Intraoperative Video Laryngoscopy as Adjunct for Nerve Monitoring
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Intraoperative video laryngoscopy as adjunct for nerve monitoring

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All versions should have a version number and a date. Use an international date format (e.g.,YYYY-MM-DD [2017-12-21] or write out the month (e.g., 21 December 2017).

For the initial submission of a protocol to the IRB, indicate "Not applicable; this is the first version of the protocol." in the table below. For any subsequent amendment being submitted to the IRB, add details of the specific changes that are being implemented in the amendment. Please note that Section 10.4 is a high-level summary of <u>all</u> formal protocol versions/amendments.

CONFIDENTIALITY STATEMENT

This document is confidential communication. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigator or other participating study leadership and as consistent with the NIH terms of award.

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STATEMENT OF COMPLIANCE

(1) The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

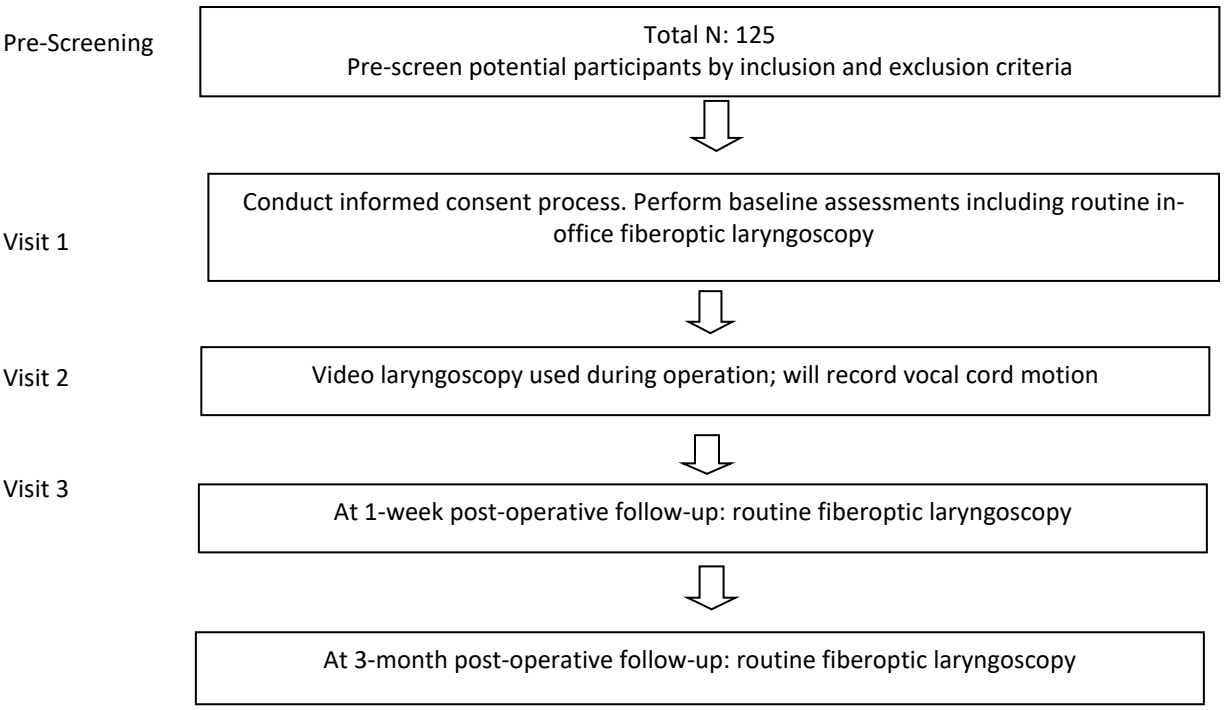
1.1 SYNOPSIS

Title:	Intraoperative video laryngoscopy as adjunct for nerve monitoring
Grant Number:	N/A
Study Description:	The purpose of this study is to describe the impact of adding intraoperative video laryngoscopy (IOVL) to intra-operative laryngeal nerve monitoring (IOLNM) during neck procedures when IOLNM is routinely used, including thyroidectomy and re-operative parathyroidectomy. Specifically, we seek to assess how frequently the use of IOVL provided confirmatory or additional information that may affect surgeon decision-making when IOLNM alone is ambiguous, or when there is equipment malfunction or failure. The IOVL is a disposable, otherwise standard fiberoptic laryngoscope (Larynxview, Neurovision Medical, Ventura CA) that is inserted alongside the endotracheal tube following intubation for surgical procedures. It allows assessment of vocal cord movement in response to nerve stimulation. Currently, the use of IOLNM is based on audio cues, and visual assessment of external laryngeal muscle movement during surgery in response to stimulation, but no direct assessment of vocal cord movement is routinely possible. This information can be ambiguous and subject to judgement of the surgeon. The addition of IOVL provides direct assessment to vocal cord movement in response to stimulus, and may be useful in light of ambiguous IOLNM data, or limited visualization of external laryngeal muscles.
Objectives*:	This is a descriptive study in which we seek to assess the degree to which intraoperative video laryngoscopy used in conjunction with routine intraoperative nerve monitoring provides additional data on nerve integrity and vocal cord function for patients undergoing neck procedures that place the recurrent and superior laryngeal nerves at risk for injury or postoperative dysfunction. Specifically, we are interested in how frequently the information gained from video laryngoscopy may provide data on the vocal cord function in situations of ambiguous data from the nerve monitor, or in cases of equipment malfunction or failure of the nerve monitor. We would also like to assess the frequency of discordance in evaluation of intraoperative nerve monitoring, which is an indirect measure of vocal cord function via nerve integrity, with direct evaluation of vocal cord function via video laryngoscopy
Endpoints*:	This is a descriptive study. There are no specific patient outcome endpoints. We will be primarily assessing the frequency with which the IOVL provides additional data to IOLNM which may be used to make further surgical decision making.
Study Population:	125 patients over the age of 18 with a medical indication for partial or total thyroidectomy, re-operative parathyroidectomy, or neck dissection will be enrolled at Mount Sinai Hospital, Mount Sinai Beth Israel, Mount Sinai Morningside, and Mount Sinai West.
Phase* or Stage:	Enrolling

Description of Sites/Facilities Enrolling Participants:	The Mount Sinai Hospital, Mount Sinai Beth Israel, Mount Sinai Morningside, Mount Sinai West
Description of Study Intervention/Experimental Manipulation:	Intraoperative video laryngoscopy will be used in conjunction with routine intraoperative nerve monitoring. We seek to asses the degree to which this will provide additional data on nerve integrity and vocal cord function for patients undergoing neck procedures that place the recurrent and superior laryngeal nerves at risk for injury or postoperative dysfunction.
Study Duration*:	We expect the study to take approximately 3 years.
Participant Duration:	3 months

1.2 SCHEMA

Flow Diagram



1.3 SCHEDULE OF ACTIVITIES

	Pre-screening (Pre-consent)	Visit 1 Day 1	Visit 2 Day of surgery	Visit 3 1 week follow-up	Visit 4 3 month follow-up
Screen Clinic Schedule and Review Eligibility	X				
Informed Consent		X			
Routine fiberoptic laryngoscopy		X			
Video laryngoscope used during standard of care operation			X		
Routine fiberoptic laryngoscopy				X	
Routine fiberoptic laryngoscopy					X

2 INTRODUCTION

2.1 STUDY RATIONALE

We seek to assess the degree to which intraoperative video laryngoscopy used in conjunction with routine intraoperative nerve monitoring provides additional data on nerve integrity and vocal cord function for patients undergoing neck procedures that place the recurrence and superior laryngeal nerves at risk for injury or postoperative dysfunction. We want to see how frequently the information gained from video laryngoscopy may provide data on the vocal cord function in situations of ambiguous data from the nerve monitor, or in cases of equipment malfunction or failure of the nerve monitor. We would also like to assess the frequency of discordance in evaluation of intraoperative nerve monitoring, which is an indirect measure of vocal cord function via nerve integrity, with direct evaluation of vocal cord function via video laryngoscopy.

2.2 BACKGROUND

Thyroid and re-operative parathyroid surgery are technically demanding surgeries involving highly intricate anatomy. The recurrent laryngeal nerve (RLN) is the most important structure at risk during these procedures. The gold standard for protecting the nerve is identifying it through careful dissection before proceeding with the removal of the thyroid gland. The variability in the nerve's course can lead to trouble with identification and increase the risk of injury when surgeons are inexperienced. Although the rate of injury to the nerve has been reported to be relatively low—up to 6% for temporary paresis and up to 2% for paralysis—the consequences of injury can be devastating and thus lowering the injury rate even more is desirable. Data on the use of IOLNM was first published in 2001, and IOLNM has become a widely used adjunct for identifying the RLN and allowing real-time identification and functional assessment of the RLN in the operative field. It also provides information on the status of the superior laryngeal nerve status and function.

IOLNM is an indirect measure of vocal cord function. It provides information on nerve integrity via electromyography (EMG). The feedback the surgeon receives from the system is based on the amount of current necessary to stimulate vocal cord movement, with higher currents indicating worse signal transduction through the nerve, and a loss of signal indicating a severely injured or divided nerve. Surgeons are extrapolating vocal cord function based on auditory cues which indicate nerve integrity, as well as graphical information of the amplitude of the signal (known as the NPI or nerve power index), but do not routinely visualize vocal cord function in real time when making decisions during the procedure.

In our experience, the current system has some limitations. The nerve power index (NPI) is a value displayed by the IOLNM system as an expression of nerve function, with higher numbers indicating better nerve conduction. The quality of conduction is audibly expressed by a two-tone system, with a higher-pitched tone occurring with an NPI

>100, and a lower-pitched tone occurring with an NPI <100. Often the actual NPI is very close to 100, either higher or lower, and interpretation of nerve integrity in this range is ambiguous. Direct interpretation of vocal cord function could be of greater use to the surgeon at these times. We have also experienced system failures, either due to a break in the small wires of the electrode leads, or computer hardware or software malfunction, any of which can lead to the inability to use the IOLNM. In our experience, some form of failure or malfunction of the IOLNM system occurs in 10-15% of operative cases.

Visualization of vocal cord function through an independent system offers another means to assess recurrent laryngeal nerve integrity in these situations.
Patients who are undergoing bilateral procedures may benefit from the addition of video laryngoscopy. At times, the decision to proceed with the second half of a procedure is made based on the perceived integrity of the recurrent laryngeal nerve. There are times when the intraoperative nerve monitor provided ambiguous data about nerve integrity, or has equipment malfunction or failure and no data are available. Video laryngoscopy may give direct information about vocal cord function, and confirmation of vocal cord function in the setting of ambiguous data from the nerve monitor may prompt surgeons to proceed with surgery, or terminate without performing contralateral procedures, based on demonstrated vocal cord function.
This represents a pilot study to first describe the use of IOVL in conjunction with IOLNM during thyroid and reoperative parathyroid procedures.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

There is minimal foreseeable additional risk to the patient in the addition of video laryngoscopy to the routine care for their respective procedures. There is a very small risk of damage to teeth or dental work, or trauma to soft tissues of the mount or oropharynx during insertion of the video laryngoscope following intubation. There risks are similar but smaller in magnitude to the risks of endotracheal intubation, which is already a routine risk of the included procedures.

2.3.2 KNOWN POTENTIAL BENEFITS

There are no direct benefits to the patients enrolled in this study.
We believe that in evaluating how frequently use of the laryngoscopy provides useful information in situations of ambiguous data from the nerve monitor, or in cases of equipment malfunction or failure of the nerve monitor, we would be able to assess whether routine use of the laryngoscopy is needed. This would perhaps prevent situations in which surgeons have insufficient information from nerve monitoring alone.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

There is minimal foreseeable additional risk to the patient in this study. The future benefits of potentially prevent situations in which surgeons have insufficient information from nerve monitoring alone outweighs this minimal risk.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
We seek to assess the degree to which intraoperative video laryngoscopy used in conjunction with routine intraoperative nerve monitoring provides additional data on nerve integrity and vocal cord functions for patients undergoing neck procedures that place the recurrent and superior laryngeal nerves at risk for injury or postoperative dysfunction.	As this is a descriptive study, there are no specific patient outcome endpoints. We will be primarily assessing the frequency with which the IOVL provides additional data to IOLNM which may be used to make further surgical decisions.	We hope that the addition of IOVL will aid in surgical decision-making and nerve monitoring.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This will be a prospective cohort study without randomization. Patients enrolled will undergo the planned procedure according to our routines of care. IOLNM will be performed per our routine of care.

Additional procedures will involve the following:

1) Following consent, but prior to the operation we will complete routine in-office fiberoptic laryngoscopy to assess baseline vocal cord function
2) Prior to intubation, the patient will receive glycopyrrolate 0.004 mg/kg, as per typical pre-anesthetic dosing regimen, to decrease airway and mucous membrane secretions
3) Upon intubation, the video laryngoscope will be passed under direct vision and secured alongside the endotracheal tube. Vocal cords will be positioned in the visual field of the laryngoscope before beginning the operation
4) Following video laryngoscopy, and initiation of the procedure, the ipsilateral vagus nerve will be tested using nerve stimulation (per standard protocol) to ensure good distal nerve conduction and identify potential non-recurrent laryngeal nerve anatomy
5) At all points during the procedure where intraoperative nerve monitoring is used, information about vocal cord motion from video laryngoscopy will also be recorded. Specifically, we will record the neuropraxia index from the nerve monitor, and whether vocal cord function in concordant with the nueropraxia index
6) At the conclusion of resection, the recurrent and superior laryngeal nerves will be assessed with IONM, the vagus will be assessed with IONM, and lastly the vocal cords will be assessed with IOVL. This sequence is consistent with the describe protocol for IONM for testing the vagus and recurrent nerve prior to resection, and then again in reverse order following resection (V1R1R2V2).
7) After conclusion of the procedure and final surgical closing, prior to extubation, vocal cord function will again be assessed with video laryngoscopy
8) At standard 1-week and 3-month post-operative follow-up we will also perform routine fiberoptic laryngoscopy, per common practice, to assess vocal cord function. Patients will be asked to complete a brief questionnaire at both of these visits

Medical records will be used to collect the vast majority of data required for this study. In addition, patients will be asked to complete a brief questionnaire at both the standard 1-week and 3-month follow up visits.
Research activities will occur at the Mount Sinai Hospital, Mount Sinai Beth Israel, Mount Sinai Morningside, and Mount Sinai West.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This study seeks to assess the degree to which IOVL used in conjunction with routine IOLNM provides additional data on nerve integrity and vocal cord function for patients undergoing neck procedures that place the recurrent and superior laryngeal nerve at risk for injury or postoperative dysfunction.

4.3 JUSTIFICATION FOR INTERVENTION

Currently, the use of IOLNM is based on audio cues, and visual assessment of external laryngeal muscle movement during surgery in response to stimulation, but not direct assessment of vocal cord movement is routinely possible. This information can be ambiguous and subject to judgement of the surgeon. The addition of IOVL provides direct assessment to vocal cord movement in response to stimulus, and may be useful in light of ambiguous IOLNM data, or limited visualization of external laryngeal muscles.

4.4 END-OF-STUDY DEFINITION

The end of the study for a participant is define as completion of the 3-month follow-up visit.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Age 18 and older with capacity to make all medical decisions
2. Medical indication for partial or total thyroidectomy, re-operative parathyroidectomy, or neck dissection

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Patients who are under the age of 18, or who are not able to make medical decisions or consent to research

5.3 LIFESTYLE CONSIDERATIONS

N/A

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in this study but are not subsequently assigned to the study intervention or entered in the study. Individuals who do not meet the criteria for participation in this trial (screen failure) because of meeting one or more exclusion criteria that are likely to change over time may be rescreened. Rescreened participants will be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

We typically see and operate on 20-25 patients per month in our endocrine surgery practice who undergo thyroid or re-operative parathyroid surgery in whom IOLNM is routine. Over a one-year period this would give us access to 200-250 patients who would meet inclusion criteria. Assuming approximately 25-50% of patients consent to participate, this should comfortably allow us to recruit 75-125 patients over the proposed study period. Based on our experience suggesting a 10-15% incidence of IOLNM system malfunction or failure, this should allow us 8-15 patients with IOLNM malfunction with which to directly compare and describe the information available to the surgeon from routine IOLNM and from the IOVL. The degree to which this information differs will allow us to determine if we think IOVL may provide information that could change outcomes and if further, larger studies are warranted.
Patients will be approached to consent in any one of the clinic spaces used by the investigators on this study. All of these locations are listed above. All surgical procedures will be performed in the operating rooms at Mount Sinai Hospital, Mount Sinai Morningside, Mount Sinai West, and Mount Sinai Beth Israel. Follow up visits will be at the previously described clinic locations.

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

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

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

Intraoperative video laryngoscopy will be used in conjunction with routine intraoperative nerve monitoring. We seek to asses the degree to which this will provide additional data on nerve integrity and vocal cord function for patients undergoing neck procedures that place the recurrent and superior laryngeal nerves at risk for injury or postoperative dysfunction.

6.1.2 ADMINISTRATION AND/OR DOSING

At the patient's standard of care surgery, prior to intubation, the patient will receive glycopyrrolate 0.004 mg/kg, as per typical pre-anesthetic dosing regimen. Upon intubation, the video laryngoscope will be passed under direct vision and secured alongside the endotracheal tube. Vocal cords will be positioned in the visual field of the laryngoscope before beginning the operation. Following video laryngoscopy, and initiation of the procedure, the ipsilateral vagus nerve will be testing used nerve stimulation (per standard protocol) to ensure good distal nerve conduction and identify potential non-recurrent laryngeal nerve anatomy. At all points during the procedure where intraoperative nerve monitoring is used, information about vocal cord motion from video laryngoscopy will also be recorded. Specifically, we will record the neuropraxia index from the nerve monitor, and whether vocal cord function in concordant with the nueropraxia index. At the conclusion of resection, the recurrent and superior laryngeal nerves will be assessed with IONM, the vagus will be assessed with IONM, and lastly the vocal cords will be assessed with IOVL. This sequence is consistent with the describe protocol for IONM for testing the vagus and recurrent nerve prior to resection, and then again in reverse order following resection (V1R1R2V2). After conclusion of the procedure and final surgical closing, prior to extubation, vocal cord function will again be assessed with video laryngoscopy.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

N/A

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

N/A

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

N/A

6.5 CONCOMITANT THERAPY

N/A

6.5.1 RESCUE THERAPY

N/A

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

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

N/A

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participation in this study is completely voluntary. Subjects are free to withdraw their participation at any time. Subjects who wish to withdraw from the study must contact the Principal Investigator or the research staff. Requests to withdraw from the study must be done in writing to the Principal Investigator at the address provided on the consent form.
The Principal Investigator or the institution may end a subject's involvement in the research study at any time without consent from the subject. This may be because the research study is being stopped, the instructions of the study team have not been followed by the subject, the investigator believes it is in the subject's best interest, or for any other reason.

7.3 LOST TO FOLLOW-UP

N/A

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

Data will be stored in the secure REDCap database. The study investigators will have access to the study data, which will be stored on a Mount Sinai secured, shared network drive. All paper documents relating to the study will be stored in the Research Office. The data will be stored with a code that can be linked to the identity of the participant.
Duration the data will be stored: The Principal Investigator will keep the data on a mass storage device, Mount Sinai's server, for a minimum period of six years after publication.
All study data collected will be entered into the electronic REDCap database. The data will be stored on a Mount Sinai network drive, accessible only to the PI and members of the research team. The data will be password protected.
Data is always de-identified prior to data analysis. In all disclosures outside of Mount Sinai, subjects are not identified by name, social security number, address, telephone number, or any other direct personal identifier unless disclosure of the direct identifier is required by law.
All data analysis will be done on de-identified data only and on a secure Mount Sinai Network computer.

All discussions with patients will be conducted in a private area away from distractions, in order to maintain patient privacy. The patient will have control of/be responsible for scheduling their appointments at a time that is convenient for them. In order to make the subject feel "at ease," study personnel will be accessible, available, and receptive to questions and concerns raised by the patient about study-related procedures.
If subjects are injured or made sick from taking part in this research study, medical care will be provided. Generally, this medical care will be billed to the subject and/or their health care insurance. In the event of injury, subjects should contact the Principal Investigator, Randall Owen.

8.2 SAFETY ASSESSMENTS

At standard 1-week and 3-month post-operative follow-up we will perform routine fiberoptic laryngoscopy, per common practice, to assess vocal cord function.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

This protocol uses the definition of adverse event from 21 CFR 312.32 (a): any untoward medical occurrence associated with the use of an intervention in humans, ***whether or not considered intervention-related***.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

N/A

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All adverse events (AEs) will have their relationship to study procedures, including the intervention, assessed by an appropriately-trained clinician based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Related** – The AE is known to occur with the study procedures, there is a reasonable possibility that the study procedures caused the AE, or there is a temporal relationship between the study procedures and the event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study procedures and the AE.
- **Not Related** – There is not a reasonable possibility that the study procedures caused the event, there is no temporal relationship between the study procedures and event onset, or an alternate etiology has been established.

8.3.3.3 EXPECTEDNESS

A clinician with appropriate expertise in hyperparathyroidism will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedures.

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

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs, not otherwise precluded per the protocol, will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical or psychiatric condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Documentation of onset and duration of each episode will be maintained for AEs characterized as intermittent.

The study coordinator will record events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At

each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

The Principal Investigator or a study team member will report adverse events to the sponsor and IRB in a timely manner.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

In consultation with the PI, a trained member of the study team will be responsible for conducting an evaluation of a serious adverse event and shall report the results of such evaluation to the sponsor and the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the event.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

N/A

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

N/A

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-

approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEMS REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number
- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

N/A

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

N/A

9.2 SAMPLE SIZE DETERMINATION

N/A

9.3 POPULATIONS FOR ANALYSES

N/A

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

All statistical analysis will be done on deidentified data only, using SPSS on a secure Mount Sinai Network computer.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

N/A

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

N/A

9.4.4 SAFETY ANALYSES

N/A

9.4.5 BASELINE DESCRIPTIVE STATISTICS

N/A

9.4.6 PLANNED INTERIM ANALYSES

N/A

9.4.7 SUB-GROUP ANALYSES

N/A

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

N/A

9.4.9 EXPLORATORY ANALYSES

N/A

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks will be given to the participant and written documentation of informed consent will be completed prior to starting the study intervention. The following consent materials are submitted with this protocol: Informed Consent Form. We do anticipate enrolling non-English speaking patients. Once this consent form is IRB approved, we will have it translated into Spanish and Russian and submit a modification to have these consent documents approved. We will also potentially enroll patients who speak other languages. However, since we do not expect to enroll a significant number of patients who speak any other language, we will be using the short form consent process to consent those patients. We will approach the IRB on a case-by-case basis to request a short form consent.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

A member of the study team identifies potential study subjects from the review of the clinic and/or operating room schedules of study physicians. A HIPAA waiver is being requested for access to this information during this pre-screening process. Potential subjects are first approached by their treating physician during a routine office visit, to asses interest in the study. If the patient expresses interest, a member of the study team will approach them for an informed consent process following Mount Sinai SOP. If patients prefer to spend extra time going over the consent form, they can also consent for participation immediately before the surgical procedure. However in this case, even if the patient has already been informed of the study they will still go through the entire document with a member of the research team before signing. Patients are considered to be enrolled in the study after signing the ICF.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, and the Institutional Review Board (IRB) and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the safety and oversight monitor(s). This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally-identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

All research activities will be conducted in as private a setting as possible.

The representatives of the Institutional Review Board (IRB), or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored on a Mount Sinai secured, shared network drive. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived on a Mount Sinai secured network drive.

Data will be stored in the secure REDCap database. Only the study investigators will have access to the study data, which will be stored on a Mount Sinai secured, shared network drive. The data will be password protected. All paper document relating to the study will be stored in the Research Office. Data is always de-identified prior to data analysis. In all disclosures outside of Mount Sinai, subjects are not identified by name, social security number, address, telephone number, or any other direct personal identifier unless disclosure of the direct identifier is required by law.
PHI will be protected in the HIPAA-compliant, secure REDCap Database. This will be accessed by password-protected, encrypted computers.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

All patient identifiers will be destroyed as soon as data collection and analysis are complete. All analysis will be conducted on de-identified data. The Principal Investigator will keep the data on a mass storage device, Mount Sinai's server, for a minimum of six years after publication.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	Medical Monitor or Independent Safety Monitor
Randall Owen, MD	N/A
Icahn School of Medicine at Mount Sinai	
[redacted] Box 1103, New York, NY 10029	
212-241-2891	
Randall.owen@mountsinai.org	

Mount Sinai's Institutional Review Board is responsible for study oversight. Study misconduct will be reported to the IRB.

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise. Members of the DSMB will be independent from the study conduct and free of conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data from each arm of the study. The DSMB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the research team.

10.1.7 CLINICAL MONITORING

N/A

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data collection, documentation and completion. All sites will follow a common quality management plan.

Quality control (QC) procedures will be implemented as follows:

Informed consent --- Study staff will review both the documentation of the consenting process as well as a percentage of the completed consent documents. This review will evaluate compliance with GCP, accuracy, and completeness. Feedback will be provided to the study team to ensure proper consenting procedures are followed.

Source documents and the electronic data --- Data will be initially captured on source documents (see **Section 10.1.9, Data Handling and Record Keeping**) and will ultimately be entered into the study database. To ensure accuracy site staff will compare a representative sample of source data against the database, targeting key data points in that review.

Protocol Deviations – The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

Should independent monitoring become necessary, the PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant consented/enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents will be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap. The data system includes password protection.

10.1.9.2 STUDY RECORDS RETENTION

The Principal Investigator will keep the data on a mass storage device, Mount Sinai's server, for a minimum period of six years after publication.

10.1.10 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.
It will be the responsibility of the site investigator to use continuous vigilance to identify and report deviations. All deviations will be addressed in study source documents and will be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator will be responsible for knowing and adhering to the reviewing IRB requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

All published data will be de-identified.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the IRB has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS AND SPECIAL TERMS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event

EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

*The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A **Summary of Changes** table for the current amendment is located in the **Protocol Title Page**.*

Version	Date	Description of Change	Brief Rationale

11 REFERENCES