Transabdominal Plane (TAP) Blocks for Inguinal Hernia Repairs
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Transabdominal plane (TAP) blocks for Laparoscopic Inguinal Hernia Repairs

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Principal Investigator: Celia Divino, MD

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CONFIDENTIALITY STATEMENT

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP), 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 and documented approval from the Institutional Review Board (IRB), and the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, if applicable, 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(s) must be obtained before any participant is consented. 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(s) 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:	Transabdominal plane (TAP) Blocks for Laparoscopic Inguinal Hernia Repair
Grant Number:	
Study Description:	Inguinal hernias are bulges in the groin region that arise from weaknesses in the abdominal wall. Often, due to discomfort, pain or cosmetic dissatisfaction, these hernias must be surgically repaired. The use of a transabdominal plane (TAP) block—a local injection given in the abdomen to block pain receptors on nerves—during surgery can presumably decrease postoperative pain. The aim of our study is to investigate whether the use of a TAP block can decrease the use of opioids and pain scores after surgery.
Objectives*:	The aim of our study is to examine outcomes and pain control after surgery in patients who underwent laparoscopic inguinal hernia repair (IHR) with the use of perioperative transabdominal plane (TAP) block. Research Question: Does transabdominal plane block improve pain when undergoing inguinal hernia repair?
Endpoints*:	To evaluate whether preoperative TAP blocks improve pain score (primary end point) and decrease opioid use (secondary endpoint) after an inguinal hernia repair. Other end points- complications after surgery.
Study Population:	We will be enrolling 100 patients from Mount Sinai Hospital undergoing laparoscopic inguinal hernia repair.
Phase* or Stage:	
Description of Sites/Facilities Enrolling Participants:	All enrollment will occur at one site (Mount Sinai Hospital) at Faculty Practice Associates and Emergency Department.
Description of Study Intervention/Experimental Manipulation:	The study intervention is the administration of a TAP Block (0.25% bupivacaine or placebo (Saline). For patients weighing <100 kg, they will receive a total of 50 mL ((25 mL on each side of the abdominal wall). If patients weigh>100 kg, they will receive a total of 60 mL (30mL on each side of the abdominal wall). The TAP plane is identified using ultrasound. All anesthesiologists working with the surgical attendings involved in this study have been trained in this technique; it is a routine part of their practice. Anesthesiologists will be performing the block.
Study Duration*:	2 Years
Participant Duration:	2 Weeks

1.2 SCHEMA

1.3 SCHEDULE OF ACTIVITIES

2 INTRODUCTION

2.1 STUDY RATIONALE

Pain after surgery is common among patients. This pain may contribute to using of opioids and other medications to control discomfort and pain. Other clinical trial studies for hernias have shown potential benefit of a perioperative block on pain post-surgery. This investigation of using the TAP block peri-operatively will provide important information on pain control for the laparoscopic inguinal hernia repair.

2.2 BACKGROUND

Inguinal hernias are bulges in the groin region that arise from weaknesses in the abdominal wall. Often, due to discomfort, pain or cosmetic dissatisfaction, these hernias must be surgically repaired. The use of a transabdominal plane (TAP) block—a local injection of bupivacaine given in the abdomen to block pain receptors on nerves—during surgery can presumably decrease postoperative pain. Currently, TAP blocks are approved for use and performed based on surgeon preference (e.g. some surgeons perform them on every case, others variably, etc.). The aim of our study is to investigate whether the use of a TAP block can decrease the use of opioids and pain scores after surgery.

Papers - PMID: 27555193, 29605459, 25558340, 23060979 - have analyzed their data using chi-square test/ Fisher exact test and Student t-test/Wilcoxon Signed rank test. This method of analysis does not take into account longitudinal nature of the data. We will take into account the fact that same patient is being examined throughout the study at different time points. In addition to the above mentioned statistical procedures we will examine the trajectory between the TAP group vs. placebo group over time using mixed effects models (will also take into account correlation structure between different time points) for the outcome of opiate consumption and pain scores.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

There always exists the potential for loss of private information. There is also always the risk that the TAP block may not provide adequate analgesia.
There is also a risk of bowel perforation during TAP injection. However, this risk is minimal given that the bowel is well visualized with ultrasound guidance and thus avoided at all costs.
All injections of anesthetic carry a <1% risk of local anesthetic systemic toxicity (LAST) which can cause seizures or even cardiac arrest.

As all risks for harm are those included as part of standard treatments, there are no provisions for harm or injury. Any follow-up tests, treatments, or procedures will performed at cost to the participant.

2.3.2 KNOWN POTENTIAL BENEFITS

It is possible that the patient may receive no benefit from this study. However, benefits may include improved postoperative pain management, decreased opioid use and quicker return to normal function and daily activities.

The larger population will benefit from the increased knowledge of TAP use for hernia repair, allowing future patients with inguinal hernia to be more knowledgeable about the benefits and risks of this option.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

All physical risks for harm are those included as part of standard treatments, there are no added provisions for harm or injury due to the study. All information will be stored securely and in accordance with IRB policies and expectations. This treatment could prove beneficial to the patient and the larger public in terms of pain control and reducing opioid use.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
Primary			
Do TAP blocks improve pain score?	Change in pain score for the intervention versus placebo groups.	Assessing causal effect of TAP block on pain levels through the RCT design is the gold standard approach.	
Secondary			
Do TAP blocks decrease opioid and other pain medication use after surgery?	Assessing number/volume of pain medication.	TAP blocks should directly impact pain medications usage.	
Tertiary/Exploratory			
Does TAP block usage affect complications after surgery?	Assessing complication rate differences between the intervention and placebo groups with regards to complications.	Complications can differ based on treatment. We want to assess if complications rates differ between the two groups.	

4 STUDY DESIGN

4.1 OVERALL DESIGN

After receiving approval for the study, we will conduct a prospective single institution randomized clinical trial assessing if using a TAP block perioperatively can reduce pain scores after surgery. Other endpoints include whether there are differences in pain medication usage and complications.

Patients will be screened by research team members and attending surgeons. If the patient is interested, we will consent them for the study after they understand the study details, procedures, and expectations. We will then consent using IRB approved study consent forms and procedures. Patients will undergo a laparoscopic inguinal hernia repair according to standard procedures. Our study will assess if a TAP block impacts pain scores. Patients will be randomized to receive the intervention or placebo. Sequentially numbered sealed opaque envelopes with group allocation inside will alert the anesthesiologist/ surgeon to order Tap block composed of 0.25% bupivacaine or placebo (normal saline).

Inguinal hernia repair will be performed in standard fashion that each individual surgeon is familiar with. No additional tests or blood work outside the standard of care for IHR will be performed for research purposes. In addition, some patients will be given TAP blocks before surgery to help in pain management. In addition, patients will be discharged with a worksheet on which they are to record analgesic use and pain scores on postoperative days one, two, three and four. They are expected to bring the completed log to their two-week follow up visit with their surgeon. Patients may also expect to receive a phone call from a member of the surgical team to remind them to record these metrics.

The TAP block is done pre-procedure using 0.25% bupivacaine. If patients weigh<100 kg, they will receive a total of 50 mL (25 mL on each side of the abdominal wall). If patients weigh>100 kg, they will receive a total of 60 mL (30mL on each side of the abdominal wall). The TAP plane is identified using ultrasound. All anesthesiologists (not surgeons) working with the attendings involved in this study have been trained in this technique; it is a routine part of their practice. It is anesthesiologists who will be performing the block.

Patients will be discharged with a worksheet /survey on which they are to record analgesic use and pain scores on postoperative days one, two, three and four. They are expected to bring the completed log to their two-week follow up visit.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The double blinded randomized clinical trial is the gold standard design with causal implications of the intervention.

4.3 JUSTIFICATION FOR INTERVENTION

The one time perioperative mode of delivery for the intervention is best design and appropriate. Post-surgery patients will complete a worksheet for pain scores and pain medication. Study procedures will remain same for all patients.

4.4 END-OF-STUDY DEFINITION

End-of-study is defined as completing the intervention and any portion of worksheet. Study times are expected to take place during a 2 week time period.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Patients undergoing laparoscopic inguinal hernia repair at the Mount Sinai Hospital

5.2 EXCLUSION CRITERIA

Patients who are younger than 18 years old, have a history of chronic opiate usage, liver or kidney disease, pain syndromes, allergy to bupivacaine, are pregnant or are unable to independently give consent will be excluded from the study preoperatively.

Pregnant patients will be excluded due to safety of surgery and anesthetics in pregnant patients

5.3 LIFESTYLE CONSIDERATIONS

N/A

5.4 SCREEN FAILURES

Patients who do not receive the intervention or placebo.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

100 patients will be recruited at Mount Sinai Hospital who are scheduled to receive a laparoscopic inguinal hernia repair. Patients will be screened by research team members and attending physicians. Recruitment will occur if a patient is interested in the study and they meet the inclusion criteria and do not meet exclusion criteria. Potential patients will receive an explanation of study procedures and expectations. If they would like to participate, they will be consented according to standard procedures. Patients will be discharged with a worksheet that asks for pain levels and pain medication usage after their operation. They will be expected to bring the completed sheet during their post-operation follow up visit. There will be no incentives for participation in the study.

Given that patients will be enrolled in the clinic and the emergency department after presenting with a disease, they may be overwhelmed and may have limited time to process the risks and benefits of enrolling in this trial. To address the increased vulnerability as described above, we will train all persons involved in the consent process in best practices for consenting a patient. Ultimately, the physician will make the decision for enrollment.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

The study intervention is 0.25% bupivacaine. This neural block will be administered at the transabdominal plane. Other clinical trials have shown benefit of a neural block for hernia repairs on pain scores. We believe this intervention will work according to similar mechanism.

6.1.2 ADMINISTRATION AND/OR DOSING

Patients are randomized to receive one time administration of either 0.25% bupivacaine or normal saline. The TAP block is done pre-procedure using 0.25% bupivacaine. If patients weigh<100 kg, they will receive a total of 50 mL (25 mL on each side of the abdominal wall). If patients weigh>100 kg, they will receive a total of 60 mL (30mL on each side of the abdominal wall). The TAP plane is identified using ultrasound. All anesthesiologists (not surgeons) working with the attendings involved in this study have been trained in this technique; it is a routine part of their practice. It is anesthesiologists who will be performing the block.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

The intervention will be administered at one time point by an anesthesiologist who is trained to administer the medication.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

This is a double blinded study. Assignment of the intervention is made prior to the study beginning in pre-numbered envelopes at a 1:1 ratio to optimize power. The data analyst will not be aware of a treatment for any specific patient. Due to the same quantity of the placebo and intervention drug, the treatment should remain indistinguishable with regards to blinding.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

The intervention is completed during the surgery thus no adherence to intervention is required of the patient. The patient will complete a form describing pain score post-surgery and pain medications which will be tracked at the post-operation visit.

6.5 CONCOMITANT THERAPY

For this protocol, participants are not restricted to the pain medication they use. Rather, they are to record opioid based and over the counter medication used for pain control.

6.5.1 RESCUE THERAPY

There will no rescue therapy for this intervention.

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

The intervention will occur at one time point during surgery. There will be no discontinuation after therapy administration.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Patients may stop participating in the study at any time without penalty. This will not affect their ability to receive medical care at Mount Sinai or to receive any benefits to which they are otherwise entitled. Patients may withdraw permission for the use and disclosure of any protected information for research, but they must do so in writing to the Principal Investigator.

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Even if they withdraw permission, the Principal Investigator for the research study may still use the information that was collected if that information is necessary to complete the study. Patients' health information may still be used or shared after they withdraw authorization if they should have an adverse event from participating in the study.

The study doctor, the sponsor or the institution may terminate patients' involvement in this study at any time without the patient's consent. This may be because the study itself has stopped, the instructions of the study team have not been followed, the investigator believes it is in patients' best interest to be

withdrawn, or for any other appropriate reason. If specimens or data have been stored as part of the study, they too can be destroyed without patient consent.

7.3 LOST TO FOLLOW-UP

Before being considered lost to follow up, every attempt will be made by the investigator and/or the research team to contact the participant.

8 STUDY ASSESSMENTS AND PROCEDURES.

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

Study recruitment will include patients who are schedule for a laparoscopic inguinal hernia repair and meet the inclusion criteria but not the exclusion criteria. The screening will be completed by the research team and/or physician. If a patient is interested, they will be approached to consent for the study. If they are still interested and understand the study and its expectations, they will consent using standard consenting procedures. The intervention will be given perioperatively and the procedure will continue according to standard procedures. No deviation from standard care will be made for the inguinal hernia repair. The patient will be discharged with worksheet asking for pain scores and pain medication usage.

8.2 SAFETY ASSESSMENTS

As all procedures are according to standard of care, all parts of care will be administered and any complications and events will be tracked.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS.

8.3.1 DEFINITION OF ADVERSE EVENTS

Any adverse event as a result of the study intervention. As the intervention in study is a standard of care drug for pain, we do not expect adverse events.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

Serious adverse events as a result of the study intervention will be classified by the attendings. As the intervention in study is a standard of care drug for pain, we do not expect adverse events.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

Severity will be graded by the PI and attendings, if required.

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

Adverse events related of the study intervention will be classified as related or not related by the PI and other attendings.

8.3.3.3 EXPECTEDNESS

A clinician with appropriate expertise in anesthesiology/surgery 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 procedures.

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

After notification of an event, the PI will be alerted regarding the event to classify as related or unrelated to the intervention.

8.3.5 ADVERSE EVENT REPORTING

Adverse events due to study intervention will be reported to IRB.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

Serious adverse events due to study intervention will be reported to IRB.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

N/A

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

Pregnant women will be excluded from the study.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

N/A

8.4.2 UNANTICIPATED PROBLEMS REPORTING

N/A

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

N/A

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Endpoint(s):

We hypothesize that patients randomized to the intervention will be have lower pain scores as compared to the placebo arm.

- Secondary Endpoint(s):

We hypothesize that patients randomized to the intervention will have lower intake of opioid and as compared to the placebo arm.

9.2 SAMPLE SIZE DETERMINATION

Based on previous clinical trials using a pain medication intervention prior to surgery, our sample of 100 will be enough to detect a difference, should one exist. Moreover, the intervention and placebo will be administered randomly with an overall ratio of 1:1 to maximize power for analysis.

9.3 POPULATIONS FOR ANALYSES

Intention to treat analysis will be used for the study. Other sensitivity analyses will include analyses for treatment as administered.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

For descriptive analyses categorical variables will be described using the frequency and proportions. Continuous variables will be described using median and the interquartile range (Q1, Q3). All p-values of statistical tests will be two-tailed with a $p<0.05$ considered statistically significant.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

The primary endpoint of differences on pain score will be analyzed using the Wilcoxon rank sum test or Mann-Whitney U test.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The secondary endpoint will be assessed using either Chi-square, Fisher's exact, Mann Whitney U or the best test for the data.

9.4.4 SAFETY ANALYSES

N/A

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Demographic and pre-intervention variables will be described as following:
Categorical variables will be described using the frequency and proportions. Continuous variables will be described using median and the interquartile range (Q1, Q3). Chi-square or Fisher's test and Student's t-test or Mann-Whitney U test will be used depending on type of data.

9.4.6 PLANNED INTERIM ANALYSES

N/A

9.4.7 SUB-GROUP ANALYSES

N/A

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

No individual data will be presented.

9.4.9 EXPLORATORY ANALYSES

Other analyses that will occur will be compare types of complications and their rates between the intervention and placebo groups.

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 in detail the study intervention, study procedures, and risks will be given to the participant and written documentation of informed consent will be completed prior to starting the study intervention.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Adults will be consented after they receive information regarding the study and express interest. All procedures will be conducted according to institutional regulations.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

Study discontinuation may be as a result of PI choice and or as a result of the oversight committee of the IRB.

10.1.3 CONFIDENTIALITY AND PRIVACY

Data will be obtained using a patient medical record number and saved on a database to be analyzed at a later time. The research data will be stored under a random research code that will be linked to a subject's medical record number. It will be separate from the data collection sheet, which uses identifiable data. To reiterate: patient names and MRNs will not be used on this separate sheet. Each patient must be linked to their information to ensure the data is accurate and corresponds to the appropriate patient. In addition, information must be stored with identifiers in the event that an additional parameter of import is found at a later time and must be retrospectively obtained. Data will be stored on a computerized database with a unique code number not related to any subject identifiers. The link between the code and the data itself will be stored in separate locations. The code sheet will be kept on a separate password protected hard drive (another computer) that only listed investigators will have access to. Data files that are not stored on a server maintained by Mount Sinai's IT department will be encrypted. All files containing identifiers that are stored on a computer connected and managed by the Mount Sinai server will be password protected and restricted to the research team.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

There is no future use or storage of data after completion of the study.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator
Celia Divino, MD
Icahn School of Medicine at Mount Sinai
5 East 98th St, 15th Fl, New York, NY
212 241 6509
Celia.divino@mountsinai.org

Dr. Divino is the principal investigator and will be overlook all parts of recruitment, study procedures, and study execution. She has ample experience running multiple clinical trials.

10.1.6 SAFETY OVERSIGHT

The research team, the PI and other investigators will be responsible for oversight.

10.1.7 CLINICAL MONITORING

Clinical site monitoring will be 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 Council on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Quality management will occur with oversight of the PI and other investigators. The research team with regular meetings will discuss and keep appropriate quality for the study.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of the research members. The investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.
All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. Hard copies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant consented/enrolled in the study.

10.1.9.2 STUDY RECORDS RETENTION

Study records will be kept for no longer than 6 years after the study.

10.1.10 PROTOCOL DEVIATIONS

All protocol deviations will be recorded and reported to IRB.

10.1.11 PUBLICATION AND DATA SHARING POLICY

Data will not be shared with any other institutions or sites. All policies as required by the IRB.

10.1.12 CONFLICT OF INTEREST POLICY

All conflicts of interest will be reported to the IRB and FCOI committee.

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS AND SPECIAL TERMS

The list below includes abbreviations utilized in this template. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list). Special terms are those terms used in a specific way in the protocol. For instance, if the protocol has therapist-participants and patient-participants, those terms could be included here for purposes of consistency and specificity.

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
IB	Investigator's Brochure
ICH	International Council 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
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
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
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 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

11 REFERENCES