For Committee Use Only
PROTOCOL NUMBER

Human Subjects Research Protocol

The Common Human Subjects Protocol Cover Form **must** be completed and **attached** to the front of this form. This Protocol form should be completed for any human subjects research proposal that does not have a specific "protocol," such as a grant application. This form must be submitted along with a copy of the complete grant proposal and all the information in this form **must** be consistent with that proposal. This protocol form, once IRB approved, will be the working protocol for that research. **When completing this document, do not refer to page numbers within your grant**. If revisions are necessary during the course of the research, amendments should refer to this protocol form, not the grant proposal. Enter responses for all sections. Check N/A if the section does not apply.

PROTOCOL SUMMARY

Project Title: Protocol Version Date:

Does precise delivery of remifentanil decrease coughing at emergence from anesthesia?	04/10/2018

Principal Investigator: Elie Sarraf, MDCM

Grant Sponsor: Grant Number:

(For grants routed through UVM, indicate the OSP Proposal ID # located at the top of the OSP Routing Form)

Lay Language Summary: *(Please use non-technical language that would be understood by nonscientific IRB members to summarize the proposed research project. The information must include: (1) a brief statement of the problem and related theory supporting the intent of the study, and (2) a brief but specific description of the procedure(s) involving the human subjects. Please do not exceed one single-spaced 8 ½ X 11" page.)*

(1) At the end of surgical procedures, for patient who have had general anesthesia, an endotracheal tube (ETT) is removed ("extubation") from a patient's windpipe prior to transportation from the operating room to the recovery room. It is common, but not dangerous, for a patient to cough just prior to the removal of the ETT. However, there are occasions where the avoidance of cough is important to ensure a good surgical outcome, specifically during certain eye operations and operations that involve the neck, where coughing can cause bleeding into the site of surgery. This may cause harm to the patient and may potentially require a new surgical procedure.

Many methods have been proposed to avoid coughing during extubation with variable success rates. The most promising method involves using remifentanil, an ultra-short acting opioid, with an advanced medication-delivery system that is not available in the U.S. We have recently demonstrated how to replicate the performance of this system using a standard medication pump and an algorithm that can be run on a spreadsheet or mobile app.

(2) The purpose of this study is to determine whether using remifentanil with our algorithm can in fact decrease or prevent coughing around the time of extubation. For eligible patients we will randomly administer remifentanil or a placebo in their intravenous line at the time that surgery is concluding. An independent observer will then determine whether or not the patient coughed at the end of surgery and qualify the intensity of the cough.

PURPOSE AND OBJECTIVES

Purpose: *The importance of the research and the potential knowledge to be gained should be explained in detail. Give background information.*

At the end of surgical procedures, for patients who have had general anesthesia, an endotracheal tube (ETT) is removed ("extubation") from a patient's trachea during emergence from general anesthesia. Extubation can be performed either while the patient remains deeply anesthetized or, more commonly, when the patient has a return of protective airway reflexes. These reflexes include coughing as a result of the stimulation from the ETT on the glottis and the trachea. While it is common for coughing to occur, it is usually not dangerous and has minimal effect on surgical outcomes. However, there are certain surgical procedures where coughing can have a detrimental effect. Examples that have been reported included bleeding into the neck

following ear, nose, and throat surgery, which can cause compression of the trachea; and bleeding into the retina following ophthalmological procedures.

Of all the different methods described in the literature, only the administration of remifentanil, an ultra-short-acting opioid, showed any promise at decreasing the occurrence of coughing on emergence. All the published studies described using remifentanil with a target-controlled-infusion (TCI) pump in order to achieve a specific concentration of the medication at its site of action ("effect site concentration"). In fact, most studies [1-6 and 8-9] recommend achieving a target effect site concentration from 1.5 to 2.5 ng/mL with varying levels of success achieved. Lee [1] identified that an effect site concentration of 2.14 ng/mL would have a 95% success at preventing coughing. A single study [7] described giving a bolus of remifentanil but was unsuccessful at decreasing the incidence and frequency of coughing. These studies are not able to be replicated in the United States as TCI pumps are not cleared for use by the FDA. No modern TCI pump manufacturer has filed or is likely to file an application with the FDA, and hence the pumps are not available for use in the U.S.

Remifentanil is particularly useful medication for this application given its safety profile and duration of action. Per the drug label information as submitted to the FDA, spontaneous respiration occurs at blood concentrations of 4 to 5 ng/mL in the absence of other anesthetic agents [10]. (This is twice the dose that will be administered in this study, and while other opioids may be prescribed with the potential to cause respiratory depression, in this study extubation will only occur once sufficient ventilation is demonstrated by the patient. Should respiratory depression or emergence from anesthesia cause more than 15 minutes of delay from the end of the case, the remifentanil infusion will be stopped). In addition, recovery from anesthesia was rapid, predictable, and independent of the duration of the infusion [10] with a rapid elimination rate: the context-sensitive half-times is approximately 3 to 6 minutes. In the manufacturer clinical submission, no case of remifentanil-induced delayed respiratory depression occurring more than 30 minutes after discontinuation of remifentanil was found[10]. Finally, the addition of supplemental opiates for post-operative pain control did not delay recovery of respiratory drive in patients undergoing major surgery with remifentanil-propofol total IV anesthesia [10].

The reason why using a TCI pump is necessary for this goal is due to the need for a precise therapeutic window for the opioid: insufficient dose will result in inadequate effect, and excess dose can lead to respiratory depression and prolonged emergence from anesthesia. While there is a certain amount of variability in the pharmacokinetics of drugs within a population, using a TCI pump will decrease the variability [11], therefore allowing for more accurate titration of the drug. This is one of the reasons why the studies that used TCI pumps [1-6] and [8-9] were successful at preventing coughing while the study that used bolus dosing alone [7] was not.

Understanding the pharmacokinetic properties of remifentanil, we have created an algorithm that can be implemented on a spreadsheet and which can be programed into a standard infusion pump in a manner that remains consistent with its direction for use. The algorithm calculates a remifentanil bolus and infusion rate, based on the patient's characteristics (age, weight, height and sex), that can achieve a desired effect site concentration. While not being a TCI system proper, we have demonstrated though simulation that this algorithm can reasonably replicate the performance of a Target Controlled Infusion pump[12]. This would negate the need for specialized devices and allow U.S. anesthesiologists access to a technology the rest of the world has employed safely for two decades. This algorithm and available to use and download for free at the following website: http://bit.ly/2lXH0m8. The purpose of our study is to determine whether our algorithm can prevent coughing with emergence and replicate the results obtained previously with a TCI pump.

References. *Include references to prior human or animal research and references that are relevant to the design and conduct of the study.*

(1) Lee B; Lee JR; Na S. Targeting smooth emergence: the effect site concentration of remifentanil for preventing cough during emergence during propofol-remifentanil anaesthesia for thyroid surgery. British Journal of Anaesthesia. 102(6):775-8, 2009 Jun.

(2) Nho JS; Lee SY; Kang JM; Kim MC; Choi YK; Shin OY; Kim DS; Kwon MI. Effects of maintaining a remifentanil infusion on the recovery profiles during emergence from anaesthesia and tracheal extubation. British Journal of Anaesthesia. 103(6):817-21, 2009 Dec.

(3) Chen J; Li W; Wang D; Hu X. The effect of remifentanil on cough suppression after endoscopic sinus surgery: a randomized study. Acta Anaesthesiologica Scandinavica. 54(10):1197-203, 2010 Nov.

(4) Lee JH; Koo BN; Jeong JJ; Kim HS; Lee JR. Differential effects of lidocaine and remifentanil on response to the tracheal tube during emergence from general anaesthesia. British Journal of Anaesthesia. 106(3):410-5, 2011 Mar.

(5) Kim H; Choi SH; Choi YS; Lee JH; Kim NO; Lee JR. Comparison of the antitussive effect of remifentanil during recovery from propofol and sevoflurane anaesthesia. Anaesthesia. 67(7):765-70, 2012 Jul.

(6) Chang CH; Lee JW; Choi JR; Shim YH. Effect-site concentration of remifentanil to prevent cough after laryngomicrosurgery. Laryngoscope. 123(12):3105-9, 2013 Dec.

(7) Mahoori A; Noroozinia H; Hasani E; Karami N; Pashaei N; Hatami S. The effect of low-dose remifentanil on the hemodynamic responses of endotracheal extubation. Acta Medica Iranica. 52(11):844-7, 2014.

(8) Soh S; Park WK; Kang SW; Lee BR; Lee JR. Sex differences in remifentanil requirements for preventing cough during anesthetic emergence. Yonsei Medical Journal. 55(3):807-14, 2014 May.

(9) Kim H; Min KT; Lee JR; Ha SH; Lee WK; Seo JH; Choi SH. Comparison of Dexmedetomidine and Remifentanil on Airway Reflex and Hemodynamic Changes during Recovery after Craniotomy. Yonsei Medical Journal. 57(4):980-6, 2016 Jul.

(10) ULTIVA (R) [package insert]. Mylan Institutional LLC, Rockford,Il; December 2016. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=dbc63b6e-f8c5-4fd0-8ec3-4f5e19125313#ID_5bc811da-9953-4a8a-8c6c-ae118f11553d. Accessed Oct 25, 2017.

(11) Hu C; Horstman DJ; Shafer SL. Variability of Target-controlled Infusion Is Less Than the Variability after Bolus Injection. Anesthes102(3):639-645, 2005 Mar.
(12) Sarraf E; Mathews DM. Building a Simplified Remifentanil Target Controlled Infusion System. ASA abstract in press (October 2017)

Objectives: *Clearly state the primary and secondary objective(s) of the study.*

Primary objective: Demonstrate that the algorithm implemented to titrate remifentanil to a concentration of 2.1 ng/mL can decrease the incidence of coughing compared to placebo during emergence from general anesthesia with endotracheal intubation.

Secondary objectives:
1) Measure the intensity of coughing
2) Measure the presence of any respiratory depression requiring intervention
3) Measure the time to emergence from anesthesia

METHODS AND PROCEDURES

Study Design: *Describe the research design, including a description of any new methodology and its advantage over existing methodologies.*

Two-arm randomized placebo-controlled trial.

Procedures: *Describe all procedures (sequentially) to which human participants will be subjected. Identify all procedures that are considered experimental and/or procedures performed exclusively for research purposes. Describe the types, frequency and duration of tests, study visits, interviews, questionnaires, etc. Include required screening procedures performed before enrollment and while on study. Please provide in table, list or outline format for ease of review. (describe and attach all instruments)*

Note: A clinical research protocol may involve interventions that are strictly experimental or it may involve some aspect of research (e.g., randomization among standard treatments for collection and analysis of routine clinical data for research purposes). It is important for this section to distinguish between interventions that are experimental and/or carried out for research purposes versus those procedures that are considered standard therapy. In addition, routine procedures performed solely for research purposes (e.g., additional diagnostic/follow-up tests) should be identified.

All patients between the ages of 18 and 80 with an ASA of 1-3 who will be undergoing elective thyroidectomy (partial or complete), parathyroidectomy, or ophthalmological surgery requiring intubation will be eligible for this study. Exclusion criteria include patients with a Lean Body Mass < 20 kg, BMI > 45, the presence of pulmonary dysfunction, any allergy to opioids and patients requiring the use of total intravenous anesthesia. The anesthesia provider may also exclude a patient from the study at any point in time if the provider has concerns for the patient's safety including an inability or expected difficulty with ventilation.

Study coordinators will identify and consent the appropriate patient on the day of surgery. Patient who agree to participate in the study will be randomized to receiving either a placebo or remifentanil in a syringe that will be blinded to the patient, the clinicians in the room as well as the study coordinator. Once the patient is in the OR, the setup which includes the syringe, the BBraun Perfusor Space syringe pump and extension tubing will be connected the IV tubing at the most proximal port to the patient. The study coordinators will then input the patient's characteristic into the spreadsheet containing the algorithm, set for a goal remifentanil effect site concentration of 2.1 ng/mL, and program the syringe pump under the guidance and supervision of anesthesia provider in the room. The study pump will be maintained in a "standby" mode until activated as described below. During the induction and maintenance of anesthesia, the provider has full liberty to manage the anesthetic plan.

In approximately the last 5-30 minutes of surgery, as identified by the surgeon, the infusion pump will start infusing as was previously programmed. Patients whose surgery will end less than 5 minutes prior to the start of infusion, or, patients who will be extubated while deeply anesthetized will be excluded from the study and will not receive any of study drug or placebo. At the conclusion of the surgery, the anesthetic gases will be discontinued, any neuromuscular blocking agent reversed, and, when clinically indicated the patient will be extubated and monitored for adequate respiratory effort. The infusion will be terminated either when the patient is extubated, or at 15 minutes after the start of anesthetic washout. Anesthetic washout occurs at the end of surgery when the anesthetic gases are turned off and high flows of oxygen are administered to purge the residual anesthetic from the system and the patient. The anesthesia provider will ensure suitability for transfer to the post-anesthesia care unit at all times as per usual clinical practice. The study period will conclude once the patient is discharged from direct anesthesia care.

The study coordinators will be tasked with documenting:
1) The incidence of cough
2) If coughing present, the cough will be graded according to the following scoring guidelines:
   a. 0=no cough
   b. 1=slight cough, cough without obvious contraction of the abdomen
   c. 2=moderate cough, strong and sudden contraction of the abdomen lasting for less than 5 seconds

d. 3=severe cough, strong and sudden contraction of the abdomen sustained for more than 5 seconds.

The above scoring will be assessed at the following four stages of extubation:
a. eyes opening on verbal commands
b. tracheal cuff deflation
c. tracheal extubation
d. 1 min after extubation.

3) Extubation time: time between the termination of the anesthetic and extubation
4) Time to recovery: time between extubation and the ability to perform purposeful movement (e.g. squeeze hand, thumbs up. Anesthesia providers ask patients to perform a purposeful movement as part of routine care.)
5) Adverse events including hypoxemia despite oxygen supplementation and other respiratory complications such as laryngospasm, upper airway obstruction requiring intervention: bag mask ventilation, oral or nasal airway insertion.

Also documented will be the duration of the infusion and quantity of drug administered.

For research involving survey, questionnaires, etc.: *Describe the setting and the mode of administering the instrument and the provisions for maintaining privacy and confidentiality. Include the duration, intervals of administration, and overall length of participation. (describe and attach all instruments)*

x ***Not applicable***

Statistical Considerations: *Delineate the precise outcomes to be measured and analyzed. Describe how these results will be measured and statistically analyzed. Delineate methods used to estimate the required number of subjects. Describe power calculations if the study involves comparisons. Perform this analysis on each of the primary and secondary objectives, if possible.*

As this a comparative study, the measure outcomes described above will compared as follows:

1) The incidence of cough will be analyzed with a Fisher Exact Test
2) The coughing grade will be analyzed with a Mann-Whitney U test
3) Extubation time and time to recovery will be analyzed with an unpaired t-test, if appropriate
4) Adverse events will be categorized and then analyzed with a Fisher Exact Test

With coughing incidence at baseline expected to be approximately 70% and a target incidence of 30%, we would need to recruit 50 patients in order to achieve an alpha or 0.05 and power of 0.9. Accounting for an exclusion of 20% (deep extubation, improper notice, failure to properly connect the system prior to the start of the case, decision by anesthesiologist to exclude patient, etc.), 60 patients would need to be recruited for this study. We will recruit 60 patients for this study.

Risks/Benefits: *Describe any potential or known risks. This includes physical, psychological, social, legal or other risks. Estimate the probability that given risk may occur, its severity and potential reversibility. If the study involves a placebo or washout period, the risks related to these must be addressed in both the protocol and consent. Describe the planned procedures for protecting against or minimizing potential risks and assess their likely effectiveness. Where appropriate, discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. Discuss the potential benefits of the research to the subjects and others. Discuss why the risks to the subjects are reasonable in relation to the anticipated benefits to subjects and others. Discuss the importance of the knowledge gained or to be gained as a result of the proposed research and why the risks are reasonable in relation to the knowledge that reasonably may result. If there are no benefits state so.*

The only major risk to the patient is transient respiratory depression which may occur in 5-10% of the population. This is expected to cease promptly (within 5 minutes) after cessation of the infusion. As the patient will be monitored at all times by an anesthesia provider, the actual risk to the patient is minimal as either the patient will be assisted by a ventilator, or the patient's ventilation will be assisted by the provider. It must be stressed that assisting respiration and ventilation is one of the principal tasks of an anesthesia provider and the provider is expected to continue to manage the patient's respiration until the patient is adequate for discharge to the post-anesthesia care unit.

Bradycardia is also a potential risk to the patient; however, it rarely occurs in the dose that will be administered to the patient. If bradycardia is sufficient to risk causing harm to the patient, the infusion will be stopped, and the anesthesiology provider will use his/her clinical discretion with regard to treating the bradycardia.

Therapeutic Alternatives: *List the therapeutic alternatives that are reasonably available that may be of benefit to the potential subject and include in the consent form as well.*

☐ ***Not Applicable***

There are no therapeutic alternatives that have been shown to consistently prevent coughing. Subjects are free to not participate in the study.

Data Safety and Monitoring: *The specific design of a Data and Safety Monitoring Plan (DSMP) for a protocol may vary extensively depending on the potential risks, size, and complexity of the research study. For a minimal risk study, a DSMP could be as simple as a description of the Principal Investigator's plan for monitoring the data and performance of safety reviews or it could be as complex as the initiation of an external, independent Data Safety and Monitoring Board (DSMB). The UVM/UVM Medical Center process for review of adverse events should be included in the DSMP.*

The principal investigator will conduct a monthly review of subject enrollment, adverse events, unanticipated occurrences, and protocol deviations. Any events meeting criteria will be reported to the IRB. Any adverse events to subjects will be reported to the PI immediately and evaluated for reporting to the IRB.

Adverse Event and Unanticipated Problem (UAP) Reporting: *Describe how events and UAPs will be evaluated and reported to the IRB. All protocols should specify that, in the absence of more stringent reporting requirements, the guidelines established in the Committees on Human Research "Adverse Event and Unanticipated Problems Reporting Policy" will be followed. The UVM/UVM Medical Center process for review of adverse events and UAPs to subjects or others should be included in the DSMP.*

All adverse events and unanticipated problems will be reported to the PI, who will evaluate them for reporting to the IRB. In the event of any significant adverse event or unexpected event, the project will immediately be placed on hold and reviewed by the Anesthesiology QA committee chair. Such events include but are not limited to: significant hemodynamic aberrations such as bradycardia requiring treatment with multiple doses of atropine; significant hypotension requiring norepinephrine infusion; cardiac arrest; and severe sedation postoperatively requiring invasive airway management such as endotracheal intubation.

Withdrawal Procedures: *Define the precise criteria for withdrawing subjects from the study. Include a description of study requirements for when a subject withdraws him or herself from the study (if applicable).*

Patients whose surgery will end in less than 5 minutes prior to the start infusion, or, patients who will be extubated while deeply anesthetized will be withdrawn from the study and will not receive any of study drug or placebo. Given the nature of the study and because the patient will be anesthetized at the time of the initiation of infusion, a patient will only be able to withdrawn him/herself just prior to induction of anesthesia. The anesthesia provider, may, at any time, request withdrawal in order to provide appropriate patient care

Sources of Materials: *Identify sources of research material obtained from individually identifiable human subjects in the form of specimens, records or data. Indicate whether the material or data will be obtained specifically for research purposes or whether use will be made of existing specimens, records or data.*

The sources of research material in this study will be 1) data obtained from identifiable human subjects specifically for research purposes while they are undergoing surgery in the operating room, and 2) demographic data obtained from subjects' medical records: Height, weight, age, gender, type of surgical procedure, and all data will be logged in a spreadsheet with no identifiable information other than time of events

DRUG AND DEVICE INFORMATION

Investigators are encouraged to consult the UVM Medical Center Investigational Pharmacy Drug Service (847-4863) prior to finalizing study drug/substance procedures.

Drug (s) ☐ ***Not applicable***

Drug name – generic followed by brand name and common abbreviations. Availability – Source and pharmacology; vial or product sizes and supplier. If a placebo will be used, identify its contents and source. (attach investigational drug brochure)

Remifentanil (Ultiva)
400 mcg in a 20 mL syringe will be provided
Placebo will be normal saline in an identical 20 mL syringe

Preparation: Reconstitution instructions; preparation of a sterile product, compounded dosage form; mixing guidelines, including fluid and volume required. Identify who will prepare.

Remifentanil: 2mg vial in 100 mL.. Stored in refrigerator until requested for study.

Storage and stability – for both intact and mixed products.

Per pharmacy

Administration – Describe acceptable routes and methods of administration and any associated risks of administration.

Intravenously with syringe pump. Risk of improperly programming pump may result in over or under administration of medication

Toxicity – Accurate but concise listings of major toxicities. Rare toxicities, which may be severe, should be included by indicated incidence. Also adverse interactions with other drugs used in the protocol regimen as well as specific foods should be noted. Address significant drug or drug/food interactions in the consent form as well. List all with above details.

Contraindication:
•Hypersensitivity to fentanyl analogs

Adverse Events:
Common

•Cardiovascular: Hypotension (19% or less)
•Dermatologic: Pruritus (less than 1% to 18%)
•Gastrointestinal: Nausea (less than 1% to 44%), Vomiting (less than 1% to 22%)
•Musculoskeletal: Muscle rigidity (11% or less)
•Neurologic: Headache (18% or less)

Serious
•Cardiovascular: Asystole
•Hematologic: Hemorrhage (2% or less)
•Immunologic: Anaphylaxis (Less than 1%)
•Respiratory: Respiratory depression (less than 1% to 7%)
•Other: Serotonin syndrome

Black box warning: Remifentanil exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing remifentanil

Is it FDA approved: (include FDA IND Number)

1. *in the dosage form specified? If no, provide justification for proposed use and source of the study drug in that form.*
   Yes
2. *for the route of administration specified? If no, provide justification for route and describe the method to accomplish.*
   Yes
3. *for the intended action?*
   No

Device (s) ☐ ***Not applicable***

Device name and indications (attach investigational device brochure)

BBraun Perfusor Space syringe pump

Is it FDA approved: (include FDA IDE Number)

1. *for indication specified? If no, provide justification for proposed use and source of the device.*

Yes

Risk assessment (non-significant/significant risk) - PI or sponsor needs to assess risk of a device based upon the use of the device with human subjects in a research environment.

No additional risk of use from the device.

SUBJECT CHARACTERISTICS, IDENTIFICATION AND RECRUITMENT

Subject Selection: *Provide rationale for subject selection in terms of the scientific objectives and proposed study design.*

The purpose of the study is to evaluate the ability of algorithm-driven administration of remifentanil to reduce coughing at emergence in patients where coughing is clinically relevant: eye surgery and head and neck procedures. Should the study be successful, this patient population will be directly impacted.

Vulnerable Populations: *Explain the rationale for involvement of special classes of subjects, if any. Discuss what procedures or practices will be used in the protocol to minimize their susceptibility to undue influences and unnecessary risk (physical, psychological, etc.).*

x ***Not applicable***

Number of Subjects: *What is the anticipated number of subjects to be enrolled at UVM/UVM Medical Center and in the case of a multi-center study, with UVM/UVM Medical Center as the lead, the total number of subjects for the entire study.*

60 patients will be recruited for the study.

Inclusion/Exclusion Criteria: *Eligibility and ineligibility criteria should be specific. Describe how eligibility will be determined and by whom. Changes to the eligibility criteria at a later phase of the research have the potential to invalidate the research.*

All patients between the ages of 18 and 80 with an ASA of 1-3 who will be undergoing elective thyroidectomy (partial or complete), parathyroidectomy, or ophthalmological surgery requiring intubation will be eligible for this study. Exclusion criteria include patients with a Lean Body Mass < 20 kg, BMI > 45, the presence of pulmonary dysfunction, known allergy to remifentanil or its congeners (fentanyl, sufentanil, alfentanil), and patients requiring the use of total intravenous anesthesia. The anesthesia provider may also exclude a patient from the study at any point in time if the provider has concerns for the patient's safety including an inability or expected difficulty with ventilation.

Inclusion of Minorities and Women: *Describe efforts to include minorities and women. If either minorities or women are excluded, include a justification for the exclusion.*

Not applicable

Inclusion of Children: *Describe efforts to include children. Inclusion is required unless a clear and compelling rationale shows that inclusion is inappropriate with respect to the health of the subjects or that inclusion is inappropriate for the purpose of the study. If children are included, the description of the plan should include a rationale for selecting or excluding a specific age range of children. When included, the plan must also describe the expertise of the investigative team in working with children,*

the appropriateness of the available facilities to accommodate children, and the inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose of the study. ***If children are excluded*** *then provide appropriate justification. Provide target accrual for this population.*

The pharmacokinetic model was not developed for use in children and it is unclear how the model will perform

For protocols including the use of an investigational drug, indicate whether women of childbearing potential have been included and, if not, include appropriate justification.

Women of childbearing potential will be recruited if they meet criteria for participation.

If HIV testing is included specifically for research purposes explain how the test results will be protected against unauthorized disclosure. Include if the subjects are to be informed of the test results. If yes, include the process and provision for counseling. If no, a rationale for not informing the subjects should be included.

x | ***Not applicable***

Recruitment: *Describe plans for identifying and recruitment of subjects. All recruitment materials (flyers, ads, letters, etc) need to be IRB approved prior to use.*

The surgeons in the divisions of Ophthalmology and Otolaryngology will introduce the study to eligible patients during the preoperative clinic visit. Study staff in the Department of Anesthesiology will review the OR schedule to identify eligible patients. One to two days before surgery, study staff will call patients to discuss the study and ascertain the patient's interest in participation. On the day of surgery, the PI or his designee (listed as key personnel) will approach the patient and, if the patient is willing, initiate a discussion of the study. The study staff person will review the study procedures and how they would affect the patient; discuss risks and possible benefits of participation, and answer any questions. The subject will then be given as much time as they need to make their decision regarding participation, up until the time the operating room staff is ready to transfer the patient. If the patient has not made a decision on participation at that point, they will be ineligible for the study.

FINANCIAL CONSIDERATIONS

Expense to Subject: *If the investigation involves the possibility of added expense to the subject (longer hospitalization, extra studies, etc.) indicate in detail how this will be handled. In cases where the FDA has authorized the drug or device company to charge the patient for the experimental drug or device,* ***a copy of the authorization letter from the FDA or sponsor must accompany the application. Final approval will not be granted until the IRB receives this documentation.***
There are very limited circumstances under which study participants may be responsible (either directly or via their insurance) for covering some study-related expenses. If the study participant or their insurer(s) will be billed for any portion of the research study, provide a justification as to why this is appropriate and acceptable. For example, if the study involves treatment that is documented standard of care and not investigational, state so. In these cases, the protocol and the consent should clearly define what is standard of care and what is research.

None

Payment for participation: *Describe all plans to pay subjects, either in cash, a gift or gift certificate. Please note that all payments must be prorated throughout the life of the study. The IRB will not approve a study where there is only a lump sum payment at the end of the study because this can be considered coercive. The amount of payment must be justified. Clarify if subjects will be reimbursed for travel or other expenses.*

X | ***Not applicable***

Collaborating Sites*. When research involving human subjects will take place at collaborating sites or other performance sites when UVM/UVM Medical Center is the lead site, the principal investigator must provide in this section a list of the collaborating sites and their Federalwide Assurance numbers when applicable. (agreements may be necessary)*

X | ***Not applicable***

INFORMED CONSENT

Consent Procedures*: Describe the consent procedures to be followed, including the circumstances under which consent will be obtained, who will seek it, and the methods of documenting consent. Specify the form(s) that will be used e.g. consent (if multiple forms explain and place identifier on each form), assent form and/or HIPAA authorization (if PHI is included). These form(s) must accompany the protocol as an appendix or attachment.*

Note: Only those individuals authorized to solicit consent may sign the consent form confirming that the prospective subject was provided the necessary information and that any questions asked were answered.

The surgeons in the divisions of Ophthalmology and Otolaryngology will introduce the study to eligible patients during the preoperative clinic visit. One to two days before surgery, study staff in the Department of Anesthesiology will call patients to confirm their interest in participation. Consent will be obtained in the preoperative area of the main hospital on the day of surgery by the principal investigator or his designees, using an informed consent form and documented on the IRB consent process template. Subjects will be given as much time as they need to make their decision regarding participation, up until the time the operating room staff is ready to transfer the patient from the preoperative area to the OR. If the patient has not made a decision on participation at that point, they will be ineligible for the study.

Information Withheld From Subjects: *Will any information about the research purpose and design be withheld from potential or participating subjects? If so, explain and justify the non-disclosure and describe plans for post-study debriefing.*

x | ***Not applicable***