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Document:
Study protocol with statistical analysis plan

Official Study Title:
Evaluating the Feasibility of VR for Pediatric Renal Biopsies

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October 9, 2021

UCSF Department of Anesthesiology
Virtual Reality (VR) for Pediatric Renal Biopsy
Clinical Research Protocol

Protocol Number:	IRB#21-35095
Version Date:	10/9/2021
Sponsor:	UCSF Department of Anesthesiology
Funding Organization:	UCSF Department of Anesthesiology
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Approval:

_____ _____

PI or Sponsor Signature (Name and Title) *Date*

This confidential information about an investigational product is provided for the exclusive use of investigators of this product and is subject to recall at any time. The information in this document may not be disclosed unless federal or state law or regulations require such disclosure. Subject to the foregoing, this information may be disclosed only to those persons involved in the study who have a need to know, with the obligation not to further disseminate this information.

PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing the UCSF Department of Anesthesiology with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: 21-35095

Protocol Title: Evaluating the feasibility of virtual reality for procedural sedation in pediatric renal biopsy patients

Protocol Date: October 7, 2021

_____ _____

Investigator Signature *Date*

_____

Print Name and Title

Site # _____

Site Name _____

Address _____

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_____

_____

Phone Number _____

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PROTOCOL SYNOPSIS

TITLE	Evaluating the feasibility of virtual reality for procedural sedation in pediatric renal biopsy patients
SPONSOR	UCSF Department of Anesthesiology
FUNDING ORGANIZATION	UCSF Department of Anesthesiology
NUMBER OF SITES	1
RATIONALE	Pediatric renal biopsies at UCSF are currently performed with pharmacologic sedation or under general anesthesia (GA) to maximize patient comfort and anxiolysis. Although this has become standard practice, there are both short-term and long-term consequences for using sedation and GA, including aspiration, laryngospasm, and neurocognitive effects. Prior studies have evaluated alternatives to pharmacologic sedation for minor medical procedures in pediatric patients, including acupressure, aromatherapy, hypnosis, and music therapy. Virtual reality (VR) is a low-cost and commercially available distraction tool that engages the user in an immersive and interactive experience. Prior studies have evaluated the potential role of VR in reducing pain and anxiety associated with IV placement, port access, induction of GA, and IUD placement. Renal biopsies are a relatively non-invasive and common pediatric procedure performed among patients admitted for transplant surveillance or evaluation. To our knowledge, there have been no studies to assess the use of VR as an alternative to pharmacologic sedation for pediatric renal biopsies. The aim of this study is to assess the feasibility of using VR to successfully complete renal biopsies in renal transplant patients as an adjunct to reduce or eliminate the need for pharmacologic sedation. In addition, secondary aims include assessing patient pain and anxiety, safety of the procedure, and patient/parent/provider satisfaction.
STUDY DESIGN	The proposed study is a feasibility study / non-randomized prospective study.
PRIMARY OBJECTIVE	The primary aim of the study is to assess if use of VR eliminates or reduces the need for intravenous pharmacologic sedation for children undergoing renal biopsy.
SECONDARY OBJECTIVES	Secondary aims include assessing patient pain and anxiety, safety of the procedure, and patient/parent/provider satisfaction.
NUMBER OF SUBJECTS	32
SUBJECT SELECTION CRITERIA	<u>Inclusion Criteria</u>: *For pediatric renal biopsy patients:* - Patients age 5-17 receiving a renal biopsy at UCSF Benioff Children's Hospital

	For providers: - The pediatric hospitalist and sedation nurse participating in the renal biopsy Exclusion Criteria: *For pediatric renal biopsy patients:* - Patients who cannot lie supine for their renal biopsy - Patients with injuries to the head/face that would prohibit wearing a headset - Patients with loss of consciousness, altered mental status, life-threatening injuries/illness or multi-trauma - Patients with open skin, lice, scabies, or other infectious skin conditions on the head/face - Patients with a history of or current symptoms of vertigo - Patients who are blind - Patients with significant developmental or cognitive delays who may not be able to engage with or tolerate the virtual reality environment, as determined by their parent/caregiver - Patients on whom the VR headset does not fit appropriately *For providers:* - Providers who cannot use the pain and anxiety scales provide - Providers with a personal relationship to the patient/caregivers
TEST PRODUCT	The study will use the Samsung Gear VR headset. The headset displays a preselected, interactive game that features an animated animal character moving through a landscape.
CONTROL PRODUCT	None
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Each renal biopsy takes approximately 30 minutes to complete, which should not be significantly different with the VR headset. Subject participation is limited to the periprocedural times; there are no other requirements to participate in the study. Subjects will be recruited throughout the year from the pool of patients being admitted for their renal biopsies at UCSF Benioff Children's Hospital. Approximately 75 to 100 pediatric renal biopsies are performed annually at UCSF, so the study is anticipated to be completed in less than one year to meet the recruitment goal of 32 subjects.
CONCOMITANT MEDICATIONS	Allowed: Standard of care local and intravenous sedation medications (e.g., fentanyl, midazolam) Prohibited: General anesthesia
PRIMARY ENDPOINT	Total sedation requirement in pediatric patients undergoing renal biopsy using VR

SECONDARY ENDPOINTS	- Patient pre- and post-procedural pain [assessed by Observation Scale of Behavioral Distress (OSBD) 11-point behavioral scale] - Patient pre- and post-procedural anxiety [assessed by Children's Fear Scale (CFS 0-4 scale), Childhood Anxiety Meter (CAM 0-10 scale)]
SAFETY EVALUATIONS	Will monitor continuously for incidence of adverse events (hypoxemia, hemodynamic instability, severe pain)
STATISTICS Primary Analysis Plan	Continuous and categorical variables will be analyzed using the student's *t* test and Chi-squared test.
Rationale for Number of Subjects	The investigators are primarily interested in precise estimates of feasibility and acceptability, as well as outcome variability that will aid in the planning of a larger, sufficiently powered efficacy trial. A sample size of 32 per group will allow the team to be relatively precise in our conclusions regarding feasibility outcomes. For example, if there is a 15% attrition rate out of the 32 enrolled in the intervention group, the 95% CI for that rate would be (2.6%, 27.4%).

1 BACKGROUND AND STUDY RATIONALE

Pediatric renal biopsies at UCSF are currently performed with pharmacologic sedation or under general anesthesia (GA) to maximize patient comfort and anxiolysis. Although this has become standard practice, there are both short-term and long-term consequences for using sedation and GA, including aspiration, laryngospasm, and neurocognitive effects. Prior studies have evaluated alternatives to pharmacologic sedation for minor medical procedures in pediatric patients, including acupressure, aromatherapy, hypnosis, and music therapy.

To the investigators' knowledge, there have been no studies to assess the use of VR as an alternative to pharmacologic sedation for pediatric renal biopsies. Virtual reality (VR) is a low-cost and commercially available distraction tool that engages the user in an immersive and interactive experience. Prior studies have evaluated the potential role of VR in reducing pain and anxiety associated with IV placement, port access, induction of GA, and IUD placement. Renal biopsies are a relatively non-invasive and common pediatric procedure performed among patients admitted for transplant surveillance or evaluation.

1.1 Risk / Benefit Assessment

With regards to the VR experience itself, there are no common side effects of using the VR headset and experiencing the VR environment. Rare side effects include headache, nausea, and dizziness. Risk and discomfort will be minimized as the intervention utilizes a non-invasive, non-pharmacological VR headset application. The study is conducted by trained personnel and designed to use a method that may reduce periprocedural pain and anxiety by providing audiovisual distraction.

There is some risk that those subjects who elect to use the VR headset without any additional pharmacologic sedation may experience more pain than those who use the VR headset in addition to pharmacologic sedation. The risk of additional pain will be minimized through a number of interventions. First, standard of care local anesthesia will be used at the biopsy site regardless of the amount of intravenous sedation. In addition, all standard of care intravenous sedation medications will be available throughout the biopsy, and the same experienced sedation nurse will perform the sedation for all the biopsies and continuously monitor pain through a validated pain scale. Subjects or their parents may request these sedation medications at any time, and they may also be administered by the providers at their discretion.

While the risks of pain and discomfort are somewhat unique to the VR intervention, they also still exist in all children undergoing renal biopsies even with standard of care intravenous sedation. That is, there always exists the possibility that sedation medications may be under-dosed or rescue doses will need to be provided to achieve adequate analgesia and anxiolysis. With the administration of local anesthesia as well as availability and rapid onset of action of available intravenous sedation medications, there is no significant added risk to those patients using the VR headset compared to the standard of care.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to assess the feasibility of using VR to successfully complete renal biopsies in renal transplant patients as an adjunct to reduce or eliminate the need for pharmacologic sedation.

2.2 Secondary Objectives

The secondary objectives of this study include assessing patient pain and anxiety, safety of the procedure, and patient/parent/provider satisfaction.

3 STUDY DESIGN

3.1 Study Overview

In this nonrandomized feasibility study, children aged 5-17 scheduled for routine renal biopsy at UCSF Benioff Children's Hospital will be offered the option to use a virtual reality (VR) headset as part of their renal biopsy experience. They will be oriented to the VR environment and headset when they arrive at the hospital prior to going to the procedure room for the biopsy. The VR experience will be the same for all patients participating in the study. The study will utilize a Samsung Gear VR headset that displays a preselected, interactive game that features an animated animal character moving through a landscape. The standard of care of sedation medications will still be available to patients who are unable to complete the procedure with only the VR headset without pharmacologic sedation. Pain and anxiety will be monitored continuously using validated scales by a pediatric hospitalist and sedation nurse who routinely perform these procedures. These providers, as well as patients and parents, may ask for additional medications for adequate analgesia and anxiolysis. All renal biopsies conducted during this study will be performed as medically indicated by the patients' routine care, and no additional biopsies will be performed for the purpose of assessing the utility of VR.

Pre- and post-procedural anxiety and pain, as well as satisfaction with the VR experience, will be assessed from the patient, parent(s)/caregiver(s), and providers. In addition, all study subjects will be continuously monitored as per standard of care throughout the procedure (including heart rate, respiratory rate and oxygen saturation), as well as total exposure to pharmacologic sedation medications and recovery time. The Children's Fear Scale (CFS 0-4 scale), Childhood Anxiety Meter (CAM 0-10 scale), and Observation Scale of Behavioral Distress (OSBD 11-point behavioral scale) are validated tools to assess pediatric anxiety and pain. As far as parent and provider experience, the additional survey questions are included in the attached study documents.

4 CRITERIA FOR EVALUATION

4.1 Primary Endpoint

The primary endpoint of the study is the reduction in the required dose of pharmacologic sedation for each subject. The cumulative sedation required for each patient (in mg/kg) will be compared to the standard of care, and patients receiving repeat biopsies will have

their cumulative sedation requirement for the biopsy with VR compared to their most recent prior biopsy without VR.

4.2 Secondary Endpoints

The secondary endpoints of the study are pain and anxiety, as well as subject, caregiver, and provider satisfaction. Pain and anxiety will be assessed using the following validated tools: the Children's Fear Scale (CFS 0-4 scale), Childhood Anxiety Meter (CAM 0-10 scale), and Observation Scale of Behavioral Distress (OSBD 11-point behavioral scale). Subjects, caregivers, and providers will also receive a post-procedural survey to assess the impact and feasibility of the VR intervention.

5 SUBJECT SELECTION

5.1 Study Population

Subjects undergoing a renal biopsy at UCSF Benioff Children's Hospital who meet the inclusion and exclusion criteria will be eligible for participation in this study.

5.2 Inclusion Criteria

1. Children ages 5-17 undergoing a renal biopsy at UCSF Benioff Children's Hospital

5.3 Exclusion Criteria

For pediatric renal biopsy patients:

1. Patients who cannot lie supine for their renal biopsy
2. Patients with injuries to the head/face that would prohibit wearing a headset
3. Patients with loss of consciousness, altered mental status, life-threatening injuries/illness or multi-trauma
4. Patients with open skin, lice, scabies, or other infectious skin conditions on the head/face
5. Patients with a history of or current symptoms of vertigo
6. Patients who are blind
7. Patients with significant developmental or cognitive delays who may not be able to engage with or tolerate the virtual reality environment, as determined by their parent/caregiver
8. Patients on whom the VR headset does not fit appropriately

For providers:

1. Providers who cannot use the pain and anxiety scales provide
2. Providers with a personal relationship to the patient and/or caregivers

6 CONCURRENT MEDICATIONS

6.1 Allowed Medications and Treatments

Local anesthesia will be administered at the biopsy site for all patients regardless of the additional sedation they may require in addition to the VR headset. Standard of care intravenous sedation medications will be available to all patients participating in the study

and may be requested by the patient or caregiver or administered at the discretion of the sedation/biopsy providers.

6.2 Prohibited Medications and Treatments

General anesthesia induction medications are prohibited, and any concurrent biopsies or treatments other than a renal biopsy are also prohibited.

7 STUDY TREATMENTS

7.1 Method of Assigning Subjects to Treatment Groups

Due to the objectives of this feasibility study and the nature of the VR intervention, the study subjects will be non-randomized and the subjects and providers will be non-blinded. A larger randomized (though also non-blinded) trial is a potential future goal of the research team.

7.2 Supply and Storage of VR Headset

The UCSF Department of Anesthesiology has access to two Samsung Gear VR Headsets that are stored at UCSF Benioff Children's Hospital. The devices will remain stored there and will be accessed as needed for the study. The headsets will be re-configured to ensure they are still functional and sanitized prior to re-use with each biopsy. There should not be issues with supply of the headsets since no more than 4 renal biopsies are conducted per week at UCSF Benioff Children's Hospital and none occur simultaneously.

8 STUDY PROCEDURES AND GUIDELINES

The study procedures are diagrammed in Appendix 1.

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

8.1 Clinical Assessments

8.1.1 Medical History

All pertinent medical history, including prior sedation requirements, comorbid depression/anxiety, and

8.1.2 Demographics

Demographic information (date of birth, gender, race) will be confirmed from the patient medical record.

8.1.3 Vital Signs

Vital signs (heart rate, respiratory rate, blood pressure, pulse oximetry) will be monitored continuously throughout the renal biopsy as per the standard of care.

9 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

9.1 Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration, outcome, and severity of these events will be reported as appropriate using the iRIS Adverse Event Reporting Form per the federal guidelines issues by the Office of Human Research Protections (OHRP).

9.2 Medical Monitoring

Omar Salman, MD should be contacted directly at these numbers to report medical concerns or questions regarding safety.

Phone: (415) 514-1815
Pager: (415) 443-3434

10 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

10.1 Early Discontinuation of VR Experience

A subject may be discontinued from the VR intervention at any time if the subject, their caregiver, the investigator, or any of the providers feel 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
- 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

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 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 Refer to Section 10 for early termination procedures.

10.2 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.

11 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

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.

12 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.

12.1 Demographic and Baseline Characteristics

The following demographic variables will be obtained: race, gender, age, medical comorbidities.

12.2 Analysis of Primary Endpoint

Cumulative sedation administered with the use of VR (in mg/kg) will be compared to the standard dose administered using the student's *t* test. For subjects receiving a repeat biopsy, the student's *t* test will be used to compare their sedation needs with the VR experience compared to their most recent prior biopsy without VR.

12.3 Analysis of Secondary Endpoints

Pre- and post-procedure pain and anxiety as measured on the scales mentioned above will be analyzed using the student's *t* test and Chi-squared test.

12.4 Sample Size and Randomization

The investigators are primarily interested in precise estimates of feasibility and acceptability, as well as outcome variability that will aid in the planning of a larger, sufficiently powered efficacy trial. A sample size of 32 per group will allow the team to be relatively precise in our conclusions regarding feasibility outcomes. For example, if there is a 15% attrition rate out of the 32 enrolled in the intervention group, the 95% CI for that rate would be (2.6%, 27.4%). Given the nature of this feasibility study, subjects will not be randomized.

13 DATA COLLECTION, RETENTION AND MONITORING

The investigators will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject who participates in the study. All other information shall remain in the electronic health record (EHR), which is secured by the University of California, San Francisco. Subjects will not be identified by name in any study documents to be collected by the UCSF Department of Anesthesiology (or designee), but will be identified by subject number.

13.1 Data Management Procedures

The data will be entered into a validated database. 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.

13.2 Availability and Retention of Investigational Records

The Investigators will 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 will be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigators will ensure the reliability and availability of source documents. All study documents will be kept secured in a locked file cabinet within the UCSF Department of Anesthesiology for 3 years per federal guidelines.

13.3 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 Investigators grant permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

13.4 Subject Confidentiality

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

14 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 Investigators will also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

14.1 Protocol Amendments

Any amendment to the protocol will be written by the UCSF Department of Anesthesiology. 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.

14.2 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 Investigators will keep the IRB/IEC informed as to the progress of the study. The Investigators 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, Investigators' 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 Investigators before the study is initiated. The IRB/IECs unconditional approval statement will be transmitted by the Investigators to the UCSF Department of Anesthesiology prior to the shipment of study supplies to the site. This approval will refer to the study by exact protocol title and number and will 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 will be obtained.

The IRB/IEC will 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.

14.3 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 Investigators have prepared an informed consent form, assent and HIPAA authorization and have submitted these documents to the study sponsor and IRB/IEC. The written consent document embodies the elements of informed consent as described in the International Conference on Harmonization and also complies with local regulations. The Investigator will send an IRB/IEC-approved copy of the Informed Consent Form to the Sponsor 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 will be given in both oral and written form and subjects (or their legal representatives) will 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.

14.4 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.

14.5 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 UCSF Department of Anesthesiology (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.

APPENDIX 1. VR STUDY METHODOLOGY