4. Presenting for IUD initiation during ambulatory care visits to the Mount Sinai Complex Family Planning service or the two sites affiliated with Yale School of Medicine
5. Opting for either LNG 52mg or copper T380A IUD

3.6 EXCLUSION CRITERIA

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

1. Contraindication to IUD initiation (i.e. pregnancy, current pelvic infection, distorted uterine anatomy)
2. Contraindication or allergy to ibuprofen
3. History of a chronic pain disorder
4. Recent opioid use in the previous 30 days
5. History of a cardiac arrhythmia
6. History of heart disease (i.e. atrial fibrillation, congestive heart failure)
7. Presence of an implantable device with an electrical discharge (i.e. pacemaker)
8. BMI > 50 (class IV obesity)
9. History of TENS use
10. Planned pain intervention outside standard of care (i.e. paracervical block, misoprotol) OR pre-procedure use of non-standard pain medication (i.e. benzodiazepines, marijuana, muscle relaxers, gabapentin, benadryl)
11. History of epilepsy

3.7 LIFESTYLE CONSIDERATIONS

Not applicable

3.8 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of choosing a device not included in our study (i.e. 19.5 mg LNG-IUD) may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

3.9 STRATEGIES FOR RECRUITMENT AND RETENTION

All patients presenting for IUD insertion who meet inclusion criteria will be recruited after they have made the decision to proceed and consented to their IUD insertion procedure. Since all study activities occur on the day of IUD insertion, we will not need to employ retention strategies.

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STUDY INTERVENTION

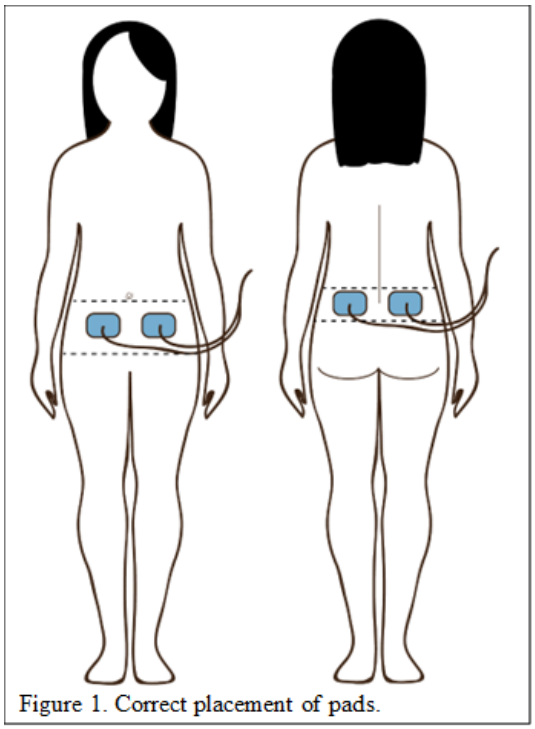
3.10 STUDY INTERVENTION(S) ADMINISTRATION

3.10.1 STUDY INTERVENTION DESCRIPTION

3.10.2 DOSING AND ADMINISTRATION

We will use a TENS 7000 digital TENS unit (see below), a low cost, over the counter, battery operated device with high consumer ratings. This device has previously demonstrated success with pain control during aspiration abortion.[22] The same device will be used for both active and placebo treatment. A research staff member will apply TENS pads to specified areas on the lower abdomen and lower back corresponding to T10-11 and S2-4 dermatomes (see below). For the active treatment group, the device will be set to 80 Hz (hfTENS)[19,21] and device intensity (0-8) will be titrated to patient comfort, as is the standard protocol for TENS use.[21,22] For the placebo group, setup will be identical, but the device will not be turned on.




Figure 1. Correct placement of pads.

3.11 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

3.11.1 ACQUISITION AND ACCOUNTABILITY

The TENS device, corresponding pads, and batteries will be available at all study sites. The device will be confirmed to be in good working order prior to use.

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3.11.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The appearance of the TENS 7000 device is included above.

3.11.3 PRODUCT STORAGE AND STABILITY

Not applicable

3.11.4 PREPARATION

Not applicable

3.12 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Participants who have used TENS in the past will be excluded, since those participants might be able to identify active versus placebo treatment. We will also not use the name "TENS" in any patient facing materials. Allocation to treatment will be based on a 1:1 blocked randomization scheme stratified by parity. Treatment allocation will be placed in sequentially numbered opaque envelopes (SNOSE) in sufficient quantity to accommodate our target sample size by a member of the research team otherwise uninvolved in study implementation. A member of the research/clinical team other than the person performing IUD insertion will identify the treatment allocation assigned to the corresponding subject ID. The team member will set up the TENS unit accordingly by applying pads to the participant and initiating treatment with the correct settings. When setup is complete (<5 minutes), the person performing the IUD insertion and other clinical staff assisting with the procedure will enter the exam room with no knowledge of TENS treatment assignment to insert the IUD. The same device will be used for both active and placebo treatment. For the placebo group, setup will be identical, but the device will not be turned on.

3.13 STUDY INTERVENTION COMPLIANCE

All study staff will be trained on proper use and application of the TENS device.

3.14 CONCOMITANT THERAPY

All participants will receive oral ibuprofen (800mg) prior to IUD insertion procedure, as is the standard of care in our practice.

3.14.1 RESCUE MEDICINE

Not applicable

STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

3.15 DISCONTINUATION OF STUDY INTERVENTION

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Discontinuation of the TENS device during the procedure does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- Time of device discontinuation
- Reason for device discontinuation

3.16 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

3.17 LOST TO FOLLOW-UP

Not applicable as all study procedures occur on Day 0.

STUDY ASSESSMENTS AND PROCEDURES

3.18 EFFICACY ASSESSMENTS

Not applicable

3.19 SAFETY AND OTHER ASSESSMENTS

Our screening protocol will maintain safety by excluding any patients with a contraindication to TENS use.

3.20 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

3.20.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

3.20.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse

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event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include abnormal cardiac response or neurological response requiring escalation of care.

3.20.3 CLASSIFICATION OF AN ADVERSE EVENT

3.20.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

3.20.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

3.20.3.3 EXPECTEDNESS

The primary investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

3.20.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

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The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The primary investigator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. Events will be followed for outcome information until resolution or stabilization.

3.20.5 ADVERSE EVENT REPORTING

3.20.6 SERIOUS ADVERSE EVENT REPORTING

The study clinician will report all AEs, whether considered study intervention related, including those listed in the protocol and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the Data Coordinating Center (DCC)/study sponsor and should be provided as soon as possible.

3.20.7 REPORTING EVENTS TO PARTICIPANTS

Participants will be informed directly by the study clinician if an AE occurs.

3.20.8 EVENTS OF SPECIAL INTEREST

Not applicable

3.20.9 REPORTING OF PREGNANCY

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Not applicable. All patients undergo routine urine pregnancy testing prior to IUD insertion.

3.21 UNANTICIPATED PROBLEMS

3.21.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("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); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

3.21.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB within one business day of the investigator becoming aware of the event.



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- Any other UP will be reported to the IRB and to the DCC/study sponsor within five business days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials and the Office for Human Research Protections (OHRP)

3.21.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Participants will be informed about UPs by the study clinician.

4 STATISTICAL CONSIDERATIONS

4.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s): Pain reduction at time of IUD insertion.

We hypothesize that pain will be significantly reduced with use of the TENS device.

- Secondary Efficacy Endpoint(s): Covariates other than exposure to hfTENS associated with higher reported pain, acceptability of hfTENS

We hypothesize that hfTENS will be acceptable to participants. We hypothesize that nulliparous patients will report higher pain during IUD insertion compared to multiparous patients.

4.2 SAMPLE SIZE DETERMINATION

To achieve 80% power to detect a 20 mm difference in pain scores reported at IUD insertion, assuming a 30 mm standard deviation and 15% inflation to account for nonparametric distribution, we need 43 participants in each treatment arm. To account for protocol deviations, we will recruit 49 participants in each arm for a total of 98 participants overall. Previous studies note that a reduction in pain scores by 20 mm on VAS is clinically significant for various conditions, guiding our choice of effect size.[25-28]

4.3 POPULATIONS FOR ANALYSES

The study population will be analyzed. No additional datasets or populations will be included.

4.4 STATISTICAL ANALYSES

4.4.1 GENERAL APPROACH

Our randomization scheme will be stratified by parity. We will present our data using descriptive statistics (means and standard deviation or medians and interquartile ranges for continuous data, as appropriate, and frequencies and percentages for categorical data).

4.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

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We will perform t-tests or Wilcoxon rank sum tests as appropriate to compare mean or median pain scores at time of IUD insertion as measured by VAS scores between TENS and placebo groups.

4.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

We will use a multivariable regression model to adjust for potential confounders of the association between the intervention and pain scores. We will report descriptive statistics reflecting on the acceptability of TENS to participants.

4.4.4 SAFETY ANALYSES

Not applicable

4.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline characteristics will be reported using descriptive statistics, as described in *General Approach*.

4.4.6 PLANNED INTERIM ANALYSES

Not applicable

4.4.7 SUB-GROUP ANALYSES

We will analyze nulliparous and multiparous patients as subgroups, and randomization will be stratified to ensure adequate numbers of each group to analyze.

4.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Not applicable

4.4.9 EXPLORATORY ANALYSES

Not applicable

5 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

5.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

5.1.1 INFORMED CONSENT PROCESS

5.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

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Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The consent materials are submitted with this protocol.

5.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Consent forms will be Institutional Review Board (IRB)-approved, and the participant will be asked to read and review the document. Those who cannot speak or read English fluently will not be eligible. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

5.1.2 STUDY DISCONTINUATION AND CLOSURE

Study discontinuation would occur if continued enrollment would be logistically impossible. For example, if the participant requested or required discontinuation of the TENS device due to discomfort or adverse event. If this were to occur, any actively enrolled participants would have already had study activities completed since all procedures occur on the day of their clinic visit. Written notification documenting the reason for study suspension or termination will be provided to actively enrolled participants and the IRB.

5.1.3 CONFIDENTIALITY AND PRIVACY

All study procedures and survey administration will occur in a private exam room. No physical documentation or records will be maintained; all patient consent forms, survey responses, and data gleaned from chart review will be stored securely in REDCap. In addition to the patient's name and signature on the consent document, identifiers will be recorded in the form of MRN to aid in chart review. No other identifying information will be collected, and these identifiers will be removed from records at the completion of data collection. Data will be maintained securely for the duration of time required by the IRB. Data will be available to study staff participating in data collection, coding, and analysis. It will not be available to any third parties or study staff who does not require it for research activities.

5.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

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Future use of stored specimens and data is not applicable to this study. Data will be maintained only for the duration of time required by the IRB.

5.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator
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As of Jun 2025, Dr. Ariella Goldman has taken over as Principal Investigator for this study. She is providing oversight for study activities at Mount Sinai. Through the data use agreement with NYU Langone, Dr. Lauren Kus will continue to work on data analyses for the study and spearhead manuscript preparation and dissemination activities. Dr. Rachel Masch will continue to provide support for data analysis. Shanell Morrison is still assisting with project operations as the clinical research coordinator. Elianna Kaplowitz was reassigned and the statistician who will continue to help us with data analysis is Guillaume Stoffels.

5.1.6 SAFETY OVERSIGHT

Not applicable

5.1.7 CLINICAL MONITORING

5.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Collected data will be reviewed periodically (every 20 – 30 enrollments) to assess for quality and completeness. Study members involved in surveying participants will discuss problems encountered with study instruments as they arise.

5.1.9 DATA HANDLING AND RECORD KEEPING

5.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

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Data will be captured from participant responses to survey and interview questions, and from review of the patient's medical record. All survey and chart review data will be directly recorded electronically in REDCap.

5.1.9.2 STUDY RECORDS RETENTION

Records will be maintained for the length of time mandated by the IRB.

5.1.10 PROTOCOL DEVIATIONS

All protocol deviations will be reported to the IRB in a timely manner.

5.1.11 PUBLICATION AND DATA SHARING POLICY

Every attempt will be made to publish results in a peer-reviewed journal.

Since Dr. Kus completed her fellowship at Mount Sinai, our study team will be sharing a de-identified data set with Dr. Kus who is now at NYU Langone through a Data Use Agreement. Currently, there are 5 REDCap data collection sheets for this project that are already de-identified (i.e. Screening Information, Procedure Info, Procedure Pain Assessment, Post Procedure Survey, Provider Survey). The research coordinator will remove identifiers (i.e. date of birth, e-mail, date of previous birth) from the REDCap Demographics data collection sheet so the only data remaining will be de-identified. After that removal, the only data that will be shared from the Demographics is the following list:

1. Insurance (i.e. Insurance Type – categories are Medicaid Managed Care, Commercial Insurance, Straight Medicaid, Medicare, and self pay)
2. Weight
3. Height
4. BMI
5. Medical History
6. Gyn Surgical History
7. Testosterone Status
8. Heavy Periods Status
9. Moderate to Severe Cramps Status
10. Previous IUD Use
11. Baseline Pain
12. Baseline Anxiety
13. Maximum Pain Expected during IUD Insertion
14. Race
15. Ethnicity
16. Gender
17. Highest Level of Education Completed
18. Deaf Status
19. Blind Status
20. Difficulty of doing errands alone
21. Difficulty concentrating
22. Difficulty walking or climbing stairs

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23. Difficulty dressing or bathing
24. PHQ4 questions (which screen for anxiety and depression)
25. PROMIS 10 Global Health Questionnaire (questions that allow patients to assess their physical, mental, and emotional health

All of the six REDCap Data Collection sheets referred to above (i.e. the 5 REDCap data collection sheets already deidentified and the Demographics REDCap data collection sheet [which will have identifiers removed]) can be found in the local site documents section of the RUTH application for this study.

The data from the REDCap Data Collection sheets will be shared in the form of Excel spreadsheets. These spreadsheets will be e-mailed to Dr. Kus at her NYU Langone e-mail address once the data use agreement is signed by the representatives from both institutions (Mount Sinai and NYU Langone). The data use agreement will be in effect for one year after the effective date (i.e. date in which all signatures provided on behalf of each institution is made). Data will be re-sent in the format listed above as many times as needed during the term (one year) until the study results are published in a peer-reviewed journal.

5.1.12 CONFLICT OF INTEREST POLICY

Any conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed.

5.2 ADDITIONAL CONSIDERATIONS

Not applicable

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5.3 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
hfTENS	High frequency TENS
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
IUD	Intrauterine device
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control

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SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
TENS	Transcutaneous electrical nerve stimulation
UP	Unanticipated Problem
US	United States

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5.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale

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