

The Role of Regional Anesthesia to Reduce Opioid Requirements Following Functional Endoscopic Sinus Surgery (FESS)

National Clinical Trial (NCT) Identified Number: NCT03757715

Principal Investigator: Bradford Woodworth, MD

Sponsor: University of Alabama at Birmingham

Version Number: v.1.0

27 November 2018

Table of Contents

STATEMENT OF COMPLIANCE	1
1 PROTOCOL SUMMARY	1
1.1 Synopsis.....	1
1.2 Schedule of Activities (SoA).....	2
2 INTRODUCTION	2
2.1 Study Rationale.....	2
2.2 Background.....	2
2.3 Risk/Benefit Assessment.....	3
2.3.1 Known Potential Risks.....	3
2.3.2 Known Potential Benefits.....	4
2.3.3 Assessment of Potential Risks and Benefits.....	4
3 OBJECTIVES AND ENDPOINTS	5
4 STUDY DESIGN	5
4.1 Overall Design.....	5
4.2 Scientific Rationale for Study Design.....	7
4.3 Justification for Dose.....	7
4.4 End of Study Definition	7
5 STUDY POPULATION	7
5.1 Inclusion Criteria	7
5.2 Exclusion Criteria.....	7
5.3 Screen Failures	8
5.4 Strategies for Recruitment and Retention	8
6 STUDY INTERVENTION	8
6.1 Study Intervention(s) Administration	8
6.1.1 Study Intervention Description	8
6.1.2 Dosing and Administration.....	8
6.2 Measures to Minimize Bias: Randomization.....	8
6.3 Study Intervention Compliance.....	9
6.4 Concomitant Therapy	9
7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL	9
7.1 Discontinuation of Study Intervention	9
7.2 Participant Discontinuation/Withdrawal from the Study	9
7.3 Lost to Follow-Up	9
8 STUDY ASSESSMENTS AND PROCEDURES	10
8.1 STUDY Assessments.....	10
8.2 Adverse Events and Serious Adverse Events	11
8.2.1 Definition of Adverse Events (AE)	11
8.2.2 Definition of Serious Adverse Events (SAE)	11
8.2.3 Classification of an Adverse Event.....	11
8.2.4 Time Period and Frequency for Event Assessment and Follow-Up.....	12
8.2.5 Adverse AND SERIOUS Event Reporting.....	12
8.3 Unanticipated Problems.....	13
8.3.1 Definition of Unanticipated Problems (UP).....	13
8.3.2 Unanticipated Problem Reporting.....	13

9	STATISTICAL CONSIDERATIONS	14
9.1	Statistical Hypotheses.....	14
9.2	Sample Size Determination.....	14
9.3	Populations for Analyses	15
9.4	Statistical Analyses.....	15
9.4.1	General Approach.....	15
9.4.2	Analysis of the Primary Efficacy Endpoint(s)	16
9.4.3	Analysis of the Secondary Endpoint(s).....	16
9.4.4	Safety Analyses.....	17
9.4.5	Baseline Descriptive Statistics	17
9.4.6	Planned Interim Analyses.....	17
9.4.7	Sub-Group Analyses	18
9.4.8	Tabulation of Individual participant Data	18
10	SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS	19
10.1	Regulatory, Ethical, and Study Oversight Considerations.....	19
10.1.1	Informed Consent Process	19
10.1.2	Study Discontinuation and Closure	19
10.1.3	Confidentiality and Privacy	20
10.1.4	Quality Assurance and Quality Control.....	20
10.1.5	Data Handling and Record Keeping.....	21
10.1.6	Protocol Deviations	21
10.1.7	Publication and Data Sharing Policy	21
10.1.8	Conflict of Interest Policy	22
10.2	Abbreviations.....	22
10.3	Protocol Amendment History	23
11	REFERENCES	24

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 participants. 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 participant 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 participant 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 participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: The Role of Regional Anesthesia to Reduce Opioid Requirements Following Functional Endoscopic Sinus Surgery (FESS)

Study Description: Opioid analgesics are prescribed for moderate to severe pain disorders, however there are contraindications and side effects that are common to all opioids. We hypothesize using local regional anesthetic during sinus surgery will reduce pain, therefore decreasing the need for post-operative opioid medication. The primary objective is to determine if a long-acting regional anesthetic applied during a surgery will reduce post-operative oral opioid usage.

Objectives: *Primary Objective:* The primary objective is to determine if a long-acting regional anesthetic applied after a surgery will reduce post-operative oral opioid usage.

Secondary Objective: The secondary objective is to measure the level of each patient's pain.

Endpoints:

- *Primary Endpoint:* The amount of post-operative pain after FESS. Participants will self-report a pain score on a scale of 0-10, with 0 being "no pain" and 10 being "worst pain imaginable" on the provided questionnaire (see Appendix 1).

- *Secondary Endpoint:* Patient's daily pain medication usage. The amount of opioid medication used post-procedure will be determined by a pill count at the first post-operative clinic visit.

Study Population: It is anticipated that 30 subjects will be enrolled in this protocol. Potential subjects will be male or female adults over the age of 18 from the United States who undergo functional endoscopic sinus surgery under the supervision of one surgeon.

Phase: 4

Description of Study	Treatment group: 20 mL of 1.3% bupivacaine with 2 mg dexamethasone injected locally in the location for sensory nerves of the sinus cavities and face during the FESS.
Intervention:	Control group: No long-acting regional anesthetic will be used during the FESS.
Study Duration:	12 months
Participant Duration:	Up to 21 days (dependent on standard of care scheduling for first post-operative clinic visit)

1.2 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening/ Baseline	Day of Surgery	Day 10-21
Informed consent	X		
Demographics	X		
Medical history	X		
Physical exam	X		
Vital signs	X		
Height & weight	X		
Nasal endoscopy	X		X
CT scans	X		
Randomization		X	
Administer study intervention		X	
Concomitant medication review	X	X	X
Adverse event review and evaluation	X	X	X
Pain diary		X	X
Visual analog scale	X	X	X
Pain medication reconciliation			X

2 INTRODUCTION

2.1 STUDY RATIONALE

Opioid analgesics are still being prescribed to help control moderate to severe pain, however these medications are not without risks. Patients are at an increased risk of dependence which is a growing national concern. We plan to conduct a clinical trial to evaluate the use of regional anesthesia after routine sinus surgery to help decrease the need for post-operative opioid use.

2.2 BACKGROUND

Opioid analgesics are prescribed for moderate to severe acute pain; however, there are contraindications, cautions, and side effects that are common with all opioids. Dependence and tolerance are also likely with regular opioid use, resulting in the current nationwide opioid epidemic. In

Alabama alone, there were 343 opioid-related overdose deaths in 2016, 124 of which were related to prescription opioids. Alabama providers have the highest prescribing rate in the country, nearly twice the national rate, per the NIH/NIDA website (<https://www.drugabuse.gov/drugs-abuse/opioids/opioid-summaries-by-state/alabama-opioid-summary>). In 2015, the Centers for Disease Control (CDC) released prescribing guidelines relating to chronic pain, and in 2018 Alabama's Blue Cross/Blue Shield insurance group limited the supply of opioids allowed to their members to 7 days (https://www.al.com/news/index.ssf/2018/03/bluecross_blueShield_changing.html).

There is currently no clinical guideline for prescribing post-operative opioid medications for functional endoscopic sinus surgery (FESS). A 2018 survey documenting prescribing patterns by 168 members of the American Rhinologic Society found that most physicians who participated prescribed, on average, 27 opioid pain pills for patients after surgery. Prior studies have been performed to help decrease the pain patient's feel after sinus surgery. Haytoglu (2016) revealed that adding non absorbable sinus packs loaded with local anesthetics such as bupivacaine achieved less pain values and improved patient satisfaction scores.

Given this current data we believe injecting patients with a long acting analgesic during the procedure will help reduce post-operative pain. If we can decrease the amount of pain patients have in the post-operative period we can theoretically decrease the number of opioid pain pills prescribed. We plan to also track the number of opioid pills consumed by patients in the post-operative period to obtain a somewhat uniform prescribing pattern within surgeons.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

All of the drugs to be used in this study are FDA-approved, commonly-used, widely available, generic medications. These drugs will be prescribed at their standard dosing for their approved indications.

As outlined in the package inserts for the medications under study in this protocol, the following adverse reactions have been identified during post approval use. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- *Risks associated with bupivacaine hydrochloride (MarcaineTM):* The most frequently reported adverse reactions are restlessness, anxiety, dizziness, tinnitus, blurred vision, tremors, nausea, vomiting, chills, and constriction of pupils (central nervous system reactions) and depression of the myocardium, decreased cardiac output, heartblock, hypotension, bradycardia, ventricular arrhythmias, including ventricular tachycardia and ventricular fibrillation, and cardiac arrest (cardiovascular system reactions). Other reported reactions include persistent anesthesia, paresthesia, weakness, or paralysis. Allergic reactions are characterized by signs such as urticaria, pruritus, erythema, angioneurotic edema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and possibly, anaphylactoid-like symptomatology (including severe hypotension). Reactions to MARCAINE are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs is excessive plasma levels, which may be due to overdosage, unintentional intravascular injection, or slow metabolic degradation. In

addition to systemic dose-related toxicity, unintentional subarachnoid injection of drug during the intended performance of caudal or lumbar epidural block or nerve blocks near the vertebral column (especially in the head and neck region) may result in underventilation or apnea ("Total or High Spinal"). Also, hypotension due to loss of sympathetic tone and respiratory paralysis or underventilation due to cephalad extension of the motor level of anesthesia may occur. This may lead to secondary cardiac arrest if untreated. Patients over 65 years, particularly those with hypertension, may be at increased risk for experiencing the hypotensive effects of bupivacaine hydrochloride. Factors influencing plasma protein binding, such as acidosis, systemic diseases which alter protein production, or competition of other drugs for protein binding sites, may diminish individual tolerance. Bupivacaine hydrochloride carries a black box warning for cardiac arrest with difficult resuscitation or death during use for epidural anesthesia in obstetrical patients.

- *Risks associated with dexamethasone sodium phosphate injection:* The most frequently reported adverse reactions are anaphylaxis, infection, seizures, hypertension, erythema, rash, urticarial, nausea, vomiting, edema, petechial, ecchymosis, skin pigmentation abnormality, acne, headache, dizziness, vertigo, insomnia, anxiety, and depression.
- *Risks associated with protocol-mandated procedures:*
 - *Surgical procedures:* All surgical procedures will be performed in the routine manner. There will be no additional clinical or surgical risks, other than the normal risks for patients undergoing this type of treatment.
 - *Questionnaires:* Completion of a questionnaire and the questions might make the subject feel uncomfortable or upset. Subjects will have the choice to not answer any such questions.

2.3.2 KNOWN POTENTIAL BENEFITS

An article published in 2015 by Knezevic evaluated 14 studies in which physicians added dexamethasone into the local anesthetic used for brachial plexus block. They concluded patients injected with local anesthetic plus dexamethasone had improved post-operative pain when compared to a control group. Our goal is to apply this to sinus surgery in providing analgesia to the sensory nerves of the face/sinus. The immediate potential benefit for the patient is reduced discomfort and pain in the post-operative period. Potential long term benefits would include decrease need for post-operative opioid consumption therefore potentially decreasing the possible addictive habit of using opioids.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Routinely dexamethasone is used for general anesthesia to help decrease inflammation and post-operative swelling. All patients will be screened for any previous reactions to the medications being used in our study. Patient medical records will also be reviewed for past drug allergies. As our study plans to evaluate the local effects of bupivacaine with dexamethasone, we anticipate only mild local reactions, as we will not systemically inject the drugs being used. The risks to participants will likely encounter only local skin reactions to the medications. The information gained will help to possibly standardize how we treat post-operative pain after sinus surgery.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary	Primary	Primary
The primary objective is to determine if a long-acting regional anesthetic applied after a surgery will reduce post-operative oral opioid usage.	The amount of post-operative pain after FESS. Participants will self-report a pain score on a scale of 0-10, with 0 being “no pain” and 10 being “worst pain imaginable.”	The use of narcotics post-operatively is to control pain; if we can reduce post-operative pain, essentially we can decrease post-operative opioid use.
Secondary	Secondary	Secondary
The secondary objective is to measure the level of each patient's pain.	Patients' daily pain medication usage. The amount of opioid medication used post-procedure will be determined by a pill count at the first post-operative clinic visit.	Pain is a subjectively based outcome that can be difficult to determine prior to a surgery. We believe if we are able to reduce pain in the majority of our patients tested then, we can apply this on a global scale to create a uniform number of opioid pain medications prescribed after surgery.

4 STUDY DESIGN

4.1 OVERALL DESIGN

Opioid analgesics are prescribed for moderate to severe pain disorders; however, there are contraindications and side effects that are common to all opioids. We hypothesize using local regional anesthetic after sinus surgery will reduce pain, therefore decreasing the need for post-operative opioid consumption.

This is a Phase 4, randomized, single-blinded, single-site, parallel-assignment intervention with a primary purpose of supportive care after functional endoscopic sinus surgery (FESS). It is anticipated that 30 subjects will be enrolled in this protocol. Potential subjects will be male or female adults over the age of 18 from the United States who undergo functional endoscopic sinus surgery (FESS) under the supervision of one surgeon.

Potential participants will be approached during their regularly-scheduled clinic visit about participation in the study. If they agree to participate, they will sign an informed consent form. During the baseline visit, demographic information, medical history, concomitant medications, vital signs, height, and weight will be collected. A routine nasal endoscopy will be performed to assess the need for surgical intervention, and routine CT sinus scans will be obtained and/or reviewed.

Participants will be randomized to one of the two following groups:

- **Treatment Group (n = 15):** participants will receive 20 mL of 1.3% bupivacaine with 2 mg dexamethasone injected locally in the location for sensory nerves of the sinus cavities and face during the FESS procedure
- **Control Group (n = 15):** participants will not receive regional anesthetic during the FESS procedure

Participants will have their scheduled functional endoscopic sinus surgery procedure. After surgery, participants will be given a pain diary to record their pain score on a scale of 1-10, and a place to record their use of opioids, as well as over-the-counter non-steroid anti-inflammatories such as acetaminophen and ibuprofen. Participants will record their scores and drug use daily for 10 days post-surgery. At their first post-operative clinic visit, the diary will be reviewed, and their opioid use will also be evaluated by counting the pills left on their prescription.

Data points/variables to be collected during the study could include the following, to be ascertained from the medical record and/or patient report:

- Name
- Medical Record Number
- Age
- Gender
- Type of surgery
- Duration of surgery
- Medications given by anesthesia intra- and post-operatively
- Post-operative pain medication used prior to and after discharge
- Post-operative complications
- Post-discharge/post-operative pain evaluation by patient diary

Participant duration will be up to 21 days, dependent on standard-of-care scheduling of the first post-operative clinic visit. It is anticipated that the study will be open to enrollment for 12 months.

Primary Objective: The primary objective is to determine if a long-acting local regional anesthetic applied after a surgery will reduce post-operative oral opioid usage.

- Primary Endpoint: The amount of post-operative pain after FESS, as determined by patient self-report of pain on a scale of 0-10.

Secondary Objective: The secondary objective is to measure the level of each patient's pain.

- Secondary Endpoint: Patient's daily pain medication usage.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The rationale for our study deals with anesthetizing the sensory nerves of the face. The nerve distribution of the face deals with the trigeminal nerve. We plan to inject a long acting local analgesic at the infraorbital, infatrocchlear, external nasal, supraorbital, supratrochlear nerves of the face after functional endoscopic sinus surgery. The control arm will be randomly chosen for which patient will not be injected. A potential problem with the control group is that patients in the PACU will have intact facial sensation. This could alert them to the fact that they were not injected with a local analgesic and thus reinforce the need for post-operative narcotic usage.

4.3 JUSTIFICATION FOR DOSE

The nasal cavity is innervated by sensory nerves via the trigeminal nerve. We believe using a standardized dose of bupivacaine 1.3% combined with 2mg preservative-free dexamethasone to areas on or around the nasal cavity that are innervated with sensory nerves will improve post-operative pain control results. A max amount of 20 mL will be injected into each study participant. The control group will receive no injection.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.2.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial.

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 years or older
2. Ability to speak English
3. Ability to sign informed consent form
4. Ability to comply with all study procedures
5. Diagnosis of chronic rhinosinusitis
6. Scheduled to receive functional endoscopic sinus surgery (FESS) at UAB

5.2 EXCLUSION CRITERIA

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

1. Current use of opioid medication
2. Known allergic reactions to components of the study intervention
3. History of IV drug use or abuse
4. History of opioid abuse
5. History of chronic pain disorder
6. Treatment with another investigational drug or other intervention within 30 days

5.3 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Patients who have presented to the UAB Department of Otolaryngology for evaluation and treatment of chronic sinusitis requiring surgery. The Principal Investigator has a practices specifically designated for treating rhinologic disorders, with potential for enrollment. Subjects will be identified from individuals treatment by the investigators in their clinics. Potential subjects will be approached by the Principal Investigator or qualified research staff authorized to conduct the informed consent discussion during their regularly-scheduled clinic visit about participation in the study.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Bupivacaine hydrochloride (MarcaineTM) is 2-Piperidinocarboxamide, 1-butyl-N-(2,6-dimethylphenyl)-monohydrochloride monohydrate. The molecular formula is C₁₈H₂₈N₂O with a molecular weight of 288.43.

Dexamethasone sodium phosphate is 9-Fluoro-11 β ,17,21-trihydroxy-16 α -methylpregna-1,4-diene-3,20-dione 21-(dihydrogen phosphate) disodium salt. The molecular formula is C₂₂H₂₈FN₂O₈P with a molecular weight of 516.41.

6.1.2 DOSING AND ADMINISTRATION

Treatment Group: 20 mL of 1.3% bupivacaine with 2 mg dexamethasone injected locally in the location for sensory nerves of the sinus cavities and face during the FESS.

Control Group: No local regional anesthetic will be used during the FESS..

6.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION

Subjects will be randomized 1:1 (parallel assignment) into the two treatment groups. The next subject to be randomized into a trial will receive the treatment corresponding to the next free number in the randomization schedule. The appropriate number and associated treatment for the next subject will only be allocated when entry of that subject to the randomized part of the trial has been confirmed.

6.3 STUDY INTERVENTION COMPLIANCE

Subjects will complete a paper medication diary during the treatment period, recording the dates and times when post-operative pain medication is taken. Subjects will bring their bottles of post-operative medication to their Post-Op Day 14 clinic visit, at which time any remaining pills will be counted and recorded on the visit source document. This count will be reconciled with the medication log to calculate compliance.

6.4 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from study intervention will mean discontinuation from the study, and those subjects will be considered screen failures and will be removed from the dataset. No further data will be collected from those who are determined to be screen failures.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

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

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

- 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 participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Non-compliance with follow-up activities

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 be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for the post-operative scheduled visit within 21 days and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and ascertain if the participant wishes to and/or should continue in the study.
- The investigator or his clinic staff will make every effort to regain contact with the participant (where possible, 3 telephone calls/portal messages/emails, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant 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.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 STUDY ASSESSMENTS

Subjects over the age of 18 who are undergoing functional endoscopic sinus surgery for chronic sinusitis as part of routine clinical care will be approached to participate in the study. Subjects screened and enrolled will follow the schedule of events provided in Section 1.2. The following evaluations will be performed:

Screening/Baseline:

- Obtain written informed consent
- Obtain demographic information
- Obtain medical history
- Obtain concomitant medication information
- Obtain routine vital signs, including height and weight
- Obtain routine nasal endoscopy
- Obtain/review routine CT scans of the sinus. This information may be obtained through review of existing data

Day of Surgery

- Randomization into the Treatment Group or the Control Group, as per measures outlined in Section 6.2
- Scheduled routine surgical procedure previously planned, based on subject's condition
- Study intervention administration to all subjects
- Post-operative medication diary will be given to all subjects
- Post-operative visual analog pain scale will be given to all subjects
- Assessment of adverse events
- Assessment of concomitant medications

Post-Operative Clinic Visit #1 (Day 10-21)

- Obtain routine nasal endoscopy
- Review of medication diary
- Review of visual analog pain scale
- Pain medication reconciliation via pill count

- Assessment of adverse events
- Assessment of concomitant medication

8.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.2.1 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)).

8.2.2 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.

8.2.3 CLASSIFICATION OF AN ADVERSE EVENT

8.2.3.1 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”.

8.2.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant 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.

8.2.3.3 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.

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

8.2.5 ADVERSE AND SERIOUS 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.

8.3 UNANTICIPATED PROBLEMS

8.3.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (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.

8.3.2 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 24 hours 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.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures) and the Office for Human Research Protections (OHRP) within the timeline in accordance with the policy of the IRB's receipt of the report of the problem from the investigator.

9 STATISTICAL CONSIDERATIONS

The following subsections should describe the statistical tests and analysis plans for the protocol. They should indicate how the study will answer the most important questions with precision and a minimum of bias, while remaining feasible. Many elements below can be found in ICH Guidance for Industry E9 Statistical Principles for Clinical Trials and the CONSORT statement which describes standards for improving the quality of reporting randomized controlled trials.

State whether there will be a formal Statistical Analysis Plan (SAP). The SAP generally includes additional statistical analysis detail (e.g., more detail of analysis populations, summary of statistical strategies). If a separate SAP will be developed, subsections below can be summarized.

9.1 STATISTICAL HYPOTHESES

State the formal and testable null and alternative hypotheses for primary and key secondary endpoints, specifying the type of comparison (e.g., superiority, equivalence or non-inferiority, dose response) and time period for which each endpoint will be analyzed.

- Primary Efficacy Endpoint(s):

<Insert text>

- Secondary Efficacy Endpoint(s):

<Insert text>

9.2 SAMPLE SIZE DETERMINATION

Include number of participants to recruit, screen, and enroll to have adequate power to test the key hypotheses for the study. Provide all information needed to validate your calculations and judge the feasibility of enrolling and following the necessary number of participants. In particular, specify all of the following:

- *Outcome measure used for calculations (almost always the primary variable)*
- *Test statistic*
- *Null and alternative hypotheses*
- *Type I error rate (alpha)*
- *Power level (e.g., 80% power)*
- *Assumed event rate for dichotomous outcome (or mean and variance of continuous outcome) for each study arm, justified and referenced by historical data as much as possible*

- *Statistical method used to calculate the sample size, with a reference for it and for any software utilized*
- *Anticipated impact of dropout rates, withdrawal, cross-over to other study arms, missing data, etc. on study power (see also 9.4.2 Analysis of the Primary Efficacy Endpoint(s) and 9.4.3 Analysis of the Secondary Endpoint(s))*
- *Method for adjusting calculations for planned interim analyses, if any (Section 9.4.6, Planned Interim Analyses).*

Further, present calculations from a suitable range of assumptions to gauge the robustness of the proposed sample size.

Discuss whether the sample size provides sufficient power for addressing secondary endpoints or exploratory analyses (e.g., subgroup analyses or moderator analyses involving an interaction term, Section 9.4.9, Exploratory Analyses).

<Insert text>

9.3 POPULATIONS FOR ANALYSES

Clearly identify and describe the analysis datasets (e.g., which participants will be included in each). As a guide, this may include, but is not limited to, any or all of the following:

- *Intention-to-Treat (ITT) Analysis Dataset (i.e., all randomized participants)*
- *Modified Intention-to-Treat Analysis Dataset (e.g., participants who took at least one dose of study intervention and/or have some particular amount of follow-up outcome data)*
- *Safety Analysis Dataset: defines the subset of participants for whom safety analyses will be conducted (e.g., participants who took at least one dose of study intervention)*
- *Per-Protocol Analysis Dataset: defines a subset of the participants in the full analysis (ITT) set who complied with the protocol sufficiently to ensure that these data would be likely to represent the effects of study intervention according to the underlying scientific model (e.g., participants who took at least 80% of study intervention for 80% of the days within the maintenance period)*
- *Other Datasets that may be used for sensitivity analyses*

<Insert text>

9.4 STATISTICAL ANALYSES

The following subsections should include a description of the planned statistical methods.

9.4.1 GENERAL APPROACH

As a guide, the following should be addressed, as appropriate:

- *For descriptive statistics, describe how categorical and continuous data will be presented (e.g., percentages, means with standard deviations, median, range).*
- *For inferential tests, indicate the p-value and confidence intervals for statistical significance (Type I error) and whether one or two-tailed.*

- *Indicate whether covariates will be pre-specified in the sections below or later in a SAP.*
- *State whether checks of assumptions (e.g., normality) underlying statistical procedures will be performed and whether any corrective procedures will be applied (e.g., transformation or nonparametric tests).*

<Insert text>

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

For each primary endpoint:

- *Define the measurement or observation and describe how it is calculated, if not readily apparent*
- *Describe the scale (nominal/binary/categorical, ordinal, interval); state if it is measured as a single endpoint/summary measure or repeated measure*
- *Describe the statistical procedure(s) that will be used to analyze the primary endpoint (e.g., multiple regression, repeated measures mixed models, logistic regression, Analysis of Covariance (ANCOVA)). Describe the covariates and factors in the model. Provide your rationale for covariates and how they will be selected to achieve a parsimonious model. If the decision to specify covariates is deferred for the SAP, indicate here.*
- *Describe how results of statistical procedure(s) will be presented (e.g., adjusted means (Least-squares means (LSMEANS)) with standard errors, odds ratios with 95% confidence intervals, prevalence rates, number-needed-to-treat)*
- *Describe details to check assumptions required for certain types of analyses (e.g., proportional hazards, transformations or, when appropriate, nonparametric tests)*
- *Describe the Populations for which the analysis will be conducted, as discussed in **Section 9.3, Populations for Analyses***
- *Describe how missing data will be handled (e.g., type of imputation technique, if any, and provide justification), and approach to handling outliers, nonadherence and lost to follow-up*
- *If there is more than one primary endpoint or more than one analysis of a particular endpoint, state the statistical adjustment used for Type I error criteria or give reasons why it was considered unnecessary.*

Note if more than one endpoint: the statistical approach for endpoints with the same analytic issues can be described as a group.

<Insert text>

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

For each secondary endpoint:

- *Note if analysis of secondary endpoint(s) are dependent on findings of primary endpoint*
- *Define the measurement or observation and describe how it is calculated, if not readily apparent*
- *Describe the scale (nominal/binary/categorical, ordinal, and interval); state if it is measured as a single endpoint/summary measure or repeated measure.*
- *Describe the statistical procedure(s) that will be used to analyze the secondary endpoint (e.g., multiple regression, repeated measures mixed models, logistic regression, ANCOVA). Describe the covariates and factors in the model. Provide rationale for covariates and how they will be*

selected to achieve a parsimonious model. If decision to specify covariates is deferred for the SAP, indicate here.

- *Describe how results of statistical procedure(s) will be presented (e.g., adjusted means (LSMEANS) with standard errors, odds ratios with 95% confidence intervals, prevalence rates, and number-needed-to-treat).*
- *Describe details to check assumptions required for certain types of analyses (e.g., proportional hazards, transformations or, when appropriate, nonparametric tests).*
- *Describe the Populations for which the analysis will be conducted as discussed in **Section 9.3, Populations for Analyses**.*
- *Describe how missing data will be handled (e.g., type of imputation technique, if any, and provide justification), and approach to handling outliers, nonadherence and lost to follow-up.*
- *If there is more than one primary endpoint or more than one analysis of a particular endpoint, state the statistical adjustment used for Type I error criteria or give reasons why it was considered unnecessary.*

Note if more than one endpoint: the statistical approach for endpoints with the same analytic issues can be described as a group.

<Insert text>

9.4.4 SAFETY ANALYSES

*Describe how safety endpoints will be analyzed (e.g., as summary statistics during treatment and/or as change scores from baselines such as shift tables). If your study is evaluating a formal safety endpoint, all of the factors to be included in **Section 9.4.2, Analysis of the Primary Efficacy Endpoint(s)** should be included here. Describe how AEs will be coded (e.g., Medical Dictionary for Regulatory Activities (MedDRA)), calculated (e.g., each AE will be counted once only for a given participant), presented (e.g., severity, frequency, and relationship of AEs to study intervention will be presented by System Organ Class (SOC) and preferred term groupings) and what information will be reported about each AE (e.g., start date, stop date, severity, relationship, expectedness, outcome, and duration). Adverse events leading to premature discontinuation from the study intervention and serious treatment-emergent AEs should be presented either in a table or a listing. The information included here should be consistent with the information contained within **Section 8.2, Safety and Other Assessments**.*

<Insert text>

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Include content in this section if applicable, otherwise note as not-applicable.

Intervention groups should be compared on baseline characteristics, including demographics and laboratory measurements, using descriptive statistics. Discuss planned baseline descriptive statistics, indicate whether inferential statistics will be used.

<Insert text>

9.4.6 PLANNED INTERIM ANALYSES

Include content in this section if applicable, otherwise note as not-applicable.

This section should describe the types of statistical interim analyses and halting guidelines (if any) that are proposed, including their timing and who reviews the interim analyses. In addition, if the interim analyses could result in an adjusted sample size, discuss the statistical algorithm to be used when evaluating results. Pre-specify, to the extent possible, the criteria that would prompt an interim review of safety and efficacy data and trial futility. Describe who performs the statistical analysis and who reviews the analysis. In addition, discuss whether they are unblinded and how the blinding will be preserved.

If statistical rules will be used to halt enrollment into all or a portion of the study (e.g., for safety or futility), describe the statistical techniques and their operating characteristics. If formal interim analyses will be performed, provide unambiguous and complete instructions so that an independent statistician could perform the analyses.

Describe safety findings that would prompt temporary suspension of enrollment and/or study intervention use until a safety review is convened (either routine or ad hoc). Provide details of the proposed rules for halting study enrollment or study intervention/administration of study product for safety, including whether they pertain to the entire study, specific study arms or participant subgroups, or other components of the study.

State how endpoints will be monitored, the frequency of monitoring, and the specific definitions of proposed halting guidelines. Examples of findings that might trigger a safety review are the number of SAEs overall, the number of occurrences of a particular type of SAE, severe AEs/reactions, or increased frequency of events.

Also, discuss the impact of the interim analysis (if being done) on the final efficacy analyses, particularly on Type I error.

*This section should be consistent with **Section 7, Study Intervention Discontinuation and Participant Discontinuation/Withdrawal**.*

<Insert text>

9.4.7 SUB-GROUP ANALYSES

Describe how the primary endpoint will be analyzed based on age, sex, race/ethnicity or other demographic characteristic(s) or provide justification for why such analyses are not warranted (e.g., study intervention only for use in men or children).

Describe how the secondary endpoint(s) will be analyzed based on age, sex, race/ethnicity or other demographic characteristic(s) or provide justification for why such analyses are not warranted (e.g., study intervention only for use in men or children).

<Insert text>

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

State whether individual participant data will be listed by measure and time point.

<Insert text>

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 are given to the participant and written documentation of informed consent is required prior to starting any study procedures. A separate screening consent form will not be used.

10.1.1.2 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 participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants 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 participants 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 participant undergoes any study-specific procedures. The rights and welfare of the participants 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.

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 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, 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 participants
- 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.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators and their staff. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. 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 sponsor.

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

Representatives of the Institutional Review Board (IRB) or other 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) 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 or Institutional policies.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored in the UAB Department of Otolaryngology Research Office. 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 research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived in the UAB Department of Otolaryngology Research Office.

10.1.4 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data collection, documentation and completion. Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. 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 and collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP).

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

10.1.5 DATA HANDLING AND RECORD KEEPING

10.1.5.1 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 PI 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.

Hardcopies of the source document worksheets will be provided for recording data for each participant 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.

10.1.5.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 3 years after the completion of the trial. Records will be retained in accordance with the Department's SOP on Research Records Retention.

10.1.6 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol or International Conference on Harmonisation Good Clinical Practice (ICH GCP) requirements. 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 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 site investigator to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity. 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.

10.1.7 PUBLICATION AND DATA SHARING POLICY

This study will comply with the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers x years after the completion of the primary endpoint by contacting <specify person or awardee institution, or name of data repository>.

5 years? UAB Department of Otolaryngology?

10.1.8 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 UAB Office of the Conflict of Interest Review Board 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 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
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
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

10.3 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

Include a list of relevant literature and citations for all publications referenced in the text of the protocol. Use a consistent, standard, modern format, which might be dependent upon the required format for the anticipated journal for publication (e.g., N Engl J Med, JAMA, etc.). The preferred format is International Committee of Medical Journal Editors (ICMJE). Include citations to product information such as manufacturer's IB, package insert, and device labeling.

Examples:

- **Journal citation**
Veronesi U, Maisonneuve P, Decensi A. Tamoxifen: an enduring star. *J Natl Cancer Inst.* 2007 Feb 21;99(4):258-60.
- **Whole book citation**
Belitz HD, Grosch W, Schieberle P. *Food chemistry.* 3rd rev. ed. Burghagen MM, translator. Berlin: Springer; 2004. 1070 p.
- **Chapter in a book citation**
Riffenburgh RH. *Statistics in medicine.* 2nd ed. Amsterdam (Netherlands): Elsevier Academic Press; c2006. Chapter 24, *Regression and correlation methods*; p. 447-86.
- **Web Site citation**
Complementary/Integrative Medicine [Internet]. Houston: University of Texas, M.D. Anderson Cancer Center; c2007 [cited 2007 Feb 21]. Available from: <http://www.manderson.org/departments/CIMER/>.
- **Electronic Mail citation**
Backus, Joyce. *Physician Internet search behavior: detailed study [Internet].* Message to: Karen Patrias. 2007 Mar 27 [cited 2007 Mar 28]. [2 paragraphs]
- **References to package insert, device labeling or investigational brochure**
Cite date accessed, version number, and source of product information.

The Role of Regional Anesthesia to Reduce Opioid Requirements Following Functional Endoscopic Sinus Surgery (FESS): A Pilot Study

Study Protocol & Statistical Analysis Plan

NCT03757715

UAB IRB Approved 16-Feb 2021 through 19-Jan 2022

Bradford A. Woodworth, MD -Principal Investigator
University of Alabama at Birmingham
Birmingham, AL 35294

CONSENT FORM TO BE PART OF A RESEARCH STUDY

Title of Research: The Role of Regional Anesthesia to Reduce Opioid Requirements Following Functional Endoscopic Sinus Surgery (FESS): A Pilot Study

UAB IRB Protocol #: IRB-300000567

Principal Investigator: Bradford Woodworth, M.D.

Sponsor: UAB Department of Otolaryngology

General Information	You are being asked to take part in a research study. This research study is voluntary, meaning you do not have to take part in it. The procedures, risks, and benefits are fully described further in the consent form.
Purpose	The purpose of the study is to determine if receiving extra pain medication during your sinus procedure affects the amount and kind of pain medication that is taken after surgery.
Duration & Visits	You will be in this study for up to 21 days.
Overview of Procedures	If you decide to take part in this study, you will assigned by chance to one of the treatment groups. This is called randomization. <ul style="list-style-type: none">• If you are picked for the Treatment Group, you will receive 10-12 mL of 0.5% bupivacaine with 1:200,000 epinephrine and 2 mg dexamethasone injected locally in the location for sensory nerves of the sinus cavities and face intraoperatively, or during the FESS procedure.• If you are picked for the Control Group, you will not receive any local anesthetic during the FESS procedure. Both groups will receive the same post-operative prescription pain medication (Norco), will complete a daily pain diary (recording pain score and medications taken), and will have a prescription pain medication pill count at the first post-operative clinic visit.
Risks	You will be assigned to a group by chance, which may prove to be less effective or to have more side effects than the other study group or alternatives. The most common side effects of the medications include nausea/vomiting, restlessness, anxiety, dizziness, rash, and headache.
Benefits	You may not benefit directly from taking part in this study. However, this study may help us better understand how to treat post-surgical pain in the future.
Alternatives	You do not have to participate in this study to receive standard of care treatment for your sinus disorder. Your doctor will tell you more about other treatments that may be available to you. You may choose to have no treatment at all. One alternative may be to not to participate in this study.

Purpose of the Research Study

We are asking you to take part in a research study because you are scheduled to have a functional endoscopic sinus surgery (FESS) procedure for your sinus issue. You will be given a prescription for opioid pain medication

as part of your routine care after your surgery. The purpose of this pilot research study is to assess whether injecting a local anesthetic during FESS is feasible and whether it may affect the amount and kind of pain medication that you will use after surgery.

There will be 30 participants enrolled at UAB.

Study Participation & Procedures

If you agree to join the study, your medical record will be reviewed to obtain information regarding your medical condition and diagnosis, as well as demographic information, such as your age and gender. During your pre-surgery clinic visit, you will have a routine nasal endoscopy, and your sinus CT scans will be obtained and/or reviewed.

You will be randomly picked (like the flip of a coin) to either receive the study intervention, or to receive the standard of care treatment during your surgery:

- If you are picked for the **Treatment Group**, you will receive 10-12 mL of 0.5% bupivacaine with 1:200,000 epinephrine and 2 mg dexamethasone injected locally in the location for sensory nerves of the sinus cavities and face intraoperatively, during the FESS procedure.
- If you are picked for the **Control Group**, you will not receive any local anesthetic during the FESS procedure.

You will then have your surgery. This surgery will be performed in the routine manner that was planned for you, based on your condition. If you are picked for the **Treatment Group**, you will receive the extra medication during the procedure. If you are picked for the **Control Group**, you will not receive any extra medication during the procedure.

After your surgery, you will be prescribed pain medication in the routine manner. These are the same medications that you would have whether you were participating in this study or not.

For study purposes, you will be given a study diary to complete for the first ten days following your surgery. This will consist of a pain scale, graded on a scale of 1-10, as well as a medication diary. You will be asked to record all of the medications you take for the pain you experience after your surgery, both the prescribed opioid as well as over-the-counter medications such as Tylenol or Advil.

At your first post-operative clinic visit, you will bring in your study diary and your medicine bottles so that we can count the number of pills you have left on your prescription. We will record these amounts for our research data only.

The daily study diary will take approximately 5 minutes per day to complete. The total amount of time you will be in the study is up to 21 days, depending on when your first post-operative clinic visit is scheduled.

Risks and Discomforts

All of the drugs to be used in this study are FDA-approved, commonly-used, widely available, generic medications. These drugs will be used at their standard dosing for their approved indications.

If you are picked for the **Treatment Group**, you will receive extra pain medication during the FESS procedure.

The most common side effects of bupivacaine with epinephrine (Marcaine™) are:

- restlessness

- anxiety
- dizziness
- tinnitus
- blurred vision
- tremors
- nausea/vomiting
- chills
- central nervous system reactions, such as constriction of the pupils
- heart block
- hypotension (low blood pressure)
- bradycardia (slow pulse)
- irregular heart beat
- rapid, life-threatening heart rhythms

The most common side effects of dexamethasone are:

- allergic reaction
- seizure
- hypertension (high blood pressure)
- skin irritation or rash
- nausea/vomiting
- edema (fluid collection under the skin)
- bruising
- acne
- headache
- dizziness
- insomnia
- anxiety
- depression

Save for the above-mentioned risks of side effects, there is no additional risk to taking bupivacaine with epinephrine and dexamethasone as part of this study. There aren't any known increased risks for taking these medications in combination. They do not have cross reactions with each other or other known interactions that may lead to increased risks, other than those listed above.

No matter what group you are assigned to, you will receive a prescription for hydrocodone-acetaminophen (commonly known as Norco) for any post-operative surgical pain you may have. There is a chance that those assigned to **Control Group** (who will not receive any local anesthetic during the FESS procedure) will have an increase use of this post-operative pain medication. Risks associated with opioid use include:

- respiratory depression
- nausea/vomiting
- allergic reaction
- constipation
- dizziness
- headache
- weakness
- dry mouth

There is a risk of a loss of confidentiality for patients involved in research studies. All of your personal and medical information will be stored in a locked area. Only qualified research staff will have access to this information. Once your research data has been collected, all information that could link your personal identity to your medical information will be deleted. There will be no personally identifying information used to report any findings from this study.

You will be assigned to a group by chance, which may prove to be less effective or to have more side effects than the other study group or alternatives.

Confidentiality and Authorization to Use and Disclose Information for Research Purposes

Federal regulations give you certain rights related to your health information. These include the right to know who will be able to get the information and why they may be able to get it. The study doctor must get your authorization (permission) to use or give out any health information that might identify you.

What protected health information may be used and/or given to others?

All medical information, including but not limited to information and/or records of any diagnosis or treatment of disease or condition, which may include sexually transmitted diseases (e.g., HIV, etc.) or communicable diseases, drug/alcohol dependency, etc.; all personal identifiers, including but not limited to your name, social security number, medical record number, date of birth, dates of service, etc.; any past, present, and future history, examinations, laboratory results, imaging studies and reports and treatments of any kind, including but not limited to drug/alcohol treatment, psychiatric/psychological treatment; financial/billing information, including but not limited to copies of your medical bills; any other information related to or collected for use in the research study, regardless of whether the information was collected for research or non-research (e.g., treatment) purposes; records about any study drug you received or about study devices used; and consent forms from past studies that might be in your medical record.

Your consent form will be placed in your medical record at UAB Health System. This may include either a paper medical record or electronic medical record (EMR). An EMR is an electronic version of a paper medical record of your care within this health system. Your EMR may indicate that you are on a clinical trial and provide the name and contact information for the principal investigator.

If you are receiving care or have received care within this health system (outpatient or inpatient), results of research tests or procedures (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in your existing medical record.

If you have never received care within this health system (outpatient or inpatient), a medical record will be created for you to maintain results of research tests or procedures.

Results of research tests or procedures may be placed in your medical record. All information within your medical record can be viewed by individuals authorized to access the record.

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time. The National Clinical Trial (NCT) identifier for this protocol is NCT03757715.

Who may use and give out information about you?

Information about your health may be used and given to others by the study doctor and staff. They might see the research information during and after the study.

Who might get this information?

All Individuals/entities listed in the informed consent document(s), including but not limited to, the physicians, nurses and staff and others performing services related to the research (whether at UAB or elsewhere). Your information may also be given to the sponsor of this research. "Sponsor" includes any persons or companies that are working for or with the sponsor, or are owned by the sponsor, or are providing support to the sponsor (e.g., contract research organization).

Information about you and your health which might identify you may be given to:

- the Office for Human Research Protections (OHRP)
- the U.S. Food and Drug Administration (FDA)
- Department of Health and Human Services (DHHS) agencies
- Governmental agencies in other countries
- Governmental agencies to whom certain diseases (reportable diseases) must be reported
- the University of Alabama at Birmingham - the physicians, nurses and staff working on the research study (whether at UAB or elsewhere); other operating units of UAB, UAB Hospital, UAB Highlands Hospital, University of Alabama Health Services Foundation, Children's of Alabama, Eye Foundation Hospital, and the Jefferson County Department of Health, as necessary for their operations; the UAB IRB and its staff
- the billing offices of UAB and UAB Health Systems affiliates and/or Children's of Alabama and its billing agents

Why will this information be used and/or given to others?

Information about you and your health that might identify you may be given to others to carry out the research study. The sponsor will analyze and evaluate the results of the study. In addition, people from the sponsor and its consultants will be visiting the research site. They will follow how the study is done, and they will be reviewing your information for this purpose.

What if I decide not to give permission to use and give out my health information?

By signing this consent form, you are giving permission to use and give out the health information listed above for the purposes described above. If you refuse to give permission, you will not be able to be in this research.

May I review or copy the information obtained from me or created about me?

You have the right to review and copy your health information. However, if you decide to be in this study and sign this permission form, you will not be allowed to look at or copy your information until after the research is completed.

May I withdraw or revoke (cancel) my permission?

Yes, but this permission will not stop automatically. The use of your personal health information will continue until you cancel your permission.

You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to continue being in this study.

When you withdraw your permission, no new health information which might identify you will be gathered after that date. Information that has already been gathered may still be used and given to others. This would be done if it were necessary for the research to be reliable.

Is my health information protected after it has been given to others?

If you give permission to give your identifiable health information to a person or business, the information may no longer be protected. There is a risk that your information will be released to others. Including others outside of UAB, without your permission.

Voluntary Participation and Withdrawal

Whether or not you take part in this study is your choice. There will be no penalty if you decide not to be in it. If you decide not to be in the study, you will not lose any benefits you are otherwise owed.

You are free to withdraw from this study at any time. Your choice to leave the study will not affect your relationship with this institution. Contact the study doctor if you want to withdraw from the study.

You may be removed from the study without your consent if the sponsor ends the study, if the study doctor decides it is not in the best interest of your health, or if you are not following the study rules.

If you are a UAB student or employee, taking part in this research is not a part of your UAB class work or duties. You can refuse to enroll, or withdraw after enrolling at any time before the study is over, with no effect on your class standing, grades, or job at UAB. You will not be offered or receive any special consideration if you take part in this research.

Cost of Participation

There will be no cost to you for taking part in this study. The costs of your standard medical care will be billed to you and/or your insurance company in the usual manner.

Payment for Participation

You will not be paid to participate in this study.

Payment for Research-Related Injuries

UAB has not provided for any payment if you are harmed as a result of taking part in this study. If such harm occurs, treatment will be provided. However, this treatment will not be provided free of charge.

New Findings

You will be told by the study doctor or the study staff if new information becomes available that might affect your choice to stay in the study.

Questions

If you have any questions, concerns, or complaints about the research or a research-related injury including available treatments, please contact the study doctor. You may contact Dr. Woodworth at (205) 937-9777.

If you have questions about your rights as a research participant, or concerns or complaints about the research, you may contact the UAB Office of the IRB (OIRB) at (205) 934-3789 or toll free at 1-855-860-3789. Regular hours for the OIRB are 8:00 a.m. to 5:00 p.m. CT, Monday through Friday.

Legal Rights

You are not waiving any of your legal rights by signing this consent form.

Signatures

Your signature below indicates that you have read (or been read) the information provided above, and that you agree to participate in this study. You will receive a copy of this signed consent form.

Signature of Participant

Date

Signature of Person Obtaining Consent

Date