THE EFFECT OF PECTORAL BLOCKS ON PERIOPERATIVE PAIN IN SIMPLE MASTECTOMY AND BREAST REDUCTION IN GENDER AFFIRMATION SURGERY

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Protocol Synopsis

TITLE	THE EFFECT OF PECTORAL BLOCKS ON PERIOPERATIVE PAIN IN SIMPLE MASTECTOMY AND BREAST REDUCTION IN GENDER AFFIRMATION SURGERY
SPONSOR	Esther Kim, MD
FUNDING ORGANIZATION	N/A
NUMBER OF SITES	1
RATIONALE	Post operative pain as well as use of narcotics is a major concern for patients undergoing breast surgery. Regional anesthesia techniques have shown favorable results in oncologic breast surgeries but have not been studied in gender affirmation breast surgery.
STUDY DESIGN	Randomized, double-blind, placebo-controlled phase 4 study.
PRIMARY OBJECTIVE	Post operative pain scores
SECONDARY OBJECTIVES	Intraoperative and post operative opioid consumption, length of stay/time to discharge after surgery
NUMBER OF SUBJECTS	50
SUBJECT SELECTION CRITERIA	Inclusion Criteria: All ASA I-III transgender patients, ages 18-65, undergoing gender confirmation breast reduction surgery by a single surgeon at a single center Exclusion Criteria: previous breast surgeries, current breast cancer or history of treatment for breast cancer, current chronic pain syndromes, coagulopathy, allergy to local anesthetics, infection at the injection site
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	20ml 0.2 % Ropivacaine injected between pectoralis minor and serratus anterior. 10ml 0.2% Ropivacaine injected between pectoralis minor and pectoralis major
CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	20ml normal saline injected between pectoralis minor and serratus anterior. 10ml 0.2% Ropivacaine injected between pectoralis minor and pectoralis major

DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will be in the study for 1 week post surgery. The total duration of the study is expected to be 1 year.
CONCOMMITANT MEDICATIONS	Post operatively, only Norco (5mg/325mg) will be prescribed
EFFICACY EVALUATIONS	
PRIMARY ENDPOINT	• Post operative pain scores
SECONDARY ENDPOINTS	• Perioperative and postoperative opioid consumption • Length of stay/time to discharge
OTHER EVALUATIONS	None
SAFETY EVALUATIONS	Incidence of adverse events
PLANNED INTERIM ANALYSES	N/A
STATISTICS **Primary Analysis Plan**	Primary endpoint will use the Numeric Rating Scale for objective data on post operative pain. The mean and standard deviation for each group will be used to apply a standard t-test to assess for statistical significance between the two groups.
Rationale for Number of Subjects	Sample size was guided by existing studies in alternate populations with similar study designs. Experiments focusing on post operative pain in breast surgery using regional nerve blocks showed statistical significance with sample sizes ranging from 34 to 80 patients. It is our conclusion, with the aid of prior data, that this study can be sufficiently powered with 50 total participants.

1 BACKGROUND

Since first described in 2011, the Pecs 1, and more recently, Pecs 2 block, have been shown to be effective in reducing post operative pain in breast surgery. Additionally, the Pecs 1 and 2 block have had success with intraoperative pain reduction leading to a decrease in intraoperative narcotic requirements. However, all of the existing data is in the oncologic breast surgery population. No data exists on the efficacy of Pecs blocks on patients undergoing gender affirming breast reduction surgery. There is also limited data on the effect of pain beyond the immediate post operative period in patients who received the Pecs blocks. It is our belief that the Pecs 1 and 2 blocks will provide perioperative and post operative pain relief in this novel population as well and reduce post operative narcotic consumption.

1.1 Overview of Non-Clinical Studies

N/A

1.2 Overview of Clinical Studies

There is ample data showing PECS I and II blocks have efficacy in reducing pain scores as well as opioid consumption postoperatively various breast surgery populations.

2 STUDY RATIONALE

Existing data for PECS blocks is restricted to oncologic breast operations. There have been no studies done on perioperative pain control techniques in gender affirmation breast reduction operations. Understanding the efficacy of this intervention will help guide management for this population.

2.1 Risk / Benefit Assessment

Nerve blocks are performed under sterile conditions with topical application of chlorhexidine to minimize risk of infection. Ultrasound guidance is used to help avoid needle-to-nerve contact and intravascular injection of local anesthetic. Intravascular injection can also be avoided by frequent aspiration during local anesthetic injection. Visualization of local anesthetic spread around the desired nerve is highly predictive of a successful block.

In this study, the nerve blocks are performed in the operating room. In the operating room, the blocks are performed while vital signs are continuously monitored using non-invasive blood pressure monitoring and pulse oximetry. Emergency medications and equipment is readily available.

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective is to assess the efficacy of PECS blocks on pain control in gender affirmation breast reduction surgery.

3.2 Secondary Objectives

The secondary objective is to analyze the rates of opioid consumption in patients in this population receiving PECS blocks

4 STUDY DESIGN

4.1 Study Overview

This is a prospective, randomized controlled study of the preoperative PECS I and II block for patients undergoing gender affirmation breast surgery at UCSF. The enrolled patients will be randomized to receive either a PECS I and II block with local anesthetic ropivacaine, or have a sham block. All patients will receive general anesthetic for the breast reduction/simple mastectomy.

The patients will be assessed intra and post operatively. Our primary outcome will be the post operative pain scores using the Numeric Rating Scale (NRS). Secondary outcomes that will also be investigated include: Opioid requirements intraoperatively and post operatively, length of stay and time to discharge from recovery room.

Total duration of subject participation will be one week. Total duration of the study is expected to be 1 year

5 CRITERIA FOR EVALUATION

5.1 Primary Efficacy Endpoint

Reduction in NRS pain score by 2 points

5.2 Secondary Efficacy Endpoints

- Opioid Consumption: Reduction in postoperative opioid consumption by 20%
- Length of stay: Reduction in length of stay by 60 minutes

5.3 Safety Evaluations

- Incidence of adverse events

6 SUBJECT SELECTION

6.1 Study Population

Subjects with a diagnosis of gender dysphoria who meet the inclusion and exclusion criteria will be eligible for participation in this study.

6.2 Inclusion Criteria

1. Ages 18-65
2. ASA 1-3
3. Undergoing gender confirmation breast reduction surgery at UCSF by study surgeon

6.3 Exclusion Criteria

1. Previous breast surgery
2. Current breast cancer or history of treatment for breast cancer
3. Chronic pain syndromes
4. Coagulopathy
5. Allergy to local anesthetics
6. Infection at injection site

7 CONCURRENT MEDICATIONS

All subjects should be maintained on the same medications throughout the entire study period, as medically feasible, with no introduction of new chronic therapies.

7.1 Allowed Medications and Treatments

Standard therapy is allowed except for treatments noted in the exclusion criteria described above and as noted in the prohibited medications section below.

Prohibited Medications and Treatments

The following medications are prohibited during the study and administration will be considered a protocol violation.

- Narcotics not prescribed as part of the study

8 STUDY TREATMENTS

8.1 Method of Assigning Subjects to Treatment Groups

Patients will be randomized into a treatment group or control group using simple randomization. Due to the objectives of the study, the identity of test and control treatments will not be known to investigators, or patients. The following study procedures will be in place to ensure double-blind administration of study treatments. A computer-generated random number will be assigned to each patient. Even number will indicate treatment while odd number will indicate control group. The surgeon and the patient will be blinded. The study coordinator will communicate with the anesthesiologist which group the patients were allocated to and therefore which medication to administer.

The study blind will be broken on completion of the clinical study and after the study database has been locked.

During the study, the blind may be broken **only** in emergencies when knowledge of the patient's treatment group is necessary for further patient management.

8.1.1 Formulation of Test Product

Naropin is a formulation of Ropivacaine, developed by Fresenius Kabi, for local or regional anesthesia.

Formulation and Placebo

	Naropin	Placebo
Active Ingredient, mg/mL	Ropivacaine 2mg/mL	Normal (0.9%) Saline

8.1.2 Formulation of Control Product

A placebo solution (0.9% saline) will be used for those in the control group

8.1.3 Packaging and Labeling

There will be no alteration of the drug labeling or packaging. The surgeon will be kept blinded by refraining from discussion with the anesthesiologist as to which group the patients are allocated to. The surgeon will also be absent during the regional anesthetic procedure. Patients will be anesthetized during the regional anesthetic procedure and will not be told which group they were allocated to until the study is completed.

8.2 Supply of Study Drug at the Site

8.2.1 Dosage/Dosage Regimen

Group 1 (control) will receive an injection of 20ml of saline between the pectoralis minor and serratus anterior muscles bilaterally and 10ml of saline between the pectoralis minor and pectoralis major muscles bilaterally.

Group 2 (treatment) will receive an injection of 20ml of 0.2% Ropivacaine between the pectoralis minor and serratus anterior muscles bilaterally and 10ml of 0.2% Ropivacaine between the pectoralis minor and pectoralis major muscles bilaterally. (Not to exceed 225mg or 3.5mg/kg).

8.2.2 Dispensing

All injections (treatment group and control group) will be performed by qualified, certified anesthesiologist. No alterations to drug dispensing will be made.

8.2.3 Administration Instructions

Performed in the supine position with the arms abducted 90 degrees at the shoulder. Using an ultrasound transducer in the parasagital plane, the axillary artery and vein are identified just inferior to clavicle and medial to coracoid process. Additionally, the 2nd rib is identified and the transducer is slid inferiorly until the 3rd and 4th rib are identified. At this point the pectoralis major, minor, and serratus anterior muscles are seen. Then the block needle is inserted through the skin and advanced into the fascial plane between pectoralis minor and serratus anterior muscles. After negative aspiration, the anesthetic is injected into the plane watching for hydrodissection of the muscles. A total volume of 20ml is injected. Then the needed is withdrawn until the tip is located in the fascial plane between the pectoralis major and minor muscles. 10ml of anesthetic is injected into this plane.

8.3 Supply of Study Drug at the Site

8.3.1 Storage

No changes will be made to the current medication storage protocol

8.4 Study Drug Accountability

N/A

8.5 Measures of Treatment Compliance

N/A

9 STUDY PROCEDURES AND GUIDELINES

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject or subject's legal representative. If appropriate, assent must also be obtained prior to conducting any study-related activities.

9.1 Clinical Assessments

9.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at the clinic visit prior to surgery. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

9.1.2 Demographics

Demographic information (date of birth, gender, race) will be recorded.

9.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent respiratory history, and information regarding underlying diseases will be recorded.

9.1.4 Physical Examination

A complete physical examination will be performed by either the investigator or a subinvestigator who is a physician at the clinic visit prior to surgery. Qualified staff (MD, NP, RN, and PA) may complete the abbreviated physical exam at all other visits. New abnormal physical exam findings must be documented and will be followed by a physician or other qualified staff at the next scheduled visit.

9.1.5 Vital Signs

Body temperature, blood pressure, pulse and respirations will documented at each visit.

9.1.6 Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates and times), severity/grade, outcome, treatment and relation to study drug will be recorded on the case report form (CRF).

10 EVALUATIONS BY VISIT

10.1 Pre-operative clinic visit

1. Review the study with the subject (subject's legal representative) and obtain written informed consent and HIPAA authorization and assent, if appropriate.
2. Assign the subject a unique screening number.
3. Record demographics data.
4. Record medical history, including a history of XX, diagnosis date, and prior XX treatments.
5. Record concomitant medications.
6. Perform a complete physical examination.
7. Perform and record vital signs.
8. Perform and record results of blood pressure testing.
9. Schedule subject for surgery
10. Randomize subject

10.2 Date of Surgery

1. Come and go surgery with PECS block or placebo depending on randomization. Postoperatively, patients discharged with standardized pain regimen as well as pain diary. While still in PACU, patients will begin documenting pain scores.

10.3 Post operative appointment (1 week post op)

1. Record any Adverse Experiences and/or Review subject diary for adverse experiences.
2. Collect pain diary
3. Record changes to concomitant medications.
4. Perform physical examination.
5. Perform and record vital signs.

11 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

11.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An

unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. If the experience is not covered in the modified criteria, the guidelines shown in Table 1 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following the guidelines in Table 2.

Table 2. AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.

Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

11.2 Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

11.2.1 Serious Adverse Experience Reporting

Study sites will document all SAEs that occur (whether or not related to study drug) per UCSF CHR Guidelines. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the site investigator will report SAEs to the IRB/IEC.

11.3 Medical Monitoring

Esther Kim should be contacted directly at these numbers to report medical concerns or questions regarding safety.

Phone: 415-353-9392

12 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

12.1 Early Discontinuation of Study Drug

A subject may be discontinued from study treatment at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent (or assent)
- Subject is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment
- Protocol violation requiring discontinuation of study treatment
- Lost to follow-up
- Sponsor request for early termination of study
- Positive pregnancy test (females)

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects who discontinue study treatment should come in for an early discontinuation visit as soon as possible and then should be encouraged to complete all remaining scheduled visits and procedures.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

12.3 Withdrawal of Subjects from the Study

A subject may be withdrawn from the study at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

12.4 Replacement of Subjects

Subjects who withdraw from the study treatment will not be replaced.

Subjects who withdraw from the study will not be replaced.

13 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject, or investigator fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Use of a prohibited concomitant medication

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by a Sponsor representative and the Investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files.

14 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

14.1 Data Sets Analyzed

All eligible patients who are randomized into the study and receive either the study drug or placebo will be included in the safety analysis.

14.2 Demographic and Baseline Characteristics

The following demographic variables at screening will be summarized: age, height and weight.

14.3 Analysis of Primary Endpoint

The study design is a prospective two treatment parallel study. The primary outcome is Numeric Pain Rating pain scores postoperatively. Mean and standard deviation for each group for each time point will be calculated. A standard t-test to assess for statistical significance between the two groups will then be performed.

14.4 Analysis of Secondary Endpoints

A similar approach for all secondary endpoints will be performed to that of the primary endpoint. Opioid consumption, and time to discharge will be calculated for each group and the means and standard deviation will be used to perform a t-test.

14.5 Sample Size and Randomization

Sample size is guided by existing studies in alternate populations with similar study designs. Experiments focusing on postoperative pain in breast surgery using regional nerve blocks showed statistical significance with sample sizes ranging from 34-80 patients. It is our conclusion, with the aid of prior data, that this study can be sufficiently powered with 80 total patients.

15 DATA COLLECTION, RETENTION AND MONITORING

15.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) OR paper CRF when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a subject number and initials.

For eCRFs: If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail. *For paper CRFs:* If a correction is made on a CRF, the study staff member will line through the incorrect data, write in the correct data and initial and date the change.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will remain at the Investigator's site at the completion of the study.

15.2 Data Management Procedures

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

15.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Query reports (Data Clarification Requests) pertaining to data omissions and discrepancies will be forwarded to the Investigators and study monitors for resolution. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

15.4 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

15.5 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB/IEC, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the IND has been discontinued. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

15.6 Monitoring

Monitoring visits will be conducted by representatives of the Sponsor according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

15.7 Subject Confidentiality

In order to maintain subject confidentiality, only a subject number and subject initials will identify all study subjects on CRFs and other documentation submitted to the Sponsor. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

16 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

16.1 Protocol Amendments

Any amendment to the protocol will be written by the investigators. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

16.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB/IEC of each participating center prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB/IECs unconditional approval statement will be transmitted by the Investigator to designee prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

16.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to the IRB/IEC. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The Investigator will send an IRB/IEC-approved copy of the Informed Consent Form to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/IEC, assent from the subject will also be obtained. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form

(and assent) will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

16.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

16.5 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.