

Efficacy of opioid-limiting pain management protocol in men  
undergoing urethroplasty

Study Protocol & Statistical Analysis Plan

NCT03859024

10 October 2020

Adam Baumgarten, MD, MBA, Principal Investigator  
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Birmingham, AL 35294

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**Principal Investigator: Adam Baumgarten**

**Sponsor: UAB Department of Urology**

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## STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator will assure that no deviation from, or changes to, the protocol will take place without prior documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial subjects. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the local Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. 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 will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from subjects who provided consent, using a previously approved consent form.

## 1 PROTOCOL SUMMARY

### 1.1 SYNOPSIS

<b>Title:</b>	Efficacy of opioid-limiting pain management protocol in men undergoing urethroplasty
<b>Study Description:</b>	
<b>Objectives:</b>	<i>The purpose of this study is to assess the difference in narcotic usage between two different pain management protocols after urethroplasty.</i>
<b>Endpoints:</b>	The primary endpoints are overall pain scores and rate of prescription filling.
<b>Study Population:</b>	The study population is adult men who are scheduled for anterior urethroplasty surgery and have no exclusion criteria.
<b>Phase:</b>	
<b>Description of Study Intervention:</b>	Participants will be randomized to a control or intervention group. The intervention group will receive acetaminophen 975mg PO, Celebrex 200mg PO, and gabapentin 300mg PO in preoperative holding, and they will receive 30mL 1/2 % bupivacaine injection and dexamethasone 4mg as a peripheral nerve block (dorsal penile nerve and pudendal branches) at the beginning of surgery. The control group will receive historical standard management of pain during and after surgery.
<b>Study Duration:</b>	16 months
<b>Subject Duration:</b>	Approximately 1 month

## 2 INTRODUCTION

### 2.1 STUDY RATIONALE

In the past the PI has participated in a study on the use of bupivacaine for pain control after penile prosthesis placement. We found that patients who received bupivacaine had statistically significantly lower pain scores after surgery in the prior surgery. We have also been using the ERAS protocol (Enhanced Recovery after Surgery), a multimodal perioperative care pathway designed to achieve early recovery after surgical procedures, for cystectomy and seen reduced narcotic usage among those patients. Given the heightened concern over narcotic usage by postoperative patients, including the risk of chronic usage by even young patients, our objective will be to assess if using this protocol can limit the need for postoperative narcotics prescriptions.

### 2.2 RISK/BENEFIT ASSESSMENT

#### 2.2.1 KNOWN POTENTIAL RISKS

Risks are minimal and include any possible reaction to the injection agent. This may include damage to local structures or an allergic reaction to the bupivacaine and the agents within it.

Risks of the enhanced recovery include the general risks of *the additional medications given*. These include: side effect or allergic reaction from acetaminophen or gabapentin, pain and discomfort from the procedure, excessive bleeding, infection, nerve damage, failed analgesia, and allergic reaction to local anesthetic. Risks are listed below.

*Allergic reaction: rare, unlikely to be severe, reversible*

*Bleeding: very rare for severe bleeding, reversible*

*Infection: uncommon, treatable with antibiotics, reversible with treatment Nerve damage: very rare, can be severe, may or may not be reversible Failed analgesia: rare, reversible with more anesthetic given*

The usual precautions taken during giving oral medication or injection of a local anesthetic will be taken – ensuring no allergy, ensuring no injection directly into a blood vessel, ensuring non-expiration status of the drug, etc. Monitoring will be done by the surgical and anesthetic team intraoperatively and postoperatively.

## 3 STUDY DESIGN

### 3.1 OVERALL DESIGN

Our management at the current time varies between giving intraoperative analgesics with peripheral nerve blocks in some patients, but others we do not. In this study, one group will continue the historical standard care of the hospital, which involves postoperative NSAIDs and narcotics for pain control. The other group will utilize a protocol to minimize narcotics usage, including acetaminophen, gabapentin, Celebrex, and local anesthetic (bupivacaine) in an attempt to reduce the usage of narcotics after urethroplasty surgery. Patient pain scores will be measured in clinic, on the day of surgery in preoperative holding, and per the standard protocol postoperatively. During surgery, patients will be randomized to receive either the standard protocol or the enhanced recovery protocol. At discharge,

men will be given a narcotic prescription in a sealed envelope after surgery, with each patient getting the same narcotic prescription regardless of group. Pain scores, time to first narcotic usage, use of narcotics in morphine equivalents, and narcotic refill requests will be assessed postoperatively. Prescription filling will be monitored via the Alabama Prescription Drug Monitoring Program (PDMP).

## 4 STUDY POPULATION

### 4.1 INCLUSION CRITERIA

men > age 18 who are scheduled for anterior urethroplasty surgery

### 4.2 EXCLUSION CRITERIA

1. Any patient not classified as an ASA II or III.
2. General Anesthesia or neuraxial anesthesia with epidural used as anesthetic techniques
3. Allergy/intolerance to local anesthetic or steroids.
4. Pre-existing neurological and/or anatomical deficit that would preclude regional block.
5. Coexisting coagulopathy such as hemophilia or von Willebrand Disease.
6. BMI > 40 or < 20.
7. History of intravenous drug or opioid abuse.
8. History of opioid use within a week prior to urethroplasty.
9. History of any chronic pain syndrome.
10. Posterior urethroplasty
11. Female gender
12. Men < 18
13. Patients with chronic kidney disease
14. Patients allergic to NSAIDs
15. Patients requiring more than one buccal graft harvest
16. Patients with graft urethroplasty with site other than buccal
17. Patients with a history of previous urethroplasty

### 4.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Patients will be recruited by the PI as they are seen in clinic. During their clinic visit they will be assessed by the PI for any exclusion criteria by examining the medical record and history of the patient and planning their procedure.

## 5 STUDY INTERVENTION

### 5.1.1 DOSING AND ADMINISTRATION

Surgery: Once they have signed the consent, on the day of their surgery, patients will be logged into the system and randomized into one of two groups. Group 1 will receive the enhanced protocol: acetaminophen, Celebrex, and gabapentin pre-op, with 30 mL of 1/2 % bupivacaine and 4mg of dexamethasone given as a perineal nerve block at the time of urethroplasty surgery. Narcotics will be

administered judiciously and as seen fit by the anesthesia and/or surgical teams. Postoperative prescriptions will include NSAIDs and narcotics, with patients encouraged to use NSAIDs primarily and narcotics as breakthrough pain control; Group 2 (standard group) will receive the historical standard, which may include narcotics during and after surgery. As in group 1, Postoperative prescriptions will include NSAIDs and narcotics, with patients encouraged to use NSAIDs primarily and narcotics as breakthrough pain control. Randomization will be performed using a random number generator. The surgeon will not be blinded as they perform the local anesthetic injection. Patients will not be blinded insofar as each patient in the enhanced recovery group will receive oral medication preoperatively that the historical group will not.

*Post-Operative Period: Upon arrival in the PACU, the (sub)investigator, using the numerical rating scale (NRS), will clinically assess post-operative pain. Assessment of patient pain levels involve a series of NRS testing postoperatively (upon arrival and every 15 minutes postoperatively until discharge from the PACU) using a 10 cm line. Patients that complain of pain intensity >5 cm/10cm on the NRS, will be given a rescue intravenous hydromorphone regimen, IV hydromorphone at 0.4mg up to a max dose of 2mg prn q 2 hours or until a VAS of <5 is obtained. Due to hydromorphone shortages, IV fentanyl at 25-50mcg dosings or morphine at 2-4mg dosings can be substituted. Post-operative PACU narcotic consumption will be recorded and quantified. Post-operative nausea and vomiting (PONV) will be assessed using a PONV rating scale every 15 minutes until PACU discharge. PONV will be rated as 0, no nausea; 1, mild nausea  $\leq$  15 minutes; 2, nausea  $\geq$  5 minutes and 3, vomiting. PONV will be treated with ondanestron 4 mg intravenously and, if persistent, with metoclopramide 10 mg intravenously.*

*If admitted, PO acetaminophen and/or ibuprofen, along with PO and IV narcotics will be available based on current standard practice. Pain scores will be charted by nursing based on current hospital protocol. Upon discharge, patient will be given prescriptions for ibuprofen 800mg and acetaminophen 1000mg to take on a scheduled basis, alternating for three days. Medications will then be taken as needed. A prescription for narcotic medication (14 pills of oxycodone) will be given in a sealed envelope, and patients will be asked to use this prescription only if needed. The men will then bring the envelope or prescription bottle back to the postoperative visit for assessment of need for narcotics using pill counts.*

## 5.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION

Randomization will be performed using a random number generator. The surgeon will not be blinded as they perform the local anesthetic injection. Patients will not be blinded insofar as each patient in the enhanced recovery group will receive oral medication preoperatively that the historical group will not.

## 6 STUDY INTERVENTION DISCONTINUATION AND SUBJECT DISCONTINUATION/WITHDRAWAL

### 6.1 SUBJECT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Subjects are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a subject from the study for the following reasons:

- Significant study intervention non-compliance



- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject

Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

## 6.2 LOST TO FOLLOW-UP

A subject will be considered lost to follow-up if he or she fails to return for 2 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a subject fails to be available for a required study visit:

- The site will attempt to contact the subject and reschedule the missed visit and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record or study file.
- Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

## 7 STUDY ASSESSMENTS AND PROCEDURES

### 7.1 STUDY ASSESSMENTS

**Screening:** Patients coming into the Urology Clinic at Kirklin Clinic to see Dr. Baumgarten will be screened for inclusion and exclusion criteria. After presenting the research to them, potential participants will have until the day of their surgery to decide whether or not they wish to enroll in the protocol.

**Surgery:** Once they have signed the consent, on the day of their surgery, patients will be logged into the system and randomized into one of two groups. Group 1 will receive the enhanced protocol: acetaminophen, Celebrex, and gabapentin pre-op, with 30 mL of 1/2 % bupivacaine and 4mg of dexamethasone given as a perineal nerve block at the time of urethroplasty surgery. Narcotics will be administered judiciously and as seen fit by the anesthesia and/or surgical teams. Postoperative prescriptions will include NSAIDs and narcotics, with patients encouraged to use NSAIDs primarily and narcotics as breakthrough pain control; Group 2 (standard group) will receive the historical standard, which may include narcotics during and after surgery. As in group 1, Postoperative prescriptions will include NSAIDs and narcotics, with patients encouraged to use NSAIDs primarily and narcotics as breakthrough pain control. Randomization will be performed using a random number generator. The surgeon will not be blinded as they perform the local anesthetic injection. Patients will not be blinded

insofar as each patient in the enhanced recovery group will receive oral medication preoperatively that the historical group will not.

**Post-Operative Period:** Upon arrival in the PACU, the (sub)investigator, using the numerical rating scale (NRS), will clinically assess post-operative pain. Assessment of patient pain levels involve a series of NRS testing postoperatively (upon arrival and every 15 minutes postoperatively until discharge from the PACU) using a 10 cm line. Patients that complain of pain intensity  $>5$  cm/10cm on the NRS, will be given a rescue intravenous hydromorphone regimen, IV hydromorphone at 0.4mg up to a max dose of 2mg prn q 2 hours or until a VAS of  $<5$  is obtained. Due to hydromorphone shortages, IV fentanyl at 25-50mcg dosings or morphine at 2-4mg dosings can be substituted. Post-operative PACU narcotic consumption will be recorded and quantified. Post-operative nausea and vomiting (PONV) will be assessed using a PONV rating scale every 15 minutes until PACU discharge. PONV will be rated as 0, no nausea; 1, mild nausea  $\leq 15$  minutes; 2, nausea  $\geq 5$  minutes and 3, vomiting. PONV will be treated with ondanestron 4 mg intravenously and, if persistent, with metoclopramide 10 mg intravenously. If admitted, PO acetaminophen and/or ibuprofen, along with PO and IV narcotics will be available based on current standard practice. Pain scores will be charted by nursing based on current hospital protocol. Upon discharge, patient will be given prescriptions for ibuprofen 800mg and acetaminophen 1000mg to take on a scheduled basis, alternating for three days. Medications will then be taken as needed. A prescription for narcotic medication (14 pills of oxycodone) will be given in a sealed envelope, and patients will be asked to use this prescription only if needed. The men will then bring the envelope or prescription bottle back to the postoperative visit for assessment of need for narcotics using pill counts.

**Data Collection:** Study personnel will use information from the patient's medical record as well as pain scale responses and number of narcotic pills used post-operatively to populate the database.

## 7.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

### 7.2.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

### 7.2.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event (of note, the term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event, rather than to an event which hypothetically might have caused death if it were more severe)
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the

subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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### 7.2.3 CLASSIFICATION OF AN ADVERSE EVENT

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#### 7.2.3.1 SEVERITY OF EVENT

For adverse events (AEs), the following guidelines will be used to describe severity:

- **Mild** – Events require minimal or no treatment and do not interfere with the subject’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 subject’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.”

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#### 7.2.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the subject based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

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

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#### 7.2.3.3 EXPECTEDNESS

The Principal Investigator 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 intervention.

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### 7.2.4 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 subject presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs 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 product (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 must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the study subject'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. AEs characterized as intermittent require documentation of onset and duration of each episode.

The Study Coordinator will record all reportable 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 Study Coordinator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

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#### 7.2.5 ADVERSE AND SERIOUS ADVERSE EVENT REPORTING

All serious adverse events must be reported to the IRB according to regulatory requirements. The Principal Investigator will immediately report to the sponsor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or package insert and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the Principal Investigator deems the event to be chronic or the subject is stable. Other supporting documentation of the event may be requested and should be provided as soon as possible.

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### 7.3 UNANTICIPATED PROBLEMS

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#### 7.3.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects 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 subject 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 subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

### 7.3.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB). 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.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB within 10 working days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB within 10 working days of the investigator becoming aware of the problem.

## 8 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

### 8.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

#### 8.1.1 INFORMED CONSENT PROCESS

##### 8.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO SUBJECTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to conducting study screening procedures. A separate screening consent form will not be used.

##### 8.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the subject will be asked to read and review the document. The investigator will explain the research study to the subject and answer any questions that may arise. A verbal explanation will be provided in terms suited to the subject's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research subjects. Subjects will have the opportunity to carefully review the written consent form and ask questions prior to signing. The subjects should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The subject will sign the informed consent document prior to any procedures being done specifically for the study. Subjects must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the subjects for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the subject undergoes any study-specific procedures. The rights and welfare of the

subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

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#### 8.1.2 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 regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study subjects and the Institutional Review Board (IRB), will provide the reason(s) for the termination or suspension. Study subjects will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB.

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#### 8.1.3 CONFIDENTIALITY AND PRIVACY

Subject confidentiality and privacy is strictly held in trust by the participating investigators and their staff. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Principal Investigator.

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

Representatives of the Institutional Review Board (IRB) 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 subjects in this study. The clinical study site will permit access to such records.

The study subject'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 and/or Institutional policies.

Study subject research data, which is for purposes of statistical analysis and scientific reporting, will be stored at the UAB Department of Otolaryngology research office. This will not include the subject's contact or identifying information. Rather, individual subjects and their research data will be identified by a unique study identification number. The study data entry and study management systems used by research staff will be secured and password protected.

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#### 8.1.4 QUALITY ASSURANCE AND QUALITY CONTROL

The site will perform internal quality management of study conduct, data collection, documentation and completion. Quality control (QC) procedures will be completed by the Data Manager during data entry into the appropriate CRF. Any missing data or data anomalies will be communicated to the Study Coordinator for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements.

The site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and inspection by local and regulatory authorities.

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#### 8.1.5 DATA HANDLING AND RECORD KEEPING

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##### 8.1.5.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

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

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

Hard copies of source document worksheets will be used for recording data for each subject enrolled in the study. Data recorded in the case report form (CRF) derived from source documents should be consistent with the data recorded on the source documents.

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##### 8.1.5.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 3 years after the completion of the study. These documents should be retained for a longer period, however, if required by local regulations.

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#### 8.1.6 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the Principal Investigator to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The Principal Investigator is responsible for knowing and adhering to the reviewing IRB requirements.

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#### 8.1.7 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.



## 8.2 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DHHS	Department of Health and Human Services
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
LSMEANS	Least-squares Means
NCT	National Clinical Trial
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOA	Schedule of Activities
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

## 9 REFERENCES