Clinical effectiveness of pre-incision versus post-incision local anesthetic during laparoscopic/robotic sacrocolpopexy (The CLAPPS Trial)

Protocol Number: 21-0422

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Principal Investigator: Harvey Winkler, MD

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale

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1. STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study 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 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. 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.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Clinical effectiveness of pre-incision versus post-incision local anesthetic during laparoscopic/robotic sacrocolpopexy
Study Description:	To compare postoperative narcotic use and pain score with pre-incisional versus post-incisional injection of local anesthetic at trocar sites in robotic/laparoscopic-assisted sacrocolpopexy
Objectives:	
	• Primary objective: Comparing postoperative Likert pain scale between patients who received pre-incisional versus post-incisional local anesthetic on postoperative day one • Secondary objectives: Total narcotic use over two weeks between patients who received pre-incisional versus post-incisional local anesthetic. To compare the pain levels reported by patients on the brief pain inventory questionnaire at POD14 between the two study groups (pre-incisional vs post-incisional) by two sample t –test or Wilcoxin rank-sum test, where appropriate.

Endpoints:	Primary Endpoint: comparing Likert-pain scale scores between pre-incisional versus post-incisional local anesthetic on postoperative day one Secondary Endpoints: total narcotic use over two weeks between patients who received pre-incisional versus post-incisional local anesthetic and to compare brief pain inventory questionnaires at POD14 between the two study groups.
Study Population:	Sample size – 64 per arm; Female gender, age ≥ 18 years old, general health status healthy
Phase:	N/A
Description of Sites/Facilities Enrolling Participants:	Northwell Health sites (Lenox Hill Hospital, Southshore Hospital, Long Island Jewish Hospital, Northshore Hospital, Huntington Hospital, Plainview, Peconic, Mather). No hospital outside of the US.
Description of Study Intervention:	Subcutaneous injection of 4-5mL of 0.25% Bupivacaine into skin before or after incision for trocar placement during robotic/laparoscopic- assisted sacrocolpopexy
Study Duration:	18 months
Participant Duration:	2 weeks

1.2 SCHEMA

Visit 0

- New patient/Surgical discussion Visit
    - Screen potential for inclusion and exclusion criteria
    - If meets criteria
        - Pamphlet provided to patient in regard to study information

Visit 1

- Preoperative visit
    - Discuss study in further detail, answer questions after patient read pamphlet, risks/benefits discussed and offer patient participation
    - If patient consents:
        - First Brief Pain Inventory Questionnaire to fill out prior to surgery. The Narcotic Diary will be given to patient with the instructions to fill out after surgery and to document all narcotic pills used including provided and any additional.
    - If a patient is undecided, then will follow up by phone call prior to surgical day. If she decides after follow up phone call then will have patient sign consent on day of surgery

Visit 2

- Day of surgery

- If patient does not consent at preoperative visit, but decides to participate after follow up phone call:
  - Obtain consent if patient has agreed by phone call (phone call which is after preoperative visit) on the day of surgery
  - Provide narcotic diary and first Brief Pain Inventory Questionnaire to fill out (if patient has not already filled it out previously). Patient only needs to fill out one brief pain inventory questionnaire prior to surgery, the patient should fill this out on the day that they sign the consent for participation (whether it is at the preoperative visit or in the preoperative suite on the day of surgery). The Narcotic Diary will be given to patient with the instructions to fill out after surgery and to document all narcotic pills used including provided and any additional.
- Randomization
  - Arm 1: 64 patients; Arm 2: 64 patients

Visit 3

- Postoperative Day 1
  - Obtain Likert-pain scale score between 18-24 hours post-surgery

Visit 4

- Postoperative Visit (14 days +/- 3 days)
  - Narcotic Diary collected
  - Second Brief Pain Inventory Questionnaire given to patient to complete

1.3 Schedule of Activities (SoA)

Procedures	Screening Visit (Visit 0)	Preoperative Visit (Visit 1)	Day of Surgery (Visit 2)	Postoperative Day#1 (Visit 3)	Final Study Visit Day 14 +/-3 day (Visit 4)
Informed consent		X			
Demographics	X	X			
Medical history	X	X			
Randomization			X		
Administer study intervention			X		
Concomitant medication review	X	X	X		X

Physical exam (including height and weight)*	X	X			X
Vital signs*	X	X	X	x	X
Height*	X	x			
Weight*	X	x	X		
Hematology*		X		X	
Serum chemistry*		X			
Pregnancy Test*			X		
EKG (as indicated)*		X			
Adverse event review and evaluation		X	X----------X		X
Radiologic/Imaging assessment*		X			X
Other assessments (e.g., immunology assays, pharmacokinetic)*		X	X	X	X
Complete Case Report Forms (CRFs)		X	X	X	X
Brief Pain Inventory Questionnaire **		x	x		x
*Results of these standard of care procedures (if available) will be collected for research purposes via medical record review **Patient will fill out this only one time prior to surgery on the day she consents to participate in the clinical trial.					

2 INTRODUCTION

2.1 Study Rationale

Pelvic organ prolapse is becoming more common as women's life expectancy is increasing and the prevalence of obesity is rising. Many women undergo pelvic reconstructive surgery to treat their prolapse and improve their quality of life. The incidence of pelvic organ prolapse is 1.5-1.8 surgeries per 1,000 women years (1). Approximately 300,000 pelvic reconstructive surgeries are performed each year in the United States (1). There is a wide variety in surgical approaches and procedures for prolapse. One such procedure is a sacrocolpopexy in which the cervix or vaginal cuff is lifted to the anterior longitudinal ligament overlying the sacrum via a mesh graft. This can be done in a minimally invasive fashion with a laparoscopic or robotic approach or in an open abdominal approach. Numerous studies have shown this procedure to have a high success rate and long-term durability (2). As robotic/laparoscopic approach to surgery has shown shorter hospital-stays and improved patient outcomes, the robotic-assisted sacrocolpopexy has been rapidly incorporated into clinical practice (2).

In general, surgery causes a release of painful chemical mediators which has led to increased narcotic use, increased narcotic addiction, and number of pills prescribed. Most individuals who undergo surgery will require narcotics postoperatively to control their pain and some individuals have to extend their hospital stay until adequate pain control is achieved. Our study is aimed to reduce narcotic use, decrease hospital stay due to pain issues and determine if timing of adjunct pain medication improves pain scales for patients.

As postoperative pain after minimally invasive surgery is complex, specialists suggest that the effective analgesic treatment should be a multimodal approach (4). Use of local anesthetic with bupivacaine at robotic/laparoscopic trocar sites is the standard of care, however, there is no standard as to optimal timing that is most beneficial for patients to decrease pain. Currently, bupivacaine is used by providers at the trocar sites at either the beginning of the case or at the end of the case. From clinical

observation, it appears that postoperative pain levels reported from patients receiving either at the beginning of surgery (pre-) or end (post-incision) of the surgery are similar. This study aims to examine the difference in POD1 pain levels reported by patients between the two infiltration methods.

2.2 Background

Subcutaneous infiltration with bupivacaine at robotic/laparoscopic port sites is standard of care. It is currently injected into incision sites during laparoscopic or robotic trocar sites before or after the incision is made. However, there is no standard as to which time during the procedure is the most beneficial for patients in order to decrease pain. Currently, there is lack of studies in the current literature that describe pre-incisional vs post-incisional local infiltration of numbing medication during robotic/laparoscopic-assisted sacrocolpopexy. There have been similar studies for patients undergoing laparoscopic cholecystectomy in which timing of the Marcaine was given to one group prior to incision and in another group at the end of the procedure, however in this study there was no difference in the pain scores at various times evaluates postoperatively. Our study is aimed to determine if the timing of local infiltration improves pain scales during robotic/laparoscopic sacrocolpopexy, which is a considerably longer procedure (approximately 3-5 hours). There is currently no literature on comparing Likert-pain scale scores in patients during robotic/laparoscopic sacrocolpopexy.

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

Bupivacaine (brand name: Marcaine)

- Immediate common risks: edema at insertion site, seroma
- Long-range common risks: hypersensitivity reaction, hypotension, localized numbness, cardiac arrest, methemoglobinemia and dose related toxicity
- Injection of Marcaine at skin incision sites will be lower than the dose that causes potential risks

This research will collect subject's personal health information, and there is a risk of breach of confidentiality.

Some of the questions on the questionnaires are personal and subjects may feel embarrassed or stressed.

Since subjects will be randomized to one of the two groups, some may receive less effective treatment and/or have more side effects than those in the other group.

2.3.2 Known Potential Benefits

Subjects will be randomized, and some may experience less pain and/or fewer side effects than those in the other group.

2.3.3 Assessment of Potential Risks and Benefits

- Local infiltration of incision sites with bupivacaine is standard of care for surgery.
- Adverse short term and long term risks: we will be using a standard dose that is currently used in the operating suite, which is lower than what would cause adverse side effects

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Difference in Likert-pain scale score difference between pre-incision versus post-incision subcutaneous infiltration with 4-5mL 0.25% Bupivacaine at 18-24 hours postoperatively	*Likert-pain scale score difference between pre-incision and post-incision subcutaneous infiltration at 18-24 hours postoperatively.*	*To determine if timing of local anesthetic affects postoperative pain scores.*
Secondary		
To compare total narcotic usage over two weeks	*Total number of narcotic tablets used in the first two weeks postoperatively between pre-incision and post-incision subcutaneous infiltration with 4-5mL 0.25% Bupivacaine*	*To decrease postoperative narcotic usage*
Secondary		
Compare brief pain inventory questionnaire survey score	*To compare score levels of the brief pain inventory questionnaire at POD14 between the two study groups*	*To decrease pain score for patient post surgery*

4 STUDY DESIGN

4.1 Overall Design

- Central Objective To examine patients reported pain levels or narcotic usage between pre-incision versus post-incision subcutaneous infiltration of 4-5mL 0.25% Bupivacaine after a robotic/laparoscopic-assisted sacrocolpopexy.

Research Plan:

- Randomized, controlled, single-blinded study

Setting of the study:

- Operating room of patients undergoing robotic/laparoscopic sacrocolpopexy

Participants:

- Patients aged 18 years old and above who are scheduled to undergo robotic/laparoscopic-assisted sacrocolpopexy (with or without hysterectomy and with or without midurethral sling)

Randomization Scheme

- Randomization will be accomplished using the Biostatistics Randomization Management System
- 1:1 Randomization, permuted blocks
- Subjects will be randomized using a computer generated table into one of two groups:
    - Arm one: subcutaneous infiltration pre-incision
    - Arm two: subcutaneous infiltration post-incision
- Surgeons will be notified by e-mail of their patient allocation on day of surgery

Pre-surgery

- Consent will be obtained and the patient will be given a Brief Pain Inventory Questionnaire to complete. The Brief Pain Inventory Questionnaire is a validated medical questionnaire to measure pain. The questionnaire measures the patient's pain intensity and the amount of interference the pain has on their being able to function in their daily living.

    - Intervention or experimental aspect of the study
        - General anesthesia will be given as per standard protocol
        - Preoperative pain medication will be ordered for each patient as per standard enhanced recovery protocol
        - Operative Time: Generally total of 180 – 300 minutes

        - Total dose of 0.25% Bupivacaine injection:
            - 8-10 mm incisions x 5 incisions = 20-25 mL (4-5 mL each)
            - 20-25mL of 0.25% Bupivacaine distributed over 5 trocar sites (4-5mL per incision)
            - Skin closure: subcutaneous closure with monofilament absorbable suture with 4-0 absorbable suture and fascia closure of the umbilical port site with #0 delayed absorbable suture and skin closure with 4-0 absorbable suture

- Pre-incision arm: Marcaine (bupivacaine) injected in the umbilical port site subcutaneously, while in the other 4 sites injection under direct visualization
- Post-incision arm: local anesthetic infiltrated subcutaneously at the end of the procedure after trocar removal and after skin closure with suture

- Postoperative pain medication will be ordered for each patient as per standard enhanced recovery protocol
- On Postoperative Day 1, the patient will be asked her pain scale on the Likert-pain scale. The Likert-pain scale is a 0-10 discrete integer scale. The investigators will check for patient's pain medication use before questionnaire administration. If a patient has received postoperative pain medication, the questionnaire will be administered at least 1.5 hours after the patient has received the pain medication.
- Discharge medications will be ordered for each patient as per standard enhanced recovery protocol
- The Brief Pain Inventory Questionnaire will be given to the patient at the 2 –week postoperative visit to be filled out and collected at the postoperative visit.
- The Narcotic diary (in which the patient writes down how many narcotic tablets they have used per day since the surgery (provided and additional included) will be collected at the postoperative visit.

4.2 Scientific Rationale for Study Design

The rationale for this study is to determine if timing of local anesthetic infiltration impacts overall pain score or narcotic usage. Although use of local anesthetic has been shown to reduce pain, there is no literature in gynecologic surgery regarding the timing of infiltration and its impact, if any, on pain.

4.3 Justification for Dose

Standard dose used.

4.4 End of Study Definition

A participant is considered to have completed the study if the patient has completed all phases of the study including the narcotic pain diary and brief pain inventory questionnaire at the first postoperative visit at approximately two weeks.

5 STUDY POPULATION

5.1 Inclusion Criteria

- Females 18+ years old who are undergoing robotic/laparoscopic assisted sacrocolpopexy
    - With/without hysterectomy
    - With/without unilateral/bilateral salpingectomy
    - With/without unilateral/bilateral oophorectomy
    - With/without midurethral sling
    - With/without anterior/posterior vaginal repair
- English or Spanish speaking
- Weight ≥ 120 lbs

5.2 Exclusion Criteria

- Females < 18 years old
- Chronic pelvic pain/chronic pain syndromes
- Fibromyalgia
- Pregnant or breastfeeding patients
- Concomitant procedure for hernia repair or rectal prolapse repair
- Undergoing primary vaginal prolapse surgery
- Contraindications to taking the following medications: Bupivacaine
- Patients who weight is < 120lb
- Hypersensitivity to bupivacaine hydrochloride, amide-type local anesthetics, or any component of the formulation
- Pudendal or spinal nerve block given during surgery

5.3 Lifestyle Considerations

Our standard post-operative instructions will remain.

5.4 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).

5.5 Strategies for Recruitment and Retention

- Patients will be screened and recruited from the Urogynecology outpatient clinic who are scheduled to undergo surgical management to correct their prolapse.

- At the visit in which the patient is considering surgical management for prolapse, all questions will be answered and she may be given a printed pamphlet that describes and details the study
- At the preoperative visit, if the patient has decided to under the robotic/laparoscopic-assisted sacrocolpopexy, patient will again have an opportunity to ask questions of the study, counseled on the risks/benefits of its participation and informed consent with be obtained
    - If she is undecided about joining the study, but is planning to undergo robotic/laparoscopic-assisted sacrocolpopexy, then she will be given additional time and called prior to surgery to answer any additional questions about the study and evaluate participation
    - If the patient did not sign on the preoperative visit, then she will be given another opportunity to sign the consent form on the day of surgery in the preoperative area and answer any further additional questions
- Email and phone call reminders to patients for postoperative appointment date and to fill out narcotic diary
- No vulnerable populations will be targeted for recruitment
- No incentives will be provided

6 STUDY INTERVENTION

6.1 Study Intervention(s) Administration

6.1.1 Study Intervention Description

Study Drug

- 0.25% Bupivacaine
    - Mechanism of action: blocks both the initiation and conduction of nerve impulses by decreasing the neuronal membranes permeability to sodium ions, which results in inhibition of depolarization with resultant blockade of conduction

6.1.2 Dosing and Administration

Study Drug

- Anesthesia team will be notified the total dose of medication being injected prior to case start
- Anesthesia team will be notified when the study drug is being injected
- 4-5 mL of 0.25% Bupivacaine given subcutaneously at each of the injection sites (total of 5 incisions)

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Acquisition and accountability

- Study drug will be obtained from the hospital pharmacy

- Any expired local anesthetic will not be used at the time of surgery, as per standard protocol
- Any remaining medication will be disposed at the end of procedure, as per standard protocol
- Study intervention will be emailed to investigator before surgery

6.2.2 Formulation, Appearance, Packaging, and Labeling

0.25% Bupivacaine is already pre-packaged and comes with the label of Marcaine (Bupivacaine) 0.25% directly to the hospital pharmacy. This drug is then pre-ordered and brought to the operating room where the designated amount will be drawn up into sterile syringes.

6.2.3 Product Storage and Stability

- Product will be obtained from the hospital pharmacy where the medication is stored at room temperature
- In the operating room, the medication seal will be broken after confirming expiration date has not passed
- The medication will be stored at room temperature in the operating room until time for administration

6.2.4 Preparation

- The medication will be provided by hospital pharmacy
- No special dilution or mixing required
- Medication will be drawn up in sterile syringes by operating room staff

6.3 Measures to Minimize Bias: Randomization and Blinding

- Patient-blinded study
- Multi-site study
- The surgeon at the time of intervention will not be blinded as to which arm the patient belongs
- Randomization will be performed using 1:1 randomization, permuted blocks

Randomization will be accomplished using the Biostatistics Randomization Management System according to hospital site.

6.4 Study Intervention Compliance

Adherence to the protocol will be confirmed and assessed by speaking directly with the primary surgeon prior to the procedure and at the end of procedure. The surgeon will be informed of each participant study allocation. The surgeons have been informed and continued to review how to inject the medication depending on the patient groups during monthly research meetings per discussion and teachings. The patient's Likert-pain scale will be assessed 18-24 hours after surgery. Documents that are mandatory to complete by the patient will be a participant drug log, in which the number of narcotic tablets used and pain score will be recorded daily by the patient.

6.5 Concomitant Therapy

Patients who participate in the study will receive the following standardized pain regimen:

- General anesthesia will be given as per standard protocol
- Preoperative pain medication will be ordered for each patient as per standard enhanced recovery protocol.
- Postoperative pain medication will be ordered for each patient as per standard enhanced recovery protocol.
- Discharge medications will be ordered for each patient as per standard enhanced recovery protocol.

6.5.1 Rescue Medicine

Not applicable

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

If the first ten patients do not tolerate the study medication, then we will evaluate which adverse reaction the patients experience and as to which arm they were randomized. We will also evaluate at which time point they experienced an adverse reaction and if it was to a preoperative/postoperative medication or if it was to the study drug. Pending the determination of these, we will halt recruitment. It is possible for a patient to discontinue participating in the study after surgery, but not during surgery.

7.2 Participant Discontinuation/Withdrawal from the Study

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

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.

7.3 Lost to Follow-Up

A participant will be considered lost to follow-up if she fails to return for her scheduled visit and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within one week and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, she will be considered to have withdrawn from the study with a primary reason of loss to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 Efficacy Assessments

Efficacy will be assessed by regular discussions with the primary surgeon by email and by phone call. We will discuss which patients have consented to the study on a weekly basis and then discussions will be had on the morning of each procedure to determine which arm the patient has been randomized into. We will be having regular weekly meetings to ensure that the protocol is being followed and that the co-investigators are aware of which patients have already consented and which patients have agreed to the study over the phone but need to have consent done on the day of surgery. We have reviewed how injections will be given in the two groups during our monthly research meetings and will continue to review these at the monthly meetings. After the surgery is complete, efficacy will be again assessed to ensure that the patient received the local infiltration pending which arm the patient was randomized into by phone call or email with the co-investigator.

8.2 Safety and Other Assessments

Patients will be screening for allergy to or contraindications to study medication. If they meet criteria and consent for the study, then each patient will be monitored for safety in multiple forms. For each patient,

vital signs are monitored in the operating room and during recovery until discharge as part of routine clinical care. Electrocardiogram monitoring will also be continuously ongoing in the operating room as part of routine clinical care. Assessment of adverse events throughout hospital stay will be done by review of charts and discussion with other members involved in patient care.

8.3 Adverse Events and Serious Adverse Events

8.3.1 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.

8.3.2 Definition of Serious Adverse Events (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes: death, a life-threatening adverse 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 allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.3 Classification of an Adverse Event

8.3.3.1 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".

8.3.3.2 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 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.

8.3.3.3 Expectedness

The Principal Investigator and all other investigators a part of the study 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.

8.3.4 Time Period and Frequency for Event Assessment and Follow-Up

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.

Dr. Vini Chopra, co-investigator, will record all adverse 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. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 Adverse Event ReportinG

Adverse events will be reported to the independent medical monitor. The independent medical monitor will record all serious and non-serious adverse events and this will be reported to the principal investigator that occurs within the 2 weeks of the study time length.

8.3.6 Serious Adverse Event Reporting

The study clinician will immediately report any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report 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.

The co-investigator will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the initial receipt of the information. In addition, the investigator must notify FDA and all participating investigators in a safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days.

8.3.7 Reporting Events to Participants

If any adverse event meets definition of an unanticipated problem that results in a consent form modification, subjects will be notified via the re-consenting process.

8.3.8 Events of Special Interest

Not applicable

8.3.9 Reporting of Pregnancy

Not applicable

8.4 Unanticipated Problems

8.4.1 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.

8.4.2 Unanticipated Problem Reporting

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB). 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 5 business days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB within 5 business days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 30 days of the IRB decision.

8.4.3 Reporting Unanticipated Problems to Participants

For unanticipated problems that result in a consent form modification, subjects will be notified via the re-consenting process. For other unanticipated problems that require reporting to participants as determined by the IRB, subjects will be as per the IRB's determination.

8.4.4 Data and safety monitoring plan

Data and Safety Monitoring Plan (DSMP)

In accordance with federal guidelines, this study requires a DSMP. The PI has identified an independent Medical Monitor (Dr. Gary Goldberg) with expertise in pelvic organ prolapse and robotic/laparoscopic-assisted sacrocolpopexy who does not have any scientific, financial, or other conflict of interest related to the study and who is not responsible for patient care at any of the participating sites. Safety will be formerly monitored by the study team and the independent Medical Monitor throughout the duration of the study, and the independent Medical Monitor will review safety data in aggregate every 6 months. The independent medical monitor and research team members will prepare a safety report for these regular reviews comprised of anticipated safety events and actions taken. The PI will contact the independent Medical Monitor for ad hoc reviews of any unanticipated safety events. The study protocol will be carried out in accordance with FDA guidelines and requirements. In the event of a serious adverse event during the study protocol, it will be reported immediately to the PI, the co-investigators, and the independent Medical Monitor. It will also be reported to the Northwell IRB for the study and to all members of the research team. With the approval of the participants and families, the information will be provided to other care providers as directed.

Risk Assessment

This study involves greater than minimal risk to the subjects. The primary concern is the development of numbness and bruising of injection site, severe allergic reaction and abnormal heart rhythm leading to death.

Subjects will be monitored throughout the study for these potential adverse events by phone call on the first postoperative day and then an office visit at two weeks post-surgery. The PI (or another designated Investigator in her absence) will be notified of any abnormal results so that the safety measures outlined below are implemented. The primary physician will also be notified of any abnormal results and any changes to the subject's care, and will also be provided with the test results. The potential risks and protections are as follows:

1. Abnormal Heart Rhythm

   Monitoring: Electrocardiogram monitoring in the operating room where the Marcaine will be given and monitoring of vital signs in the operating room and after surgery is complete

   Actions:

   - If severe abnormal heart rhythms at screening, subject will not be enrolled.
   - If severe abnormal heart rhythms at any study visit, subject will be taken off therapy, but will continue to be followed until end of study.
   - If the subject complains of symptoms concerning for abnormal heart rhythm (shortness of breath, chest pain, dizziness, abnormal heart beat), Abnormal heart rhythm will be checked in addition to any other clinical testing requested by primary physician.

2. Severe allergic reaction**:**

   Monitoring: vital sign monitoring and patient monitoring before, during and after surgery

   Actions:

- If patient has an allergy to local numbing medication at screening, subject will not be enrolled.
- If severe allergic reaction at any study visit, Marcaine (generic name: Bupivacaine) will not be furthermore given and the patient will be followed for two weeks post procedure.

- If the subject complains of symptoms concerning for severe allergic reaction (chest pain, shortness of breath, rashes), Severe allergic reaction will be checked in addition to any other clinical testing requested by primary physician.

3. Methemoglobinemia
   - Monitoring: oxygen status and any skin discoloration will be monitored in the operating room after injection has been given and after surgery
   - Actions:
     - Immediate discontinuation of bupivacaine injection
     - Depending on the severity of the signs and symptoms, patients may respond to supportive care (oxygen, continued ventilation, and hydration)
     - A more severe clinical presentation may require treatment with methylene blue, exchange transfusion or hyperbaric oxygen.

9. STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

- Primary Efficacy Endpoint(s):

  - Assessment of infiltration at pre-incision (pre) and infiltration at post-incision (post) associated pain score using a Likert-pain scale. The Likert-like pain scale is a validated, subjective measure for acute and chronic pain. The primary endpoint of pain score measurement will take place on postoperative day 1 (18-24 hr post-surgery, postoperative day 1). Scores are recorded by choosing an integer only number on a 0-10 scale that represents between “no pain” and “worst pain”.

- Secondary Efficacy Endpoint(s):

  - The need for additional narcotic usage over 2 weeks between the 2 arms
  - Compare questionnaires between the initial brief pain inventory questionnaire (pre-surgery) and postoperative brief pain inventory questionnaire

9.2 Sample Size Determination

We used pain score measured at POD1 as our primary outcome of interest. Sample size calculation was calculated using two independent sample t test, under the assumption that the pain scores are normally distributed. At the following test settings:

H_{null}: Mean difference of pain levels reported on a Likert-pain scale by patients between pre- and post-incision arms at POD1 = 0;
H_a: Mean difference of pain levels reported on a Likert-pain scale by patients pre- and post- incision arms at postoperative day one ≠ 0, and the expected mean difference of pain levels between the two groups is 1 likert point*.

Further we assume,
Standard deviation (std) = 2;

With the following default set-up values:
Alpha = 0.05
Power = 0.8
Weight between study arms = 1 (equal sample size in each arm)
Drop-out rate = 0

The required sample size for the current study is **64 per arm or 128 in total**.

*No well-established mean difference between the two study groups can be found in the literature. Based on clinical observations and experience from physicians that the two different infiltration methods are currently used interchangeably with no obvious difference in patients reported POD1 pain, we hypothesize the likely difference of pain levels between the two study groups to be 1. With standard deviation of 2 (see below), our targeted effect size is 0.5, or a median size effect based on Cohen's rule (Cohen, 1989).

**This SD value was estimated from the study by Yeung et al. (Liposomal Bupivacaine During Robotic Colpopexy VOL. 131, NO. 1, JANUARY 2018) using data from Table 3, average pain with rest at POD1 for the Bupivacaine group. Yeung et al. showed that the mean pain level with rest at POD1 in patients treated with liposomal Bupivacaine was 18.0, with the range of data being 81, on a 100mm-VAS scale. Therefore, a 'rule-of-thumb' of estimating standard deviation: range of data/4 was taken, yielding sd of ~20mm on a VAS scale. This was further translated to a sd of 2 on a 10-point Likert scale as one of the parameters for the sample size calculation for the current study.

9.3 Populations for Analyses

Intention to Treat (ITT) and Per Protocol (PP) analysis data sets:
The ITT dataset will consist of all randomized patients. If applicable, a modified ITT (mITT) dataset will consist of all ITT patients who receive the actual assigned timing of infiltration. We expect no protocol violation based on the design of the study. The safety population will consist of all mITT patients.

9.4 Statistical Analyses

9.4.1 General Approach

Summary statistics: Demographic and clinical data will be summarized according to treatment arm using means, S.D.s, medians, quartiles, and proportions, as appropriate. As per ICH E-9 guidelines, no inferential comparisons of the two arms will be carried out.

9.4.2 Analysis of the Primary Efficacy Endpoint(s)

Analysis of the primary outcome: For the primary outcome, which we assume will be normally distributed, the two independent sample t test comparing two independent groups will be used to compare the pain scores from study arms at POD1. In the event that normal assumption does not hold, a suitable data transformation (e.g., arcsine square-root, logit) will be applied.

A 95%, two-tailed confidence interval for the difference of mean pain scores between the two arms will be constructed. If both upper and lower confidence intervals lay within the ± 1-unit margin, we will conclude that the pain scores associated with the two routes of wound infiltration are equivalent. Otherwise, we cannot conclude that the effects between the two modes of wound infiltration on postoperative pain are equivalent.

As per ICH E-9 guidelines, a supporting analysis will be conducted whereby analysis of covariance (ANCOVA) will be used to compare the two groups, adjusting for nuisance covariates.

All continuous secondary outcomes will be analyzed using two sample t-test or Mann-Whitney test depending on whether normal assumption holds or not. ANCOVA will be used adjusting for baseline values and other associated covariates and will be considered as supportive analysis.

All categorical secondary outcomes will be analyzed using chi-square test for proportions or Fisher's exact test, as appropriate.

9.4.3 Analysis of the Secondary Endpoint(s)

Analysis of the secondary outcome:

- The need for additional Narcotic usage over 2 weeks between the 2 arms

All patients will be discharged with 12 standard narcotic pills for managing post-operative pain by needs. However, patients can request additional narcotic pain killers if needed. The needs for extra amount of pain reliever is an indicator of pain level and a secondary aim of the current study.
The need for additional narcotic usage is a binary-coded variable with values of 'yes' or 'no'. The rate/percentage of patients requesting additional narcotic medication will be calculated for each study arm, and compared in a 2 by 2 contingency table format using chi-square test or Fisher's exact test, as appropriate.

- Compare pain scores between each arm at 2 weeks post-operative visit

At the two-week post-operative visit, patients will be asked to fill out the brief pain inventory to indicate their current pain levels, as well as the mildest and worst pain scores within the past 24 hours. The pain scores will also be evaluated by Likert-pain scale (the same pain assessment tool used at POD1. The mean pain scores between the two arms will be compared by a two-sample t-test or a Wilcoxon rank-sum test, where appropriate. Statistical significance between the two arms is considered if the p-value for the tests are <0.05.

9.4.4 9.4.4 Safety Analyses

Patients will be screening for allergy to or contraindications to study medication. If they meet criteria and consent for the study, then each patient will be monitored for safety in multiple forms. For each patient, vital signs are monitored in the operating room and during recovery until discharge. Electrocardiogram monitoring will also be continuously ongoing in the operating room. Assessment of adverse events throughout hospital stay will be done by review of charts and discussion with other members involved in patient care.

9.4.5 Baseline Descriptive Statistics

Demographic and clinical data (including operative time and procedure performed) will be summarized according to treatment arm using means, S.D.s, medians, quartiles, and proportions, as appropriate. As per ICH E-9 guidelines, no inferential comparisons of the two arms will be carried out.

All continuous secondary outcomes will be analyzed using two sample t-test or Mann-Whitney test depending on whether normal assumption holds or not. ANCOVA will be used adjusting for baseline values and other associated covariates and will be considered as supportive analysis.

All categorical secondary outcomes will be analyzed using chi-square test for proportions or Fisher's exact test, as appropriate.

9.4.6 Planned Interim Analyses

No interim analysis will be conducted.

9.4.7 Sub-Group Analyses

No planned subgroup analysis.

9.4.7 Tabulation of Individual participant Data

Not applicable

9.4.9 Exploratory Analyses

Not applicable.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Informed Consent Process

10.1.1.1 Consent/assent and Other Informational Documents Provided to participants

Consent forms describing 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 following consent materials are submitted with this protocol.

10.1.1.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. 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 should have the opportunity to discuss the study with their family 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 must 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.

10.1.2 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, and IRB. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants and the Institutional Review Board (IRB), and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants

- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB and any other regulatory bodies.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators and their staff. This confidentiality is to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval.

All research activities will be conducted in as private a setting as possible.

Representatives of the Institutional Review Board (IRB), regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB or Institutional policies.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in REDCAP. This will include the participant's contact or identifying information. Individual participants and their research data will be identified by their name into REDCAP. The study data entry and study management systems used by clinical sites and by REDCAP research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived in REDCAP.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored in REDCAP. After the study is completed, the de-identified, archived data will be transmitted to and stored in REDCAP. Permission to transmit data to the REDCAP will be included in the informed consent.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	Independent Medical Monitor
HARVEY WINKLER, MD	*GARY GOLDBERG, MD*
NORTHWELL HEALTH	*NORTHWELL HEALTH*
865 NORTHERN BLVD	*270-05 76th AVENUE*
516-622-5100	*516-390-9242*
HWINKLER@NORTHWELL.EDU	*GGOLDBERG2@NORTHWELL.EDU*

10.1.6 Safety Oversight

Safety oversight will be under the direction of an independent medical monitor, Dr. Gary Goldberg, who has the appropriate expertise, including prior research experiences in clinical trials. The medical monitor is independent from the study conduct and free of conflict of interest, or measures will be in place to minimize perceived conflict of interest. The independent medical monitor (Dr. Goldberg) will review safety data in aggregate every 6 months to assess safety and efficacy data on each arm of the study.

10.1.7 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by the independent medical monitor Dr. Gary Goldberg and associates
- Central monitoring to occur by investigators to ensure that safe practices are being performed
- Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.
- Independent audits will be conducted by investigators to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the CMP.

10.1.8 Quality Assurance and Quality Control

Each clinical site will perform internal quality management of study conduct, data, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of inspection by local and regulatory authorities.

10.1.9 Data Handling and Record Keeping

10.1.9.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the medical monitor at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCAP, a 21 CFR Part 11-compliant data capture system provided by the REDCAP. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations.

10.1.10 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation, or within 3 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to REDCAP. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 Publication and Data Sharing Policy

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 2 years after the completion of the primary endpoint by contacting Vini Chopra.

10.1.12 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual 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. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the Northwell has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 Additional Considerations

Not applicable.

10.3 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
DSMP	Data Safety Monitoring Plan
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
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
ISO	International Organization for Standardization
ITT	Intention-To-Treat
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
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 Protocol Amendment History

Version	Date	Description of Change	Brief Rationale

10 11 REFERENCES

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