

Title: Esophageal Manometry During Recovery from Anesthesia: Pilot Study

NCT number: NCT02661386

Document date: July 21, 2015

**University of California, San Francisco
PROTOCOL TEMPLATE**

Instructions to User:

1. **Sections and text that are in regular font and that have not been highlighted in grey** represent standard language. In general, these sections should be present in your final protocol and the language should not be changed. However, every protocol is unique and changes to standard sections and language may be necessary to meet the needs of your protocol. Please review the language carefully to make sure that it is accurate for your study.
2. **Sections that are highlighted in grey, but that have regular font**, represent sections or information that needs to be customized as applicable to your study, but the language that is present is generally considered to be standard if that section (or procedure) applies to your protocol.
3. **Sections that are highlighted in grey, and where the text is italicized**, represent instructions with some example text. All require complete customization for your study.
4. As you customize each section of the protocol, **remove the highlighting and restore the font to regular (from italics)** to denote that section as having been completed.
5. When your protocol is complete, **review** it to ensure that all highlighting and italics have been removed.

STANLEY J. ROGERS, M.D.**Clinical Research Protocol****Esophageal Manometry During Recovery from Anesthesia: Pilot Study**

Protocol Number:	14-14466
Version Date:	07/21/2015
Investigational Product:	N/A
IND Number:	
Development Phase:	Pilot Study
Sponsor:	Stanley J. Rogers, MD, Department of Surgery 521 Parnassus Avenue San Francisco, CA 94143
Funding Organization:	UCSF, Department of Surgery
Principal Investigator:	Name: Stanley J. Rogers, MD Telephone: 415-476-0762 Fax: 415-641-0745 E-mail: stan.rogers@ucsf.edu
Medical Monitor:	Name: Telephone: Fax: E-mail:
Coordinating Center:	If applicable

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 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: 14-15466

Protocol Title: Esophageal Manometry During Recovery from Anesthesia: Pilot Study

Protocol Date: July 21, 2015

Investigator Signature

Date

Stanley J. Rogers, M.D.

Print Name and Title

Site #

Site Name San Francisco General Hospital

Address 1001 Potrero Ave., Main Hospital 3D

San Francisco, CA 94110

Phone Number 415-206-4767

TABLE OF CONTENTS

1 BACKGROUND.....	10
1.1 Overview of Non-Clinical Studies.....	10
1.2 Overview of Clinical Studies.....	10
2 STUDY RATIONALE	11
2.1 Risk / Benefit Assessment	12
3 STUDY OBJECTIVES	12
3.1 Primary Objective	12
3.2 Secondary Objectives	12
4 STUDY DESIGN	12
4.1 Study Overview	12
5 CRITERIA FOR EVALUATION.....	12
5.1 Primary Efficacy Endpoint	12
5.2 Secondary Efficacy Endpoints	13
5.3 Safety Evaluations	13
6 SUBJECT SELECTION	13
6.1 Study Population.....	13
6.2 Inclusion Criteria	13
6.3 Exclusion Criteria	13
7 STUDY PROCEDURES AND GUIDELINES	13
7.1 Clinical Assessments	14
8 EVALUATIONS BY VISIT	14
8.1 Visit 1 (Day/Week/Month #)	14
9 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION	15
9.1 Adverse Events	15
9.2 Serious Adverse Experiences (SAE)	16
9.3 Medical Monitoring	16
10 DISCONTINUATION AND REPLACEMENT OF SUBJECTS	16
10.1 Withdrawal of Subjects.....	16
10.2 Replacement of Subjects.....	16
11 PROTOCOL VIOLATIONS.....	17
12 STATISTICAL METHODS AND CONSIDERATIONS.....	17
12.1 Data Sets Analyzed.....	17
12.2 Analysis of Primary Endpoint.....	17
12.3 Analysis of Secondary Endpoints	17
12.4 Interim Analysis.....	18
12.5 Sample Size and Randomization	18
13 DATA COLLECTION, RETENTION AND MONITORING.....	18
13.1 Data Collection Instruments	18
13.2 Data Management Procedures	18

13.3	Data Quality Control and Reporting	18
13.4	Archival of Data.....	19
13.5	Availability and Retention of Investigational Records.....	19
13.6	Monitoring	19
13.7	Subject Confidentiality	19
14	ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS.....	19
14.1	Protocol Amendments.....	20
14.2	Institutional Review Boards and Independent Ethics Committees.....	20
14.3	Informed Consent Form.....	20
14.4	Publications.....	21
14.5	Investigator Responsibilities.....	21

LIST OF ABBREVIATIONS

AE	adverse event
CFR	Code of Federal Regulations
CRF	case report form
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
EGD	Endoscopy
EMAP	Esophageal Manometry during recovery from Anesthesia
ERCP	Endoscopic retrograde cholangiopancreatography
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HRM	High resolution manometry
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	intravenous
PI	Principal Investigator
SAE	serious adverse experience

PROTOCOL SYNOPSIS

TITLE	Esophageal Manometry During Recovery from Anesthesia: Pilot Study
SPONSOR	Stanley J. Rogers, MD
FUNDING ORGANIZATION	Department of Surgery, UCSF
NUMBER OF SITES	1
RATIONALE	1. An intact pharyngoesophageal reflex is essential to protect the upper airway from aspiration of either mouth contents or regurgitated gastric refluxate. This reflex is essential at protecting the airway in all patients. 2. In patients, while under general anesthesia, it is postulated that an identifiable upper esophageal sphincter and esophageal peristalsis are not present. 3. With the cessation of general anesthetics, accompanied by the reversal of nerve block, normal pharyngoesophageal peristaltic activity correlates with awakening the patient from anesthesia. This would be identified by the performance of esophageal manometry. 4. A return of normal <u>verbally stimulated</u> pharyngoesophageal swallowing sequence accurately identifies a safe time to remove endotracheal tubes and/or reverse anesthesia. This verbally stimulated swallowing sequence correlated precisely with the return of objective pharyngoesophageal function.
STUDY DESIGN	Our pilot study will examine esophageal manometry in patients emerging from routine general anesthesia. Manometry of the esophagus is not a standard part of surgery or general anesthesia. We will be using standard solid state high resolution manometry. One of the authors (JPC) evaluates all routine manometry for patients undergoing such procedures at both UCSF and SFGH. The use of manometry in patients recovering from anesthesia will permit us to assess the recovery of a normal swallowing mechanism. An adequate determination of return of normal swallowing sequence is likely to determine the safe time for extubation. We propose to, as a research study, investigate esophageal motor function using standard high resolution esophageal manometry in 10 patients recovering from general anesthesia. These studies are likely to document that the return of normal pharyngoesophageal function will coordinate with verbal commands to initiate swallowing. This pilot study will help clarify the precise timing of the return of normal function in the oropharynx and the proximal esophagus and thus determine the safe

	time for removal of the endotracheal or nasotracheal intubation.
PRIMARY OBJECTIVE	Our primary objective is to determine the timing of the return of normal pharyngoesophageal function upon withdrawal of general anesthesia.
SECONDARY OBJECTIVES	Our second objective is to correlate the return of normal pharyngoesophageal function with other markers generally used to indicate a safe time for removal of endotracheal tubes. Our third objective is to determine that esophageal manometry studies can be performed in patients recovering from general anesthesia.
NUMBER OF SUBJECTS	10
SUBJECT SELECTION CRITERIA	<u>Inclusion Criteria:</u> 1. Patients between 18 and 70 years of age. 2. Already scheduled for routine general anesthetic procedure requiring an endotracheal tube for anesthesia administration. 3. Scheduled abdominal surgical procedure including endoscopy, colonoscopy, ERCP, cholecystectomy, appendectomy, colectomy or small bowel resection. 4. Willing and able to give informed consent in either English or Spanish. <u>Exclusion Criteria:</u> 1. Patients not meeting entry criteria above. 2. Refusal to give informed consent. 3. Coagulopathy (INR > 2 and/or platelet count < 100,000. 4. White Blood Cell count < 5,000/mm³ 5. Arrhythmia 6. Serum creatinine > 2 mg/dl 7. Prior known or suspected nasal obstruction. 8. Known or suspected Zenker's diverticulum of esophagus, esophageal stricture, head/neck radiation therapy, hereditary telangiectasis, esophageal varices, cirrhosis.
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will be on study for about 15 minutes. Patients will have the standard manometry catheter passed approximately 5 minutes prior to intended routine removal of endotracheal tube. Subjects will be asked to participate in the study during their consent to undergo the primary surgical or endoscopic procedure. Once manometry is completed subjects will be done with study.
EFFICACY EVALUATIONS	Adequate standard HRM as demonstrated by sample printout.

PRIMARY ENDPOINT	• HRM determination of return of cricopharyngeal function
SECONDARY ENDPOINTS	• Feasibility of performing HRM in patients recovering from general anesthesia.
OTHER EVALUATIONS	Standard routine recovery anesthesia recovery markers.
SAFETY EVALUATIONS	Incidence of adverse events
PLANNED INTERIM ANALYSES	When approximately 50% of patients have completed the study through, an interim analysis for safety will be conducted by an investigator. Serious adverse events will be monitored by the committee on an ongoing basis throughout the study.
STATISTICS Primary Analysis Plan	Standard HRM report characteristics as exemplified in sample form.
Rationale for Number of Subjects	This is a proposed pilot study and it is estimated that 10 patients will enable the investigators to gauge the accuracy and feasibility of performing routine standard bedside solid state manometry in patients recovering from general anesthesia.

1 BACKGROUND

The emergence from routine general deep anesthesia is a potentially dangerous time for patients. They cannot reliably maintain competence of the upper esophageal sphincter, thus aspiration of the contents from the mouth or regurgitated material from the stomach can be aspirated into the lungs leading to serious complications. In normal awake individuals the upper esophageal sphincter (also known as the cricopharyngeus or the inferior pharyngeal constrictor) is contracted and relaxes precisely timed with voluntary or involuntary swallowing. The swallowing sequence in normal awake persons begins with 1) the contraction of the upper and middle pharyngeal constrictors, 2) the posterior movement of the tongue and 3) the prompt relaxation of the contracted upper esophageal sphincter. Peristalsis then begins in the body of the esophagus leading contents to the stomach. The above is the normal sequence in humans, a process which maintains absolute separation of the airway and digestive passageways despite being in intimate proximity. During the early period of emergence from anesthesia, the aspiration risk is highest due to the sluggish return of the resting pressure in the upper esophagus and the lack of normal coordination with

involuntary swallowing. Thus patients can't protect their airway by maintaining competence and appropriate relaxation of the upper esophageal sphincter. Routine high resolution solid state manometry is a standard routine technique is currently performed in awake patients sitting upright voluntarily requested to swallow small boluses of liquid.

One of the authors, JPC, has reviewed and interpreted thousands of such solid state manometries at both UCSF and SFGH. The entire sequence of events is studied using high resolution solid state manometry.

1.1 Overview of Non-Clinical Studies

Pharyngeal function has been studied in awake, healthy volunteers, by administration of small quantities of neuromuscular blocking drug and monitoring of esophageal sphincter tone, train-of-four (TOF) ratio, and the volunteer's ability to protect the larynx and trachea from instillation of a liquid bolus.³ At levels of recovery judged "adequate" by conventional nerve stimulators (TOF ratio 0.6-0.8), the volunteers showed decreased resting pressure in the upper esophageal sphincter, (i.e. cricopharyngeus) and 6 of 14 patients actually aspirated the liquid bolus into the larynx.

In a large randomized trial, 691 patients were randomly assigned to receive long versus intermediate-acting neuromuscular blocking drugs during surgery, and patients were followed for 6 days during their hospitalization for evidence of postoperative pulmonary complications (SpO₂ < 90% with radiographic findings of pulmonary infiltrate). Patients receiving longer-acting neuromuscular blocking drugs had higher risk of residual paralysis, and higher risk of postoperative pulmonary complications. Using multiple regression, these investigators found that residual neuromuscular block after pancuronium, along with advanced age and lengthier surgery, were independently predictive of pulmonary complications in this patient population.⁴

A case-control study of over 869,000 consecutive patients receiving anesthetics was conducted at numerous teaching and private hospitals in the Netherlands between 1995-1997. This study sought to identify factors that predicted mortality within 24 hours of

surgery.⁵ Among the findings of this particular study was that failure to reverse neuromuscular blocking drugs was associated with a six-fold greater mortality risk. Another case-control study from the recovery room at one of the Northwestern University Hospitals showed that residual neuromuscular block was independently associated with respiratory complications.⁶ Among 7459 patients recovering during a one-year period, 61 suffered critical respiratory events (hypoxia or airway obstruction).⁵ In all 61 patients, the code team measured train-of-four with a quantitative neuromuscular monitor. The investigators subsequently found control subjects whose age, sex, and procedure matched those of each case. Among cases, TOF ratio = 0.62 ± 0.20 , with 74% of these subjects showing ratio < 0.7 . In contrast, the controls showed TOF ratio = 0.98 ± 0.07 , with no control subjects having TOF < 0.7 . The differences between groups was highly statistically significant, with greater (95% CI= 59-85%) TOF among the controls versus the cases.

Finally, most clinicians consider that impairment of ventilation by partially antagonized neuromuscular blockers to be essentially an impairment of skeletal muscles (diaphragm and intercostal groups) and inadequate airway protection (pharyngeal muscles). However, because neuromuscular blocking drugs act by competitive inhibition of acetylcholine at nicotinic receptors, they also exert activity within the carotid body, and their presence impairs normal chemical control of ventilation.⁷ Therefore, the stimulus normally elicited by hypoxic conditions is profoundly obtunded by presence of unopposed residual neuromuscular block. In addition to the influence of the neuromuscular blocking drug, residual volatile anesthetic, at partial pressures below those at which patients awaken, also blunt hypoxic ventilatory response. In clinical reality, patients typically receive concomitant depressant medications that blunt chemical ventilatory drive during early recovery in the PACU (opioids, anxiolytics) which have likely additive, if not synergistic, effects. Therefore, sensitive monitoring for presence of adequate neuromuscular recovery can eliminate an important source of ventilatory depression during the postoperative period.

2 STUDY RATIONALE

1. An intact pharyngoesophageal reflex is essential to protect the upper airway from aspiration of either mouth contents or regurgitated gastric refluxate. This reflex is essential at protecting the airway in all patients.
2. In patients, while under general anesthesia, it is postulated that an identifiable upper esophageal sphincter and esophageal peristalsis are not present.
3. A return of pharyngoesophageal reflex indicates a safe time to remove endotracheal tubes.

With the cessation of general anesthetics, accompanied by the reversal of nerve block, normal pharyngoesophageal peristaltic activity correlates with awakening the patient from anesthesia. This would be identified during the performance of esophageal manometry. A return of normal verbally stimulated pharyngoesophageal swallowing sequence accurately identifies a safe time to remove endotracheal tubes and/or reverse anesthesia. This verbally stimulated swallowing sequence correlated precisely with the return of objective pharyngoesophageal manometrics.

2.1 Risk / Benefit Assessment

This study will be performed in 10 patients already scheduled to undergo general anesthesia. The return of normal pharyngoesophageal reflex likely will correlate with the determination of “safe” times to remove airway protection.

3 STUDY OBJECTIVES

3.1 Primary Objective

Our primary objective is to determine that cessation of general anesthesia is associated with return of normal pharyngoesophageal reflex.

3.2 Secondary Objectives

Our second objective is to document that the return of normal pharyngoesophageal function indicates a safe time for removal of endotracheal tubes.

Our third objective is to determine that esophageal manometry studies are feasible in patients recovering from general anesthesia.

4 STUDY DESIGN

4.1 Study Overview

Our pilot study will examine esophageal manometry in patients emerging from routine general anesthesia. We will be using standard solid state high resolution manometry. One of the authors (JPC) evaluated the routine manometry for all patients undergoing such procedures at both UCSF and SFGH. This use of manometry in patients recovering from anesthesia will permit us to assess the recovery of a normal swallowing mechanism. An adequate determination of return of normal swallowing sequence there is likely to be definitive documentation of the safe time for extubation. We propose to study esophageal motor function using standard high resolution esophageal manometry in 10 patients recovering from general anesthesia. These studies are likely to document that the return of normal pharyngoesophageal function coordinated with verbal commands to initiate swallowing. This pilot study will help clarify the precise timing of the return of normal function in the oropharynx and the proximal esophagus and thus determine the safe time for removal of the endotracheal or nasotracheal intubation.

Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be entered into the study.

Total duration of subject participation will be 15 minutes (end of procedure, recovery from anesthesia). Total duration of the study is expected to be 15 minutes.

5 CRITERIA FOR EVALUATION

5.1 Primary Efficacy Endpoint

HRM determination of return of crycopharyngeal function.

5.2 Secondary Efficacy Endpoints

- Feasibility of performing HRM in patients facing standard awake manometry

5.3 Safety Evaluations

- Incidence of adverse events: nasal bleeding, nasal irritation, esophageal pain, dysphagia

6 SUBJECT SELECTION

6.1 Study Population

Subjects who meet the inclusion and exclusion criteria will be eligible for participation in this study. It is anticipated that the largest number of subjects will come from general anesthesia patients undergoing endoscopy, colonoscopy or ERCP.

6.2 Inclusion Criteria

1. Patients between 18 and 70 years of age.
2. Already scheduled for routine general anesthetic procedure requiring an endotracheal tube for anesthesia administration.
3. Scheduled abdominal surgical procedure including EGD, colonoscopy, ERCP, cholecystectomy, appendectomy, colectomy or small bowel resection.
4. Willing and able to give informed consent in either English or Spanish.

6.3 Exclusion Criteria

1. Pregnant, breastfeeding, or unwilling to practice birth control during participation in the study.
2. Presence of a condition or abnormality that in the opinion of the Investigator would compromise the safety of the patient or the quality of the data.
3. Patients not meeting entry criteria above.
4. Refusal to give informed consent.
5. Coagulopathy (INR > 2 and/or platelet count < 100,000.
6. White Blood Cell count < 5,000/mm³
7. Ahythmia
8. Serum creatinine > 2 mg/dl
9. Prior known or suspected nasal obstruction.
10. Known or suspected Zenker's diverticulum of esophagus, esophageal stricture, head/neck radiation therapy, hereditary telangiectasis, esophageal varices, cirrhosis.

7 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Appendix 1.

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. If appropriate, assent must also be obtained prior to conducting any study-related activities.

7.1 Clinical Assessments

7.1.1 Demographics

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

7.1.2 Medical History

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

7.1.3 Physical Examination

A complete physical examination will be performed by either the investigator or a subinvestigator who is a physician at Screening.

7.1.4 Vital Signs

Body temperature, blood pressure, pulse and respirations will be performed as per routine for general anesthesia.

7.1.5 Oximetry

Oximetry will be measured as per routine for general anesthesia.

7.1.6 Adverse Events

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

8 EVALUATIONS BY VISIT

8.1 Visit 1 (Screening/Procedure Day)

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. Perform and record vital signs as per Anesthesia.
5. At 15 minutes prior to anticipated removal of the endotracheal tube, pass the routine manometry catheter per naris to 30 cms.
6. Record routine HRM for terminal 10-15 minutes of general anesthesia.
7. Routine anesthesia stimulation of patient at time of intended withdrawal of endotracheal tube.

8. Remove HRM catheter at time of removal of endotracheal tube by anesthesia.

9 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

9.1 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.

9.2 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.

9.2.1 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.

9.3 Medical Monitoring

John P. Cello, MD should be contacted directly at these numbers to report medical concerns or questions regarding safety.

Phone: (415) 206-4767

Pager: (415) 719-1018

10 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

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.

10.1 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.

10.2 Replacement of Subjects

Subjects who withdraw from the study treatment will be replaced.

Subjects who withdraw from the study will be replaced.

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

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The Investigator will determine if a protocol violation will result in withdrawal of a subject.

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 Data Sets Analyzed

All eligible patients who are randomized into the study will be included in the safety analysis.

12.2 Analysis of Primary Endpoint

Normal crycopharangeal function will be determined by standard HRM criteria as outlined on sample HRM form used routinely.

12.3 Analysis of Secondary Endpoints

The adequacy of performing standard HRM will be determined by comparison with standard monograms for HRM as outlined on sample form enclosed.

Safety and tolerability data will be summarized by treatment group.

Adverse event rates will be coded by body system and MedDra classification term.

Adverse events will be tabulated by treatment group and will include the number of patients for whom the event occurred, the rate of occurrence, and the severity and relationship to study drug.

12.4 Interim Analysis

We anticipate interim analyses at the completion of 5 of the planned 10 subjects in the pilot study.

12.5 Sample Size and Randomization

This is a small sample pilot study to determine the feasibility of conducting HRM in patients recovering from anesthesia and the correlation of HRM with standard indicators for safely removing endotracheal tubes.

13 DATA COLLECTION, RETENTION AND MONITORING

13.1 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 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.

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.

13.2 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.

13.3 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. The

study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

13.4 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.

13.5 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.

13.6 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.

13.7 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.

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 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).

14.1 Protocol Amendments

Any amendment to the protocol will be written by the Sponsor. 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 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 the Sponsor or 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.

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 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.

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 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.

APPENDIX 1. STUDY SCHEDULE

	VISIT 1 (Day/Week/Month #)^a
Informed Consent	X
Medical History	X
Abbreviated Physical Exam	X
HRM catheter passage	X
Recording HRM	X
Determine Standard Anesthesia criteria for extubation	X
Correlate results of HRM with extubation	X
Remove HRM catheter	X
Adverse Experiences	X

^a ±2 days