Effect of nasal positive airway pressure versus standard care on oxygenation and ventilation during propofol- based sedation for colonoscopy in patients with high risk of airway obstruction: a prospective randomized controlled trial.

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Effect of nasal positive airway pressure versus standard care on oxygenation and ventilation during propofol-based sedation for colonoscopy in patients with high risk of airway obstruction: a prospective randomized controlled trial.

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SUMMARY TABLE

Title	Effect of nasal positive airway pressure versus standard care on oxygenation and ventilation during propofol-based sedation for colonoscopy in male and female patients with high risk of airway obstruction: a prospective randomized controlled trial.
Project Office	
Study Size (# of patients)	150 patients
Study Design	Prospective randomized controlled single site trial.
Primary Outcome	Elapsed time from initiation of induction to the first airway intervention.
Secondary Outcome	1. Compare the amount of propofol administered during induction and total dose administered for procedure 2. Compare Modified Observer's Assessment of Alertness/Sedation Scale (MOAAS) scores immediately prior to endoscopic intubation and during the procedure 3. Compare the length of time from induction to endoscopic insertion 4. Compare the incidence and duration of procedural interruptions (ie: number of times and length of time the endoscope is removed from the patient) 5. Compare the incidence, duration, and reason for airway maneuvers 6. Compare the length of time for the procedure (ie: length of time from procedure start to procedure end) 7. Compare recovery times a. Ready to discharge b. Actual discharge 8. Compare patient satisfaction scores (visual analog scale (VAS)) immediately after procedure a. Overall experience b. Quality of sedation c. Pain experienced during procedure d. Pain after the procedure e. Nausea after awakening f. Vomiting after awakening g. Dizziness after awakening h. Recollection of scope insertion i. Recollection of scope removal j. Awake during the procedure 9. Compare patient tolerance to SuperNO_2VA™EtCO2 compared to control (ie: face mask at 10LPM) 10. Compare anesthesiologists satisfaction scores a. Overall experience b. Rating of sedation c. Difficulty of patient to sedate 11. Compare the incidence of cardiac complications
Inclusion Criteria	1. Age 18 years of age or older 2. All Patients undergoing colonoscopy (male and Female) 3. American Society of Anesthesiology (ASA) Physical Status I-III 4. BMI ≥30 kg/m^2 or documented Obstructive Sleep Apnea

	5. Has provided written informed consent
Exclusion criteria	1. Inpatient status 2. Active Congestive Heart Failure Exacerbation 3. Untreated ischemic heart disease 4. Acute exacerbation of respiratory disorders, including COPD and asthma 5. Emergent procedures 6. Pregnancy 7. Previous enrollment in this study 8. Inability to provide informed consent 9. Additional medical testing planned for the same day 10. History of allergic reaction to Propofol 11. Tracheostomy 12. Supra-glottic or sub-glottic tumor 13. Gastrointestinal tract obstruction or delayed transit (including delayed gastric emptying, gastric bezoar, achalasia, toxic megacolon). 14. Prisoners 15. Unable to fit SuperNoVa
Study Procedures	
Pretreatment Evaluation	Candidates will be assessed if the SuperNova fit is difficult or impossible
On-Study Visits	N/A
Follow-up Visits	N/A
End of Study Visit	Subjects will be assessed in PACU before he or she is discharged
Brief Analysis Plan	Based on the literature, the elapsed time from anesthesia induction to the first airway intervention was 19 ± 10 min in the Mask group (***n***=63) vs. 10 ± 12 min in the Control group (***n***=73, ***P*** < 0.001)[15]. For sample size calculation we used the standard sample size calculation equation[16]: $n = \frac{2(Z_{\alpha} + Z_{1-\beta})^2 \sigma^2}{\Delta^2}$ σ = variation of the measurement Δ= difference to be detected σ and Δ are based on the outcome values from previous publication. [15] This publication showed a time difference (Δ) of 9 minutes with a standard deviation (σ) of ± 10 minutes in both intervention groups. To be able to detect an even smaller time difference of 5 minutes and with a standard deviation of 10 minutes and a drop of percentage of 20% *(α = 0,05 and 1-β = 0,80)* we calculated n1=n2= 75. A total of 150 patients will be enrolled.

1. OBJECTIVES

Primary Objective

The primary objective of the study is to prospectively and randomly compare elapsed time from initiation of induction to the first airway intervention in patients considered high risk for hypoxia (ie: BMI ≥35 kg/m^2 and/or documented Obstructive Sleep Apnea.

Endpoints of Interest

1. Compare the amount of propofol administered during induction and total dose administered for procedure
2. Compare Modified Observer's Assessment of Alertness/Sedation Scale (MOAAS) scores immediately prior to endoscopic intubation and during the procedure
3. Compare the length of time from induction to endoscopic insertion
4. Compare the incidence and duration of procedural interruptions (ie: number of times and length of time the endoscope is removed from the patient)
5. Compare the incidence, duration, and reason for airway maneuvers
6. Compare the length of time for the procedure (ie: length of time from procedure start to procedure end)
7. Compare recovery times
8. Compare patient satisfaction scores (visual analog scale (VAS)) immediately after procedure
9. Compare patient tolerance to SuperNO_2VA EtCO2 compared to control (ie: face mask at 10LPM)
10. Compare endoscopist satisfaction scores for
11. Compare anesthesiologists satisfaction scores
12. Compare the incidence of cardiac complications

Study Design

This is a prospective randomized controlled single site trial.

2. BACKGROUND

Colonoscopy is a common procedure performed in the U.S. Most patients undergoing endoscopy require sedation to have an acceptable experience.[1-2] It is a necessity because the ability to interpret images and perform therapeutic or diagnostic procedures are dependent on the subjects cooperation. Reliable imaging cannot be obtained if the patient is not cooperative. Propofol is a commonly used sedative that has been used in several studies for endoscopic procedures and is associated with low complication rates in healthy patients (ie: ASA I and III).[3-5] However, recent prospective studies have shown that hypoxemia frequently occurs during endoscopic procedures in patients with a BMI > 30kg/m^2 or have a history of OSA [6-9] and the mortality rate for sedation in the endoscopy suite is significantly higher than that of the comparable cases performed in operating room.[10] Although the cause of the high mortality in GI suite has yet to be determined, it seems to be related to hypoxia and/or hypercarbia due to respiratory depression and upper airway obstruction from sedation.[10]

Continuous positive airway pressure (CPAP), applied nasally or via facemask, has been shown to be more effective at minimizing hypoxia than other devices under sedation or general anesthesia.[11-12] However, it requires a special mask and CPAP machine with high-fresh gas flows which may not be routinely equipped in GI endoscopy suites due to space and cost constraints.[13] Therefore, a simplified CPAP system could be a surrogate for a conventional CPAP machine for procedures requiring sedation or general anesthesia with spontaneous breathing via a natural airway. Recently, a simple, novel CPAP device was developed, which

includes a sealed nasal mask and disposable, flow-inflating hyperinflation bag (SuperNO_2VA Et™ Satellite Set, Revolutionary Medical Devices, USA).[14] A small pilot study by Ghebremichael, et al. demonstrated safety and efficacy with the use of the SuperNO_2VA Et™ device for nasal mask ventilation (NMV) in anesthetized and paralyzed patients.[14] It is also demonstrated that this device reduces the incidence and severity of hypoxia under sedation during colonocscopy.[15] The objectives of our study are 1) to compare oxygenation and ventilation spontaneously ventilating obese patients or those with diagnosed or undiagnosed OSA undergoing day colonoscopy under propofol based sedation in between the SuperNO_2VA Et™ nasal positive airway pressure (PAP) device and routine care with face mask for O2 supply and 2) to determine its capacity to monitor expired CO2.

2. DISCUSSION OF SUBJECT POPULATION

2.1. Subject Characteristics

The study population for this investigation is all adults who have a BMI ≥30 kg/m^2 and/or documented OSA scheduled to receive Propofol based sedation for colonoscopy.

2.2. Inclusion and Exclusion Criteria

a) Inclusion Criteria:

1. Age 18 years of age or older
2. Patients undergoing lower endoscopy procedure (may be upper and lower)
3. American Society of Anesthesiology (ASA) Physical Status I-III
4. BMI ≥30 kg/m^2 and/or documented Obstructive Sleep Apnea
5. Has provided written informed consent

b) Exclusion Criteria:

1. Inpatient status
2. Active Congestive Heart Failure Exacerbation
3. Untreated ischemic heart disease
4. Acute exacerbation of respiratory disorders, including COPD and asthma
5. Emergent procedures
6. Pregnancy
7. Previous enrollment in this study
8. Inability to provide informed consent
9. Additional medical testing planned for the same day
10. History of allergic reaction to Propofol
11. Tracheostomy
12. Supra-glottic or sub-glottic tumor
13. Gastrointestinal tract obstruction or delayed transit (including delayed gastric emptying, gastric bezoar, achalasia, toxic megacolon).
14. Prisoners

2.3. **Discussion of Subject Population**:

Patients with either a BMI ≥30 kg/m^2 and/or a documented Obstructive Sleep Apnea scheduled for colonoscopy with Propofol sedation at are increased risk for severe hypoxemia intra-operatively and post-operatively. In addition patients with OSA usually fall into three scenarios. Those that are diagnosed with OSA and are using their CPAP, those that are diagnosed with OSA but do not use CPAP, and the undiagnosed OSA patient. Therefore, this patient population is at higher risk for respiratory depression and hypoxia and the associated morbidity.

3. SUBJECT IDENTIFICATION, RECRUITMENT AND CONSENT

3.1. Method Of Subject Identification And Recruitment

Subject consenting will take place at the LBJ medical center prior to the procedure by key research personnel such as PI, Co-PIs, and/or study coordinators. Subject initials and/or study identification number will refer to the subjects.

3.2. Consent Process

Subjects deemed eligible to participate in the study will be explained in detail the purpose, nature and procedures of the study, as well as the potential risks, benefits and alternatives. They will be given a consent form to read and if they so choose, to discuss with friends, family, and other clinicians. They will be invited to ask questions and, after all questions are answered to their satisfaction, invited to sign the consent form. The key research personnel (with proper delegation of authority) will participate in the consenting process to ensure the subject has full understanding of the procedure and risks. No study-specific procedure will be performed before the consent form is signed.

Subject participation in this investigation is voluntary. Written informed consent is required from all subjects prior to the subject's participation in the investigation. Also, an obtained permission of the faculty anesthesiologist, in charge of the patient's anesthesia care, must also be granted for subject participation. If the subject is illiterate or unable to adequately read the informed consent form, a witness' signature and a cross mark or a fingerprint of the subject is required. In accordance with FDA regulation 21 CFR Part 50, informed Consent shall be obtained prior to any study procedure. The original of the signed consent will be retained at the investigational site. A signed copy of the consent will be given to the subject. While not anticipated, Sponsor will report any failure to obtain subject consent to the IRB within 5 days of learning of such an event, as required by regulation.

Prior to participating in this investigation, the site will be required to have an IRB-approved Informed Consent Document. Any modifications to the consent must be approved by Sponsor and by the IRB of record. The Principal Investigator is responsible for obtaining and maintaining the approved informed consent and forwarding an IRB-stamped copy to Sponsor.

3.3. Costs to the Subject

None

3.4. Payment for Participation

A total of $30 will be paid to each subject for the index participation of this stud.

3.5. Return of Individual Research Results

Not Applicable.

4. METHODS AND STUDY PROCEDURES

5.1 Instruments

The SuperNO_2VA™EtCO2 (Nasal Oxygenating Ventilating Apparatus) mask is indicated to deliver gas, create a seal, and provide positive pressure while placed over a patient's nose and connected to either an anesthesia circuit or hyperinflation bag during respiratory, anesthesia, and resuscitation procedures. The SuperNO_2VA™EtCO2 mask is also intended to facilitate simultaneous oxygenation and ventilation during intubation, as the mask covers only the patient's nose, leaving the clinician with an unobstructed view of the airway.

5.2 Methods:

This study involves the oxygenation, continuous positive airway pressure, and ventilation of a subject via nasal mask and oxygenation via a closed facemask. The interventions directly related to this study are that of supplement oxygen, and continuous nasal CPAP intra-operatively
Patients will be randomized in groups of ten to one of two groups using a random number table. Group A: Standard care with a facemask. Group B: SuperNO_2VA™EtCO2.

For each anesthetic case, a preoperative history and physical and intraoperative record will be documented (table 1).

Table 1: General Patient characteristics	
Age (years)	
Gender (M/F)	
Height (cm)	
Weight (kg)	
BMI (kg/m^2)	
ASA classification (I-III)	
Diagnosed OSA on home CPAP	
Diagnosed OSA *not* on home CPAP	
STOP-BANG Score	
Patient Co-morbidities*	

*Co-morbidities include any history of: hypertension, diabetes, coronary disease, valvular disease, arrhythmia, cerebrovascular disease, active cancer, tobacco use, pulmonary disease, renal disease, liver disease.

Once in the endoscopy suite, the patients will have continuous monitoring of heart rate, end tidal CO2 (EtC02), O2 saturation, and non-invasive blood pressure monitoring with an interval no longer than 5 minutes. Patients randomized to group A, the anesthesia provider will supply oxygen via facemask at 10LPM. Patients randomized to group B, the anesthesia provider will attach the SuperNO_2VA™ EtCO2 circuit port to the hyperinflation bag with the oxygen flow rate to 10 L/min. Initial dosing bolus 0.5-1.0 mg/kg actual body weight of Propofol will be administered for sedation and MOAA/S scores will be assessed. Nursing or the research assistant will then record the patient's MOAA/S score. If the patient's MOAA/S score is ≥ 4, additional 10-20mg boluses will be administered every 30 – 90 seconds until a MOAA/S score of <4 reached. Once a MOAA/S score of < 4 is reached the endoscopist will perform endoscopic intubation and the goal will be to maintain a MOAA/S score of <4 until the procedure is over. If the patient's MOAA/S score ≥4, additional 10 – 40mg bolus of propofol will be administered every 30-

90 seconds until the MOAA/S is <4. The measurements that will be made are the following: Elapsed time from initiation of induction to the first disappearance of expired CO2 on capnography, the incidence, severity, and time of oxygen desaturation, number of airway maneuvers performed, duration of airway maneuvers, reason for performing the airway maneuver, the onset time of administration of sedation, the duration of the procedure, the total dosage of the medication, vital signs - blood pressure, heart rate, and oxygen saturation, the time to full recovery, and patient cooperation. Nursing or the research assistant will document their patient's depth of sedation, cooperation with procedure, and safety. Patients will recover in the endoscopy suite. The patients will have continuous monitoring of heart rate, O2 saturation, and BP monitoring and MOAAS Score. The time to discharge will be obtained for each patient. Patients will also complete a satisfaction and pain questionnaire before they are discharged. A statistician using student T-test, Fishers exact test, and other statistical methods they deem appropriate will analyze the collected data.

5.3 Definitions of Events

- Airway maneuver: consists of either airway maneuvers such as chin lift, jaw thrust, , mask ventilation, or the insertion of a nasal or oral airway, supraglottic device, or ETT
- Oxygen desaturation: $SpO_2 \leq 90\%$ for ≥ 15 seconds
- Cardiac complications is defined by a change in either SBP or DBP > 25% from baseline, a change in heart rate > 25% from baseline, arrhythmias, and ST-changes on EKG (ST depression or elevation).
- Full recovery is defined as the time from endoscope withdrawal until a MOAA/S score of 5 was achieved and the patient could drink liquids and ambulate independently.
- Full recovery until actual discharge is defined as the interval from full recovery until the patient exited the recovery room.
- Induction to full sedation is the time from initial administration of intravenous sedative or analgesic to the insertion of the endoscope
- Intra-procedural period was defined as the time of first scope insertion until the last scope removal.
- Procedural interruption is defined as the removal of the endoscope due to a respiratory complication
- Modified Observer's Assessment of Alertness/Sedation Scale (MOAAS) from 1 – 5

MOAAS:
0 No response after painful trapezius squeeze
1 Responds only after painful trapezius squeeze
2 Responds only after mild prodding or shaking
3 Responds only after name is called loudly and/or repeatedly
4 Lethargic response to name spoken in normal tone
5 Responds to name spoken in normal tone

5.4 Crossover to Other Group After Randomization

Patients in either Group A or Group B will be eligible for crossover to the other group at the discretion of the anesthesiologist in order to safely complete the procedure and minimize the likelihood of future adverse events.

Group A (Standard care with a facemask) to Group B (SuperNO_2VA™EtCO2) group will occur when during the procedure either: 1) after insertion of an oral or nasal airway and hypoxia is persistent, and 2) before supraglottic airway endo tracheal tube insertion if the care team wishes.

Group B to Group A: If any of the following occur: 1) patient refusal to wear the mask once placed due to claustrophobia, poor fit or discomfort or any other reason; 2) if a nasal or oral airway is needed.

6. SUBJECT WITHDRAWALS

Subjects may be withdrawn from the study for the following reasons:

1. Unacceptable adverse events (safety or tolerability)
2. The subject's may withdraw from the study at any time and for any reason
3. Clinician decision that it is in the best interest of the subject to withdraw from the study

7. SAFETY AND REPORTABLE EVENTS

7.1 Adverse Event Definition

Adverse Event (AE): An Adverse Event is any undesirable clinical event occurring to the subject during clinical study, whether or not it is considered related to the investigational product. This includes a change in a subject's condition or laboratory results, which has or could have a deleterious effect on the subject's health or well-being. An Adverse Event that is related to the investigational device may be referred to as an Adverse Device Effect (ADE).

7.2 Adverse Events

For study conduct purposes, adverse events will be categorized at the investigative site into two groups: Serious Adverse Events, and Non-Serious Adverse Events. The Investigator as either related to the device or its deployment, or not related to the device or its deployment will assess the causal relationship of each adverse event. Each Adverse Event assessed as being related to the device or its deployment will also be assessed by the Investigator as being anticipated or unanticipated.

7.3 <u>An adverse event does not include</u>:

- Medical or surgical procedures; the condition that leads to the procedure is not an adverse event
- Pre-existing disease, conditions, or laboratory abnormalities present at the start of the study that do not worsen in frequency or intensity
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalizations for cosmetic or elective surgery or social/convenience admissions)
- Expected ICU course

7.4 Unanticipated Adverse Device Effect (UADE)

Any device related adverse event, the nature or severity of which is not consistent with or listed in the applicable product information (e.g., instructions for use, subject informed consent document, subject information brochure [if applicable], promotional literature) or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

7.5 Responsibilities for Reporting Serious Adverse Events

All adverse events, whether observed by the Investigator, elicited from or volunteered by the subject, should be documented. Each adverse event will include a brief description of the experience, the date

of onset, the date of resolution, the duration and type of experience, the severity, the relationship to investigational product (i.e., drug or device), contributing factors, and any action taken with respect to the study drug/device.

Investigators and research coordinators will be instructed that all AE and corresponding relevant information should be recorded on the Adverse Event Form. In addition, the clinical site will be responsible for notifying Sponsor within 24 hours of any UADE. All relevant information regarding an UADE should be recorded on the Adverse Event Form and reported to Sponsor via Fax within 24 hours of the event. In addition to the event form, copies of adverse device effect related source documents should be forwarded to the Sponsor.

The Principal Investigator is responsible for reporting AEs to the IRB of record in accordance with IRB procedures. The Sponsor is responsible for informing the appropriate regulatory authorities and other Investigators of any UADEs that have occurred.

The Principal Investigator will record all serious adverse experiences that occur during the study period in the appropriate source documents and/or AE log as applicable.

8. RISK/BENEFIT ASSESSMENT

8.1 Potential Risks

As with use of all medical devices, complications may occur. Recognized risks associated with the use of the study intervention include, but are not limited to, the following:

- Allergic reactions: although the materials being used are hypoallergenic and the risk is small, there remains a risk for an allergic reaction that may result in hives, swelling, or anaphylaxis.
- Ocular injury: although the SuperNO_2VA Et™ Mask was designed to contour away from the eyes, mishandling of the mask or accidental slippage from its intended position may result in contact with the subject's eye, resulting in a corneal abrasion and/or other ocular injury.
- Pressure ulcer: although the clinical protocols states to remove the SuperNO_2VA Et™ after successful placement of an invasive airway, if the SuperNO_2VA Et™ is mistakenly left on the subject for an extended period of time it can lead to a pressure ulcer.

8.2 Risks Minimization

- To minimize the risk of allergic reactions the SuperNO_2VA Et™ has undergone and successfully passed biocompatibility testing. However, there is still a very small risk for an allergic reaction that may result in hives, swelling, or anaphylaxis.
- To minimize the risk of an ocular injury, it is recommended that all clinicians be properly trained on how to use the SuperNO_2VA™EtCO2 and be familiar with the Instructions For Use (IFU).
- To minimize the risk of a pressure, it is recommended that all clinicians be properly trained on how to use the SuperNO_2VA™EtCO2, be familiar with the Instructions For Use (IFU), and monitor the subject's face for redness every 30 minutes that the SuperNO_2VA™ EtCO2 is secured to the subject.

8.3 Potential Benefits to Subjects

- Improved oxygen delivery, administration, and oxygenation
- Potentially able to reduce post-op respiratory complications

8.4 Alternatives to Participation

The alternative for not participating in this study is not using the SuperNO_2VA™ EtCO2 for gastrointestinal endoscopy.

9. CONFIDENTIALIATY OF DATA AND INFORMATION STORAGE

All study participants will be assigned a study number. The PI will maintain the key to the study number and medical record number in a password locked UTH computer. Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Patient data will be entered into a password protected electronic spreadsheet and online database (i.e. REDCap). Only the investigators, who have been invited to participate in the study and who are registered with the IRB, as well as have documented completion of all IRB and HIPAA regulations will have access to patient data, but not the medical record key.

Electronic records will be stored for 5 years after study conclusion on the institution's password protected computer, after which time they will be deleted. If there is a breach in confidentiality or violation of IRB and HIPAA regulations, the IRB will be notified in a timely manner (within 7 days) and appropriate actions taken thereafter. All data used in the analysis and reporting of this investigation will be de-identified.

In order to ensure compliance with the Health Insurance Portability and Accountability Act (HIPAA), all subjects enrolled in the study will be required to provide authorization to disclose Protected Health Information (PHI). This authorization will be included in the informed consent document as required by the IRB. In all study reports and in any resulting publications, subjects will not be referred to by their initials and/or study identification number.

The co-PIs will monitor for safety. Data safety will be ensured by having all patient consents and information stored in the REDCaps system. After randomization patient and study data outside the REDCaps system will only be identified by study number. Any recruitment data and randomization tables will be stored as a single copy in a locked cabinet in a PI's secured Faculty office.

10. SAMPLE SIZE DETERMINATION AND DATA ANALYSIS

10.1 Sample Size Determination

For sample size calculation we used the standard sample size calculation equation[16]:

$$n = \frac{2(Z_{\alpha} + Z_{1-\beta})^2 \sigma^2}{\Delta^2}$$

σ = variation of the measurement
Δ= difference to be detected

σ and Δ are based on the outcome values from previous publication. [15]
This publication showed a time difference (Δ) of 9 minutes with a standard deviation (σ) of ± 10 minutes in both intervention groups.
To be able to detect an even smaller time difference of 5 minutes and with a standard deviation of 10 minutes and a drop of percentage of 20% *(α = 0,05 and 1-β = 0,80)* we calculated n1=n2= 75. A total of 150 patients will be enrolled.

4.1. Randomization

A random number generator program will be used to assign sequential qualified study cases to control group (N = 69) or SuperNO_2VA™EtCO2 group (N = 69) before collection of additional demographic information and before anesthetic and surgical care. After study group assignment, baseline data will be collected, including age, gender, height, weight, and BMI.

4.2. Planned Statistical Analysis

Although randomization into treatment groups should minimize differences between the groups, basic bivariate analyses will be performed to determine if there are any clinical or demographic differences, using the data collected in table 1. Logistic regression models will be performed to determine if there are significant differences between the groups for both incidence and severity. Student's t-tests will be performed to determine if there is a significant difference between groups for duration, with Wilcoxon non-parametric tests being performed if the data are non-linear. If significant differences in clinical or demographics characteristics were found, multivariable models will be performed to adjust for these possible confounding variables using logistic regression and ANCOVA models (with GEE models being used to model non-linear data with the appropriate exponential family distribution). All analytic assumptions will be verified and all analyses performed with SAS v9.4, SAS Institute, Cary, NC), analyzing the data as both per-protocol and intention-to-treat.

A Data Safety and Monitoring Board (DSMB) will be convened once half the necessary study population has been enrolled, to discuss the current status of primary endpoints and adverse events, all of which will be tabulated throughout the study. If effect sizes are larger than originally planned and there is a statistically significant decrease in the primary event at this halfway mark, the study will end at this time.

5. ETHICS

Institutional Review Board (IRB)

Prior to participating in this investigation, the site will be required to obtain approval from its governing IRB. The Principal Investigator is responsible for obtaining and maintaining IRB approval to participate in this investigation. Prior to subject enrollment, a signed copy of the IRB approval letter addressed to the Investigator certifying study approval must be submitted to the Sponsor. The IRB for this study is the local IRB at McGovern Medical School (University of Texas School of Medicine at Houston) The Investigator will report to the Sponsor immediately if, for any reason, the approval to conduct the investigation is withdrawn. This report will include a complete description of the reason(s) for which approval was withdrawn.

6. DATA MONITORING

Data Review

The Sponsor will review all CRFs for completeness and clarity upon receipt. Missing or unclear data will be requested as necessary throughout the study. The Sponsor will request further documentation such as physician procedure notes when UADEs and/or malfunctions are observed and reported.

The Sponsor will provide clinical monitoring including comparison of CRFs to source documentation for accuracy and appropriateness, review of/for adverse events, prompt evaluation of UADE, and site compliance. To this end, the Principal Investigator will permit inspection of the study files and subject CRFs by Sponsor representatives and/or responsible government agencies.

Prior to initiation of the study, sites will be trained on the clinical protocol, accepted clinical practices and Federal regulations pertaining to clinical research. Study sites will receive interim monitoring, as needed, and a final visit prior to study closure.

Compliance and Deviations

It is expected that sites (Investigators, study coordinators, ancillary site personnel, and study subjects) will be compliant with the study protocol. Should it be determined that the site is non-compliant, reasonable efforts will be made to secure compliance. These efforts/actions shall be documented in writing and maintained within the study administration file at the Sponsor's location.

Should the site continue to remain non-compliant, the study Sponsor may restrict device availability and/or notify the governing IRB. Should efforts to bring the site into compliance fail, the site may be suspended from study participation until the noncompliance is resolved. Federal regulations require the Sponsor to report non-compliances in the study to the appropriate regulatory authorities. Therefore, in the event of an Investigator or site suspension, the governing IRB and other appropriate regulatory authorities shall be notified.

Protocol Deviations

Protocol Deviations (PDs) will be documented on a Protocol Deviation Case Report Form. PDs are reportable to the institution's governing IRB and regulatory agencies during the annual reporting process, unless otherwise directed by the individual governing IRB requirements or as the specific circumstance dictates. Every attempt shall be made to adhere to the study protocol. However, should an Investigator be required to deviate from the protocol to protect the life or physical well-being of a study subject in an emergent circumstance, such notice shall be given to the study Sponsor as soon as possible, but no more than 5 working days from the date the event occurred. With the exception of an emergent circumstance, prior approval from Sponsor and the appropriate regulatory authorities is required for any change in, or deviation from, the study protocol as such changes may affect the soundness of the investigation or the rights, safety, and welfare of study subjects.

Data Safety Monitoring

Anesthesiologist (Dr. Yandog Jiang, MD.), who is not a part of the study, will review adverse events, serious adverse and protocol deviations at the Lyndon B Johnson Hospital (Harris Health) site. These events and deviations will also be reported to the McGovern Medical School IRB as required. They will review all serious adverse events within 24 hours of their occurrence. Once 62 participants have been randomized, an interim analysis will be completed to review efficacy of primary endpoint, adverse events, serious adverse and protocol deviations. A final safety review will be performed once all the subjects complete the study.

Investigator Reports and Responsibilities

Investigators are responsible for ensuring the investigation is conducted in accordance with the study protocol and applicable Federal regulations (21 CFR, Part 812, Subpart E).

Investigators are also responsible for:

- Obtaining IRB approval for study conduct and re-approval as applicable (if more than one Investigator is participating in the study at a site, the Principal Investigator shall be responsible for the IRB approval and re- approvals)
- Obtaining informed consent of study subjects prior to enrollment into the clinical study
- Protecting the subject rights, safety, and welfare

- Maintenance of subject records and confidentiality
- Record retention as defined in Federal regulations 21 CFR, Part 812.140 (a), (d), and (e)
- Management of investigation and study related activities according to the Clinical Investigator Agreement and the Study Research Agreement
- Submission of site-specific study closure report to governing IRB within 3 months of notification from study Sponsor (if more than one Investigator is conducting the study, the Primary Investigator is responsible for submission of the study closure report)
- Return of any unused investigational product to the study Sponsor upon request or at the conclusion of the clinical study

***In addition**:*

- An Investigator shall report to the Sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the Investigator's part of an investigation
- If an Investigator uses a device without obtaining informed consent, the Investigator shall report such use to the Sponsor and the reviewing IRB within 5 working days after the use occurs
- An Investigator shall, upon request by a reviewing IRB or regulatory agency official, provide accurate, complete, and current information about any aspect of the investigation

Sponsor Reports and Responsibilities

The study Sponsor is responsible for ensuring the study is conducted in accordance with the study protocol and applicable federal regulations (21 CFR, Part 812, Subpart C). Further, the study Sponsor is responsible for the following:

- Selecting qualified Investigators and providing Investigators with appropriate information for study conduct
- Ensuring review and approval process for governing IRB is obtained
- Training all clinical investigators in the study
- Appropriate monitoring of the clinical study
- Prompt notification to the appropriate regulatory and all Investigators of UADE
- Record maintenance and retention per Federal regulations (21 CFR, Part 812.140 (b), (d), and (e)
- Submission of final study closure report that details cumulative study experience to the appropriate regulatory authorities, governing IRBs, and Investigators within 6 months of completing the clinical investigation in addition to fulfilling annual reporting requirements

***In addition**:*

- A Sponsor who conducts an evaluation of an UADE shall report the results of such evaluation to all reviewing IRBs and participating Investigators within 10 working days after the Sponsor first receives notice of the effect. Thereafter the Sponsor shall submit such additional reports concerning the effect as an IRB request
- A Sponsor shall notify all reviewing IRBs and participating Investigators of any withdrawal of approval of an investigation or a part of an investigation by a reviewing IRB within 5 working days after receipt of the withdrawal of approval
- At regular intervals, and at least yearly, a Sponsor shall submit progress reports to all reviewing IRBs. In the case of a significant risk device, a Sponsor shall also submit progress reports to the regulatory authority

- A Sponsor shall notify all reviewing IRBs of any request that an Investigator return, repair, or otherwise dispose of any units of a device. Such notice shall occur within 30 working days after the request is made and shall state why the request was made
- In the case of a significant risk device, the Sponsor shall notify the IRB within 30 working days of the completion or termination of the investigation and shall submit a final report to all reviewing IRBs and participating Investigators within 6 months after completion or termination. In the case of a device that is not a significant risk device, the Sponsor shall submit a final report to all reviewing IRB's within 6 months after termination or completion
- A Sponsor shall submit to the IRB a copy of any report by an Investigator of use of a device without obtaining informed consent, within 5 working days of receipt of notice of such use
- If an IRB determines that a device is a significant risk device, and the Sponsor had proposed that the IRB consider the device not to be a significant risk device, the Sponsor shall submit to the appropriate regulatory agency a report of the IRB's determination within 5 working days after the Sponsor first learns of the IRB's determination
- A Sponsor shall, upon request by a reviewing IRB, provide accurate, complete, and current information about any aspect of the investigation

Study Termination

The Sponsor may terminate the study at any time. If terminated, the Sponsor will promptly notify the Investigator to cease enrollment of subjects. The study will also be terminated when the objectives have been fully met and all of the designated data collected.

Study Registration

The study will be listed at www.clinicaltrials.gov.

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