

Auricular Neuromodulation and Surgical Conditions During Functional Endoscopic Sinus Surgery
National Clinical Trial (NCT) Identified Number: NCT06662422
Principal Investigator: Daniel Katz
Document Date: 3-29-2025

Auricular Neuromodulation and Surgical Conditions During Functional Endoscopic Sinus Surgery

Unique Protocol Identification Number:

National Clinical Trial (NCT) Identified Number:

Principal Investigator: Daniel Katz

IND/IDE Sponsor:

Draft Number: 0.035

11 January 2024

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale

Table of Contents

[Table of Contents - Please right-click and choose 'Update Field'.](#)



STATEMENT OF COMPLIANCE

*Provide a statement that the trial will be conducted in compliance with the protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP) and applicable state, local and federal regulatory requirements. Each engaged institution must have a current Federal-Wide Assurance (FWA) issued by the Office for Human Research Protections (OHRP) and must provide this protocol and the associated informed consent documents and recruitment materials for review and approval by an appropriate Institutional Review Board (IRB) or Ethics Committee (EC) registered with OHRP. Any amendments to the protocol or consent materials must also be approved before implementation. Select one of the two statements below. If the study is an **intramural** NIH study, use the second statement below:*

1. The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:
 - United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

OR

2. The trial will be conducted in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the [specify NIH Institute or Center (IC)] Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the funding agency and documented approval from the Institutional Review Board (IRB), and the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, if applicable, 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.

For either option above, the following paragraph would be included:

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



1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Auricular Neuromodulation and Surgical Conditions During Functional Endoscopic Sinus Surgery		
Study Description:	In this blinded prospective randomized control trial we will investigate the impact of cutaneous vagal nerve stimulation on surgical conditions in patients undergoing functional and ascorbic sinus surgery (FESS)		
Objectives:	Primary Objective:	1. Determine the impact of cutaneous vagal nerve stimulation during FESS on surgical field conditions.	
	Secondary Objectives:	1. Determine the impact of cutaneous vagal nerve stimulation during FESS on overall blood loss 2. Determine the impact of cutaneous vagal nerve stimulation during FESS on total operative time, post operative nausea and vomiting, as well as postoperative pain.	
Endpoints:	Primary Endpoint:	1. Average intraoperative Boezaart score over the duration of the surgery	
	Secondary Endpoints:	1. % of patients requiring multiple interventions to optimize surgical conditions 2. Overall estimated blood loss 3. Total operative time 4. Incidence of PONV 5. Postoperative pain scores	
Study Population:	ASA 1 and 2 patients presenting for elective FESS surgery		
Phase:	1		
Description of Sites/Facilities	Mount Sinai Hospital		
Enrolling Participants:			
Description of Study Intervention:	Placement of the Spark Biomedical Sparrow Ascent Transcutaneous Auricular Neurostimulation (tAN) System prior to surgery and removal in the recovery room		



Study Duration: 6 months
Participant 2 days
Duration:

1.2 SCHEMA

Upon obtaining consent, the patient will be randomized by opaque envelope to either the study or control arm. Patients in both arms will have the electrodes and generator placed in the holding area. Only in the intervention arm will the generator be turned on. After 30 min of time the device will be removed and the patient will enter the OR. During the surgery, 10 minutes after surgery start, and for every 15 minutes after that point, surgeons will be asked to report the Boezaart score which will be recorded. Additionally, requests for hypertension, additional agents to control bleeding, for the utilization of vasoactive agents will also be recorded. Total estimated blood loss operative time will be recorded as well. The device will be reapplied in the post anesthesia care unit after surgery for 30 more minutes. We will record the incidence of postoperative nausea and vomiting and pain scores in the recovery room period along with time to discharge.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Activity	Recruitment Day	Follow Up
Determination of eligibility/consent	X	
Medical history obtained and sensor applied	X	
Boezaart Scoring	X	
Post-procedure check for skin irritation	X	
Follow Up Call		X



2 INTRODUCTION

2.1 STUDY RATIONALE

Functional endoscopic sinus surgery is an important procedure for controlling a variety of sinus disease.¹ Given the proximity to the brain and vascularity of tissues, good visualization is paramount.^{1, 2} Intraoperative bleeding obscures the view of the surgeon.² In this study, we will use a neuromodulation device that will decrease bleeding and lead to better surgical conditions during the surgery.³ The device used has already been studied in other bleeding environments.⁴ We believe it will also work for this case.

2.2 BACKGROUND

The study on Functional Endoscopic Sinus Surgery (FESS) will focus on the use of an innovative device designed to control bleeding and enhance visualization during surgery. FESS, a critical procedure for treating sinus-related conditions, often faces challenges related to bleeding and poor visibility, impacting surgical outcomes.^{1, 2} This study aims to address these challenges by introducing a device used in other areas that promises to revolutionize the standard procedure.³

The device for the study, the Spark Biomedical Sparrow Ascent Transcutaneous Auricular Neurostimulation (tAN) System, should decrease bleeding, a common obstacle in sinus surgery.⁴ This not only improves visibility for the surgeon but is also expected to lead to more accurate surgical interventions, reduced operation times, and fewer complications. The study will explore the efficacy and safety of this device, making a significant contribution to the field of sinus surgery and medical technology. This technology has been used in other areas, namely opiate use disorder, for which it has an FDA approval.³

We plan to conduct a detailed investigation into the device's performance, employing a methodology that may include randomized controlled trials, adequate sample sizes, and comprehensive data collection methods. The study will assess various parameters such as the effectiveness of bleeding control, the impact on surgical duration, and overall patient outcomes.

This research is not only significant for its potential to improve surgical techniques but also for its broader implications in patient care and medical innovation. By testing the hypotheses related to the device's performance and expected outcomes, the study aims to provide valuable insights that could transform the practice of sinus surgery, enhancing patient safety and surgical efficiency.

The device will be provided by the manufacturer who will also provide training for the research staff on how it is to be utilized.

The device has been trialed in the perioperative period, albeit not with a focus on bleeding listed below:

We would also like to report to the board additional information about the device and safety:

- The device has been used commercially on over 500 OUD patients, several of whom have risk factors for VTE, with no thrombotic complications

- The device has been used in a study to treat neonates for opioid withdrawal syndrome with 8 neonates, a follow up study is in progress with 31 neonates completed with no thrombotic complications⁵



An unpublished (going through the process of manuscript submission) study in patients who are hypercoagulable (end stage renal disease currently on dialysis) who had the device placed for reduced blood loss during port placement surgery (12 patients, no thrombotic complications.

An ongoing imaging study in patients who are using the device with 111 subjects thus far, no thrombotic complications

A study in orthopedic surgery patients with 124 participants who received stimulation during their surgery with 0 thrombotic complications⁶

A study in thoracic surgery with 100 patients who received stimulation starting 24 Hours before surgery and continuing for 4 Days postoperatively with 0 thrombotic complications.⁷

A recent meta analysis of 177 studies that included over 6,300 subjects that used auricular neurostimulation (albeit with different devices but the same concept) that found 0 adverse events related to thrombosis.⁸

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The Spark Biomedical Sparrow Ascent Transcutaneous Auricular Neurostimulation (tAN) System has been used some time for other indications. The only known risks include skin irritation at the site of the electrode. There is also a risk of loss of private information, however, this is always possible with any study.

2.3.2 KNOWN POTENTIAL BENEFITS

By decreasing bleeding and improving surgical conditions we believe this will decrease surgical times and potentially decrease surgical complications.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

We believe for this study the benefits outweigh the risks.



3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Determine the impact of cutaneous vagal nerve stimulation during FESS on surgical field condition	1. Average intraoperative Boezaart score over the duration of the surgery	Surgical conditions are an important metric in FESS
Secondary		
- Determine the impact of cutaneous vagal nerve stimulation during FESS on overall blood loss - Determine the impact of cutaneous vagal nerve stimulation during FESS on total operative time, post operative nausea and vomiting, as well as postoperative pain.	- Average intraoperative Boezaart score over the duration of the surgery % of patients requiring multiple interventions to optimize surgical conditions - Overall estimated blood loss - Total operative time - Incidence of PONV - Postoperative pain scores	These are important parameters that can impact patient care in FESS.
Tertiary/Exploratory		



4 STUDY DESIGN

4.1 OVERALL DESIGN

Prospective blinded randomized control trial. The device used is described above and is an externally placed vagal nerve stimulator. The device will be applied to participants after consent and induction of anesthesia. The study team will place the device according to manufacturer recommendations after training. They will then open the randomization envelope and if the participant is assigned to stimulation the device will be turned on. There will only be one setting for the device (on/off). The device will remain on (if randomized to on) for 30 minutes and removed before entering the OR. Device will be reinserted in the post anesthesia care unit after surgery for another 30 minutes. Outcomes are recorded as described above in the endpoints section. The data will be input into REDCAP a secured, password protected, encrypted research tool. Interoperative data (such as Boezaart score) will be obtained by the research team.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This is the best study design to evaluate our endpoints.

4.3 JUSTIFICATION FOR DOSE

The neuromodulation comes in one setting which has been used in other bleeding conditions.

4.4 END OF STUDY DEFINITION

After the final endpoint has been collected from the patient.



5 STUDY POPULATION

5.1 INCLUSION CRITERIA

ASA 1 and 2 patients presenting for elective FESS surgery

5.2 EXCLUSION CRITERIA

1. Antifibrinolytic use within 30 days of enrollment
2. Acquired or inherited bleeding disorder
3. Participant has received a blood transfusion within 30 days prior to study
4. Participant has a history of epileptic seizures
5. Participant has presence of devices (e.g., pacemakers, cochlear prostheses, neurostimulators)
6. Participant has abnormal ear anatomy or ear infection present
7. Participant has any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial
8. Pregnancy (All patients are pregnancy tested the day of surgery as per hospital policy)
9. Patients with known hypercoagulable conditions such as morbid obesity, active smoking, prior venous thromboembolism or pulmonary embolism or any condition the investigators or clinical team believe would put the participant at increased risk of blood clots.

5.3 LIFESTYLE CONSIDERATIONS

None

5.4 SCREEN FAILURES

Participants who are consented to participate in the clinical trial, who do not meet one or more criteria required for participation in the trial during the screening procedures, are considered screen failures. Screen failures will be documented as required, there will be no re-screening of participants.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

With our HIPAA waiver, the research team will notify the clinical team of a potential participant prior to their surgery at their clinic visits. The clinical team will then obtain



assent from the patient to be approached. At that point, the research team will approach the patient and obtain consent at the clinic visit. If the research team cannot obtain consent at the clinic visit then they will call the patient as they have already assented to be contacted for the research study. At this point, the research team will forward the participant a copy of the consent form and outline the study for them and obtain verbal consent. Written consent will then be obtained on the day of surgery.



6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The Spark Biomedical Sparrow Ascent Transcutaneous Auricular Neurostimulation (tAN) System provides transcutaneous auricular neurostimulation (tAN), which targets the auricular branch of the vagus nerve (ABVN) and the auriculotemporal nerve (ATN).

6.1.2 DOSING AND ADMINISTRATION

The device will be applied in the preoperative holding area and then based on randomization will either be turned on or left off after induction of anesthesia.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The device will be acquired and stored as per best handling practices. The manufacturer is providing the device as well as training.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

N/A

6.2.3 PRODUCT STORAGE AND STABILITY

The device will be stored according to device manufacturer recommendations in a locked secured environment.

6.2.4 PREPARATION

N/A

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Given this is an RCT and all eligible patients will be approached we will have good randomization. The stimulator will not be turned on until after induction so the patient will not know what group they are in. The surgical team will not see the device, and the treating anesthesiologist will also not be able to view the device.



6.4 STUDY INTERVENTION COMPLIANCE

We expect this to be 100% as the device is applied in the holding area.

6.5 CONCOMITANT THERAPY

6.5.1 RESCUE MEDICINE

N/A



7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

At any time the patient may withdraw from the study by informing a study coordinator or the PI

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

As above

7.3 LOST TO FOLLOW-UP

We do not anticipate a large amount of follow up loss; those who do not answer the post-operative phone call will be lost to follow up.



8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

1. Average intraoperative Boezaart score over the duration of the surgery which will be obtained every 10 minutes after incision
2. % of patients requiring multiple interventions to optimize surgical conditions
3. Overall estimated blood loss
4. Total operative time

8.2 SAFETY AND OTHER ASSESSMENTS

1. Incidence of PONV
2. Postoperative pain scores

Both of these will be obtained in the PACU prior to discharge home.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

The only foreseeable adverse event is skin irritation at the site of the electrode placements and loss of private information.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Not anticipated

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

Will be determined by the PI

8.3.3.1 SEVERITY OF EVENT

Will be determined by the PI

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

Will be determined by the PI

8.3.3.3 EXPECTEDNESS



Will be determined by the PI

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

Will be determined by the PI

8.3.5 ADVERSE EVENT REPORTING

Will follow IRB notification protocols.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

Will follow IRB notification protocols.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Will follow IRB notification protocols.

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

N/A

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

Will be determined by the PI

8.4.2 UNANTICIPATED PROBLEM REPORTING

Will be reported to patients and the IRB as required

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Will be reported as required



9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):
 1. Average intraoperative Boezaart score over the duration of the surgery (Wilcoxon Rank Sum Test)
- Secondary Efficacy Endpoint(s):
 1. % of patients requiring multiple interventions to optimize surgical conditions Chi square test
 2. Overall estimated blood loss Wilcoxon rank sum test
 3. Total operative time Wilcoxon rank sum test
 4. Incidence of PONV Chi square test
 5. Postoperative pain scores wilcoxon rank sum test

9.2 SAMPLE SIZE DETERMINATION

Given the novelty of the device, a formal power calculation is not possible. Other studies in this area have utilized around 100 patients to obtain significant differences, however, given the novel nature of the study we will perform a pilot group of 20 patients.

9.3 POPULATIONS FOR ANALYSES

All populations recruited will be analyzed

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Best statistical practices will be used.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

See above

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

See above



9.4.4 SAFETY ANALYSES

See above

9.4.5 BASELINE DESCRIPTIVE STATISTICS

As per distribution, mena and sd or median and IQR

9.4.6 PLANNED INTERIM ANALYSES

N/A

9.4.7 SUB-GROUP ANALYSES

N/A

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

With statistical software

9.4.9 EXPLORATORY ANALYSES

N/A



10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

Patients will be screened for eligibility (HIPAA Waiver) prior to their surgery. If eligible, they will be approached by the care team to assess interest in participation in research. After assent, the study team will approach the patient and obtain informed written consent. We will follow the IRB SOP as described and provide a private environment for the consent to be signed.

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

All provided to participants

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

As per IRB policy

10.1.2 STUDY DISCONTINUATION AND CLOSURE

As per IRB policy

10.1.3 CONFIDENTIALITY AND PRIVACY

We will obtain the minimum necessary information for this study. All best practices to protect private information will be followed.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

N/A

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	Medical Monitor

10.1.6 SAFETY OVERSIGHT

The PI will oversee safety of the study

10.1.7 CLINICAL MONITORING

N/A



10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

N/A

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

The PI will maintain an encrypted red cap database for the study

10.1.9.2 STUDY RECORDS RETENTION

As per institutional requirements

10.1.10 PROTOCOL DEVIATIONS

Will be reported to the PI and documented.

10.1.11 PUBLICATION AND DATA SHARING POLICY

As per IRB policy

10.1.12 CONFLICT OF INTEREST POLICY

As per IRB policy

10.2 ADDITIONAL CONSIDERATIONS

10.3 ABBREVIATIONS

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



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



[illegible]

11 REFERENCES



1. Alanin MC, Hopkins C. Effect of Functional Endoscopic Sinus Surgery on Outcomes in Chronic Rhinosinusitis. *Curr Allergy Asthma Rep.* 2020;20:27.
2. Pavlov VE, Polushin YS, Kolotilov LV, Karpishchenko SA. Intraoperative Bleeding Control with Terlipressin in Functional Endoscopic Sinus Surgery. *Laryngoscope.* 2023;133:3313-3318.
3. Yue Y, Zou L, Li H, et al. Therapeutic effect of implanted and non-invasive vagus nerve stimulation on heroin-induced anxiety. *Biochem Biophys Res Commun.* 2023;652:46-54.
4. Bravo-Iniguez CE, Fritz JR, Shukla S, et al. Vagus nerve stimulation primes platelets and reduces bleeding in hemophilia A male mice. *Nat Commun.* 2023;14:3122.
5. Jenkins DD, Khodaparast N, O'Leary GH, et al. Transcutaneous Auricular Neurostimulation (tAN): A Novel Adjuvant Treatment in Neonatal Opioid Withdrawal Syndrome. *Front Hum Neurosci.* 2021;15:648556.
6. Zhou Q, Yu L, Yin C, et al. Effect of transcutaneous auricular vagus nerve stimulation on delayed neurocognitive recovery in elderly patients. *Aging Clin Exp Res.* 2022;34:2421-2429.
7. Salama M, Akan A, Mueller MR. Transcutaneous Stimulation of Auricular Branch of the Vagus Nerve Attenuates the Acute Inflammatory Response After Lung Lobectomy. *World J Surg.* 2020;44:3167-3174.
8. Kim AY, Marduy A, de Melo PS, et al. Safety of transcutaneous auricular vagus nerve stimulation (taVNS): a systematic review and meta-analysis. *Sci Rep.* 2022;12:22055.



