Title: Bispectral Index and Levels of Sedation with Propofol with/without Remifentanil in Healthy Volunteers (SONORA)

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Medtronic

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	[redacted] (SONORA)
Clinical Investigation Plan Identifier	MDT19049SONORA
Study Product Name	BIS™ Complete Monitoring System
Sponsor/Local Sponsor	Medtronic Minimally Invasive Therapies Group (MITG) Respiratory, Gastrointestinal & Informatics (RGI) 6135 Gunbarrel Avenue, Boulder, CO 80301 U.S.A.
Document Version	5
Version Date	28 Sep 2020
Principal Investigator(s)	David MacLeod, FRCA Human Pharmacology & Physiology Lab Duke University Medical Center Durham, NC 27710 U.S.A.

1. Investigator Statement

Study product Name	BIS™ Complete Monitoring System
Sponsor	Medtronic Minimally Invasive Therapies Group (MITG) Respiratory, Gastrointestinal & Informatics (RGI)
Clinical Investigation Plan Identifier	MDT19049SONORA
Version Number/Date	5/ 28 Sep 2020
I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated. I agree to comply with International Conference on Harmonization Guidelines on Good Clinical Practice, United States Food and Drug Administration regulations. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of Medtronic. I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Medtronic. I will discuss this material with them to ensure that they are fully informed about the products and the study.	
Investigator's Signature:	
Investigator's Name:	
Institution:	
Date:	

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2. Glossary

Term	Definition/Acronyms
AE	Adverse Event.
ASA	American Society of Anesthesiology
BIS™	Bispectral Index (BIS) technology monitoring uses processed EEG signals to measure sedation depth based on the level of consciousness
CBC	Complete Blood Count
CO_2	Carbon Dioxide. It can be measured with a capnograph, a device that measures the concentration of carbon dioxide from each inspired and expired breath. Gases are collected with non-invasive side stream from the inhaled and exhaled gases of the subject. Capnograph outputs numeric values and waveforms of the fractioned concentration of CO_2 of each breath
CRF	Case Report Form. Forms where the clinical data are collected. eCRF is the electronic version of the CRF
EC	Ethics Committee
ECG	Electrocardiogram. A diagnostic tool that measures and records the electrical activity of the heart
ED	Effective dose
EDC	Electronic Data Capture. Electronic systems where the data are collected through the eCRF (Oracle Clinical). May also be referred to as RDC (Remote Data Capture).
EEG	Electroencephalogram
ET	End-tidal concentration
EMR	Electronic Medical Record. Digital version of a patient's medical record within a single facility.
$EtCO_2$	End-tidal Carbon Dioxide. The value of exhaled carbon dioxide displayed by the capnograph device
FD	Financial Disclosure
GCP	Good Clinical Practice
ICF	Informed Consent Form
IRB	Institutional Review Board
ISF	Investigator Site File. Regulatory binder supplied by the sponsor
LMA	Laryngeal mask

Term	Definition/Acronyms
LOC	Level of consciousness
MOAA/S	Modified Observer's Assessment of Alertness/Sedation
NCM	Non-contact monitoring
NMS	Nerve Monitor Stimulation
PI	Principal Investigator. The person is responsible for overseeing the study and assuring study completion in compliance with applicable regulations.
PIC	Patient Interface Cable
PK/PD	Pharmacokinetics and pharmacodynamics
RA	Regulatory Authority
SpO_2	A non-invasive spectroscopic estimate of arterial oxygen saturation measured transcutaneously by a pulse oximeter
SOP	Standard Operating Procedures
TES	Tetanic Electrical Stimulation
TCI	Target-controlled infusion
TIVA	Total Intravenous Anesthesia
UADE	Unanticipated Adverse Device Effect

3. Synopsis

Title	Bispectral Index and Levels of Sedation with Propofol with/without Remifentanil in Healthy Volunteers (SONORA)
Clinical Study Type	Prospective
Product Name	BIS™ Complete Monitoring System
Product Status	BIS™ is commercially available in the United States.
Sponsor	Medtronic Minimally Invasive Therapies Group (MITG) Respiratory, Gastrointestinal & Informatics (RGI) 6135 Gunbarrel Avenue Boulder, CO 80301
Investigation Purpose	To investigate the relationship between BIS™ and propofol with/ without remifentanil across a wide range of hypnotic states.
Primary Objective	To determine BIS_{50} (BIS™ value at which 50% of patients will be unresponsive at given drug concentrations)
Secondary Objective	To determine BIS_{95} (BIS™ value at which 95% of patients will be unresponsive at given drug concentrations) To determine Prediction Probability (P_k) for correctly predicting if the subject was responsive or unresponsive
Study Design	This is a single-center, prospective, non-randomized, cross-over study to collect data to evaluate the relationship between BIS™ and anesthetic regimens. The subjects will receive two regimens of anesthesia with different drug combinations, with at least a 1-week washout period between regimens. Subjects will be sequentially assigned to start with either Propofol (P) or Propofol with 4 ng/ml of Remifentanil (R) regimens with the BIS™ bilateral sensor placed on the subject's forehead. The Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale will be used to measure the level of alertness in sedated subjects, with Tetanic Electrical Stimulation (TES) being used once the patient is unresponsive to tactile stimuli (e.g., MOAA/S < 2). The loss of tactile stimulus response will be defined according to the MOAA/S score value <2.

	TES will then be initiated once the subject reaches an MOAA/S <2, with a one-time stimulation of 50mA, 50 Hz delivered for 5 seconds. The subject's response will be recorded along with the BIS™ value prior to stimulation, at the time of stimulation and 2 minutes following stimulation. The data will be used to gauge the influence of stimulation on the subject's level of sedation, pre-TES and post-TES. [redacted]
Sample Size	To collect 20 complete data sets, up to 30 subjects will be enrolled to account for anticipated screen failures and subject dropouts. Based on the dose-response Hill equation with an allowable error of ± 15% for BIS_{50} and coefficient of variation of 25% at the alpha level of 0.05, the sample size will provide sufficient power (>80%) to evaluate the performance of anesthetic agents/ regimens.
Duration	The study duration is expected to be up to approximately 4 months. The expected duration of each subject will be approximately (~) 10 hours. The Enrollment Visit should take approximately 2 hours to complete, and each Study Visit will be approximately 4 hours per subject. Each subject will be contacted by phone within 48 hours of the study participation.
Planned number of sites	1 site in the US
Inclusion/Exclusion Criteria	Inclusion Criteria: 1. Healthy (ASA physical status 1), male or female subjects between the ages of 18 to 60 years; 2. Completion of a health screening for a medical history by a licensed physician, nurse practitioner or physician assistant; 3. Vital signs must be within the following ranges to be included: Vital signs measured sitting after 3 minutes rest; heart rate: 45-90 bpm; systolic blood pressure: 110-140; diastolic blood pressure: 50-90. Out-of-range vital signs may be repeated once. [Pre-dose vital signs will be assessed by the Principal Investigator or designee (e.g., a medically qualified sub-investigator) before study drug administration. The Principal Investigator or designee will verify the eligibility of each subject before dosing]; Exclusion Criteria: 1. Has severe contact allergies that may cause a reaction to standard adhesive materials found in pulse oximetry sensors, ECG electrodes,

	respiration monitor electrodes, or other medical sensors [self-reported]; 2. Known neurological disorder (e.g., epilepsy, the presence of a brain tumor, a history of brain surgery, hydrocephalic disorders, depression needing treatment with anti-depressive drugs, a history of brain trauma) [self-reported and assessment by PI or delegate]; 3. Known cardiovascular disease (e.g., hypertension, coronary artery disease, prior acute myocardial infarction, any valvular and/or myocardial disease involving a decrease in ejection fraction, arrhythmias, which are either symptomatic or require continuous medication/ pacemaker/ automatic internal cardioverter defibrillator), current implanted pacemaker or automatic internal cardioverter defibrillator [self-reported and assessment by PI or delegate]; 4. Has a clinically significant abnormal finding on medical history, physical examination, clinical laboratory tests, or ECG at the screening [self-reported and assessment by PI or delegate]; 5. Recent use of psychoactive medication (e.g., benzodiazepines, antiepileptic drugs, ADHD medication, Parkinson's medication, anti-depressant drugs, opioids) [self-reported and assessment by PI or delegate]; 6. Subjects with known gastric diseases [self-reported and assessment by PI or delegate]; 7. Has a positive urine cotinine test or urine drug screen or oral ethanol test [POC testing]; 8. Known history of allergic or adverse response to drugs to be administered [self-reported]; 9. Known history of complications relating to previous general anesthesia or conscious sedation [self-reported and assessment by PI or delegate]; 10. Known history of malignant hyperthermia [self-reported and assessment by PI or delegate]; 11. Has a room air saturation less than 95% by pulse oximetry [measurement by PI or delegate]; 12. Has a clinically significant abnormal ECG [assessment by PI or delegate]; 13. Has a clinically significant abnormal pulmonary function test via spirometry [assessment by PI or delegate]; 14. Pregnant or lactating women [assessed by urine test and self-reported];

	15. Subjects with tattooed skin specific to the sensor placement areas (forehead, fingers, chest) [self-reported and assessment by PI or delegate]; 16. The subject must not take any prescription medication, except female hormonal contraceptives or hormone replacement therapy, from 146 days before the dosing until the end-of-study visit without evaluation and approval by the Investigator. Subjects who participated in a previous clinical trial who received a required FDA approved concomitant medication, for example, naltrexone, but were not randomized may be considered for participation in this study if they meet the washout requirement [assessment by PI or delegate];
Study Procedures and Assessments	Prescreening Visit: • Online or phone call pre-screening survey Enrollment Visit (Visit 1): • Informed Consent Process • Demographics • Medical screening • Medical history • Physical Examination • ASA physical assessment • Electrocardiogram (ECG) • Complete Blood Count (CBC) • Urine testing for presence of: • Cotinine (nicotine metabolite) • Pregnancy- for female subjects of childbearing age • Concomitant Medication Collection The subject will be instructed not to consume beverages and foods containing alcohol, grapefruit, or caffeine/ xanthine prior to dosing until the end-of-study visit per Institutional guidance. All subjects will fast as it will be instructed by the Investigator or designee before the start of the drug administration. The per dosing instructions will be provided to the subject. Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled.

	Procedure Visit: Pre-Procedure Assessments (Visits 2 & 3): • Vitals • Urine testing for presence of: • Cotinine (nicotine metabolite) • Drugs and Alcohol • Pregnancy- for female subjects of childbearing age • Breathalyzer • Concomitant Medication Collection • Adverse Event Assessment Procedure Assessments (Visits 2 & 3): • BIS™ sensor application and connected to BIS™ Monitor • TES sensor application to the calf with a stimulation of 2mA, 2 Hz for 1-5 seconds provided to ensure proper application • EEG waveform recorded in real-time during the study • IV Catheter Placement for fluid and drug administration • Blood pressure monitoring • Continuous EEG, Pulse Oximeter for SpO_2, and $EtCO_2$ • Anesthesia Administration • The propofol and remifentanil will be administered using the target-controlled infusion (TCI) computer-controlled program, e.g., TIVA Trainer, or another computer-controlled program/pump, to ensure that the targeted effect-site concentration of a drug is reached and maintained at each drug concentration plateau • 1% propofol and remifentanil diluted to a single concentration of 50 µg/ml will be used for this study. Infusion rate between 0 and 1200 ml/hr. will be used to achieve a target effect-site concentration of propofol and remifentanil • For propofol, the effect-site concentration for propofol will be predicted using Schneider pharmacokinetics and pharmacodynamics (PK/PD) model, and for remifentanil, Minto PK/PD model will be used

	• The assisted ventilation of the subject with either facemask or LMA may be used. • Each subject will receive one of the anesthetic regimens. The subject will rest for ~ 15 minutes before starting any regimen • MOAA/S Assessment • Once subjects reach a MOAA/S score of <2, they will receive noxious electrical stimulation using Tetanic Electrical Stimulation (TES). The BIS™ value will be recorded, followed by the MOAA/S assessment. Then, TES will be initiated with one stimulation to the tibial nerve at 50mA, 50Hz for 5 seconds. The subject's pain avoidance behavior, such as withdrawal of extremity, facial grimace or verbal groan, will be noted. The BIS™ value will then be recorded at the time of subject's response and 2 minutes following the TES assessment • Adverse Event Assessment • Device Deficiency Assessment A clinician will be monitoring respiratory and cardiac functions to determine if interventions are needed to maintain an adequate airway. The respiration support will be provided to ensure an unobstructed airway, adequate oxygenation (SpO_2 >92%), and CO_2 homeostasis throughout the study. As needed for airway support, the anesthesiologist may gently lift chin or jaw thrust (with or without manually assisted breathing), insertion of an airway device (oropharyngeal airway or laryngeal mask airway) and/or intermittent positive pressure ventilation (IPPV). Mask or nasal cannula will be used for supplemental O_2 delivery. **For Propofol group**, the initial target effect-site concentrations of propofol will be 0.5 µg/ml followed by incremental increases in the target effect-site concentrations of 1.5, 2, 2.5, 3, 4, 6, and a maximum of 8 µg/ml until a BIS™ value not less than 30 is reached or per Investigator's discretion. The BIS™ value should not intentionally be taken below 30. The equilibration time for each targeted effect-site concentration will be at approximately 12 minutes. The BIS™ value and MOAA/S scale will be assessed when the patient is awake and at different propofol concentrations. TES will then be initiated following the MOAA/S assessment and once the subject reaches a MOAA/S <2. The BIS™ value will be recorded at the time of subject's response and 2 minutes following the TES assessment. The propofol concentration will be decreased by the same steps until consciousness occurs with BIS™ values and MOAA/S assessments being captured.

	For the Propofol with Remifentanil group, where remifentanil is administered with propofol, approximately 2 minutes before starting propofol, to attain an effect-site targeted concentration of remifentanil of 4 ng/ml, remifentanil will be given by a continuous infusion. Within approximately 7 minutes, the infusion rate of Remifentanil may be adjusted to maintain the effect-site concentration of remifentanil of 4 ng/ml throughout the study. The equilibration time for each targeted plateau will be approximately 12 minutes. The BIS™ value and MOAA/S scale will be assessed when the patient is awake and at different propofol concentrations. TES will then be initiated following the MOAA/S assessment once the subject reaches a MOAA/S <2. The BIS™ value will be recorded approximately 2 minutes following the TES assessment. The cardiac output will be monitored, and subjects could be discontinued per PIs discretion. The respiratory rate will be monitored, a respiratory rate of 4 breaths/minute or less will be considered evidence of respiratory toxicity, and remifentanil will be discontinued. The start time of any drug infusion, target effect-site concentrations and infusion rate will be noted in the electronic Case Report Forms (eCRFs). The BIS™ value prior to MOAA/S assessment and TES will be noted along with the BIS™ value at the time of subject's response and 2 minutes following the TES assessment. Any adjustments to the infusion rate and time of adjustment as well as any changes to the subject management during the procedure will be recorded. The device data (raw signals), including Heart Rate, Blood Pressure, Respiration Rate, $EtCO_2$, SpO_2, BIS™, TCI, if available, will be recorded in real-time during the procedure and files will be provided to Medtronic by the site. The instructions on the secure data transfer will be provided by Medtronic. Each subject will be contacted by phone within 48 hours after completion of the procedure to perform a safety assessment
Safety	An anesthesiologist authorized to administer sedation drugs will be responsible for administering any procedural drugs for the sedation and monitoring of subject safety and physical state. All other personnel involved with the safety monitoring of subjects must be trained in and familiar with the management of recovery of sedated patients. The study site should have a setting that is fully equipped for the monitoring and support of the respiratory and cardiovascular function. Subjects will be continuously monitored throughout the study. Subjects will be monitored for Adverse Events, Serious Adverse Events, and Device-Related Adverse Events from BIS™ sensor application throughout the follow-up phone call.

Statistics	Data will be analyzed by Medtronic or its designee. Any changes in statistical methods will be detailed in the Clinical Study Report. Standard demographic information and baseline characteristics will be summarized using descriptive statistics. For safety assessments, adverse events (AEs) will be summarized using frequency counts and percentages. Descriptive statistics will be provided by severity and relationship as needed. The primary effectiveness analysis will be based on all evaluable data collected from the left side of the brain to reflect the typical operation of the device from this study. The BIS™ index value collected from the right side of the brain will be used for research. Subjects who discontinue participation prematurely will be included in the analysis of results. Subjects who withdraw from the study prior to completing both regimens will be replaced by a new subject. The data will be analyzed for each regimen to evaluate the dose-response relationship of the anesthetic agent concentration and BIS™ values. Any subject who responds to any verbal command with MOAA/S assessment score of 2, 3, 4, and 5 will be considered as responsive. Subjects with MOAA/S assessment scores <2 will be considered unresponsive. The value of BIS™ will be assessed at the different targeted-controlled drug concentrations or infusion rates. The logistic regression (simplified E_{max} model) will be used to analyze the relationship between the BIS™ index and loss of responsiveness through the probability of response curves. The values of BIS™, at which 50% (BIS_{50}) and 95% (BIS_{95}) of subjects are unresponsive, and their 95% confidential intervals will be derived. The systematic variance between groups will be evaluated. The Prediction Probability score (P_k) for correctly predicting if the subject was responsive or unresponsive will be assessed.

4. Introduction

4.1. Background

4.1.1. Basics of Anesthesia & Anesthetics

General anesthesia (GA) is a reversible state of controlled unconsciousness that is achieved with drugs that prevent awareness, pain, recall, distress, and movement in patients during surgery. General anesthesia is performed by medical professionals, generally anesthesiologists and nurse anesthetists, with extensive education and training in the physiology, pharmacology, techniques, and risks involved.

Two critical components of general anesthesia are hypnosis and analgesia. Maintaining an adequate level of anesthesia depth is critical to the attenuation of these responses. The hypnotic component can be

defined as the probability of tolerance to non-painful stimulus, e.g., name-calling, shaking, and shouting. The analgesic component may be considered as the probability of tolerance to a painful stimulus. Tolerance means the absence of a response being either a somatic response (*e.g.*, movement, sweating, eye-opening) or a hemodynamic response (increase in heart rate or blood pressure). When the state of general anesthesia is inadequate for the level of nociceptive stimulation from surgery, the heart rate and blood pressure can increase dramatically, alerting the anesthesiology provider to the possibility of increased nociception and arousal. Higher doses of an anesthetic are necessary to prevent reactions to more intense surgical stimuli. This fact has suggested that different states of anesthesia fall along a continuum of depth, with deeper anesthesia eliminating reactions to stronger stimuli. Thus, the anesthesiologist needs to know when a patient has reached a depth of anesthesia commensurate with an impending stimulus. Very superficial or deep depth levels can be disastrous in both the short and long run. The patient expects a surgical procedure to be safe and painless, with the assurance that throughout the procedure, s/he is asleep, without any perception or memory of what happened during that period. Intravenous anesthetics, including propofol, barbiturates, and benzodiazepines, produce a concentration-dependent reduction in wakefulness, ultimately leading to complete loss of consciousness. The effective dose (ED_{50}) of intravenous anesthetics for obtaining general anesthesia is calculated as the effect-site concentration at which 50 percent of patients will not respond upon noxious stimulation. Despite different mechanisms and sites of action, most anesthetic agents appear to cause unconsciousness by targeting, directly or indirectly, a posterior lateral corticothalamic complex centered around the inferior parietal lobe, and perhaps a medial cortical core of the brain.[1]

4.1.2. EEG Monitoring in Anesthesia

Since 1939, anesthesiologists have known about changes in the electroencephalogram (EEG) that are produced by anesthetic agents.[2] Many of the changes that occur in the brain with changes in anesthetic states can be readily observed in unprocessed EEG recordings. Different behavioral and neurophysiological states induced by anesthetics are associated with different EEG waveforms. The earliest use of the EEG in anesthesia tested the effects of barbiturates, eventually leading to the recognition of particular sequential effects shown in Figure 1. [3] The first changes induced by barbiturates in the EEG are 20-30 Hz (initial rapid response) waves, followed by the superimposition of 5-12 Hz alpha waves. Loss of consciousness occurs just as the initial rapid response yields to the slower oscillations. Spindle bursts of 5-12 Hz become prominent, and in turn, decline as the EEG develops large polymorphic waves of 1-3 Hz. When this slow polymorphic activity becomes dominant, the patient tolerates skin incision. At still higher concentrations of barbiturates, the EEG displays periods of suppression, each terminating with “burst” of renewed activity, which contains high-frequency components. The burst gradually subsides as it leads into the next episode of suppression. This combination of alternating phases of high-amplitude and low-amplitude periods is called “burst suppression.”

Monitoring the depth of anesthesia could help the anesthesia professional avoid intraoperative awareness and help to ensure that an appropriate dose of anesthetic drugs is given for each patient. The

lightness of anesthesia can result in awareness with recall of events that happen in the operation room. Too deep anesthesia could cause hemodynamic disturbances necessitating the use of vasoconstrictor agents, which constrict blood vessels to maintain normal blood pressure and cardiac output. Overly deep anesthesia can also result in respiratory depression requiring respiratory assistance postoperatively [4]. There is no objective scale that measures "too light" or "too deep" anesthesia. Bispectral Index (BIS) technology monitoring uses processed EEG signals to measure sedation depth based on level of consciousness (LOC) signals and allows anesthesia providers to titrate general anesthesia to achieve the desired LOC on the brain [4, 5]. BIS™ technology consists of a sensor, a digital signal converter, and a monitor. The sensor is placed on the patient's forehead to pick up the electrical signals from the cerebral cortex and transfer them to the digital signal converter. BIS™ values quantify changes in the electrophysiologic state of the brain during anesthesia. Overall, a BIS™ value below 60 is associated with a low probability of response to commands. The BIS™ is a continuously processed EEG parameter that correlates to the patient's level of hypnosis, where 100 = awake and 0 = flat-line EEG. The BIS™ parameter was designed to correlate with "hypnotic" clinical endpoints (sedation, lack of awareness, and memory) and to track changes in the effects of anesthetics on the brain. Figure 1 reflects a general association between clinical state and BIS values. Ranges are based on results from a multi-center study [5] of the BIS system involving the administration of specific anesthetic agents. BIS™ values and ranges assume that the EEG is free of artifacts that can affect its performance. Titration of anesthetics to the BIS™ range should be dependent upon the individual goals established for each patient. These goals and associated BIS™ ranges may vary over time and in the context of patient status and treatment plan.

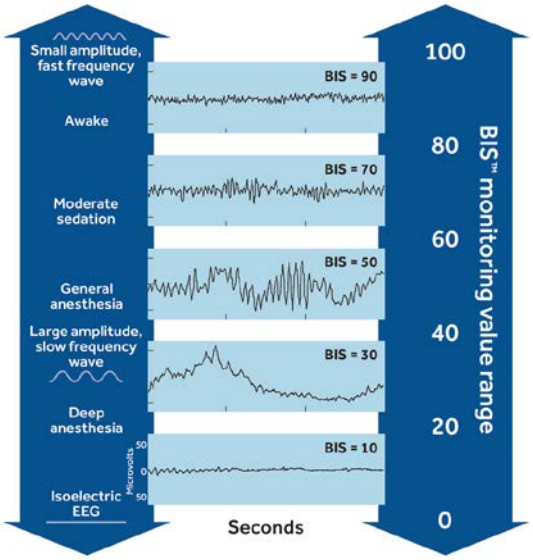


Figure 1: BIS™ Range Guidelines; a general association between clinical state and BIS™ values

4.1.3. Clinical Summary

The BIS™ system has been on the market for 20 years, and there is a large amount of clinical data available to assess the performance and safety of the device. **Table 1** summarizes overall clinical experience regarding the use of the BIS™ System found on the performance and safety of the device in the published clinical literature. The total number of individuals with device experience related to safety data from the clinical literature is 7,627. The patient populations included in these studies varied between infants, pediatrics, adults, obese adults, and the elderly.

Table 1: Clinical Data from Literature

Performance Data		Safety Data	
Number of Publications	**Number of Patients**	**Number of Publications**	**Number of Patients**
32 Publications addressing performance [6-37]	43,247	11 Publications with safety data [7, 10, 16, 22, 23, 25, 31-33, 38, 39]	7,627

Also, the anesthetic state is achieved with a hypnotic or sedative and an analgesic to provide the absence of consciousness, amnesia, and analgesia. Several studies examined and evaluated the usefulness of the BIS™ as a measure of the depth of anesthesia [40-42]. The relationship between BIS™ and blood concentration of propofol was demonstrated in many studies, and during propofol anesthesia, increasing doses of alfentanil or additional administration of nitrous oxide do not affect the BIS™ value [5, 43, 44]. In addition, propofol and remifentanil are commonly combined for total IV anesthesia. A prospective study of 45 adult patients scheduled for elective surgery under general anesthesia was undertaken using BIS™ monitoring to evaluate a pharmacokinetic (PK) and pharmacodynamic (PD) based model for target-controlled infusions of propofol and remifentanil [29]. The Schnider [45, 46] and Minto [47] models include an assessment of both the PK and PD effects of propofol and remifentanil, respectively, and include the covariates of age and BMI. It demonstrated the effective use of BIS™ monitoring as a guide for evaluating target-controlled infusion-based anesthesia models. The clinical literature review did not identify any new risks/side effects or safety concerns for the target device and its intended indications. The data form published clinical studies included in safety assessment did not reveal any new complications directly related to the use of the devices.

4.2. Purpose

To investigate the relationship between BIS™ and propofol with/ without remifentanil across a wide range of hypnotic states.

5. Objectives

5.1. Objectives

5.1.1. Primary Objective(s)

To determine BIS_{50} (BIS™ value at which 50% of patients will be unresponsive at a given drug concentration).

5.1.2. Secondary Objective(s)

To determine BIS_{95} (BIS™ value at which 95% of patients will be unresponsive at given drug concentrations).

To determine Prediction Probability (P_k) for correctly predicting if the subject was responsive or unresponsive.

6. Study Design

This is a single-center, prospective, non-randomized, cross-over study to collect data to evaluate the relationship between BIS™ and anesthetic regimens. The subjects will receive two regimens of anesthesia with different drug combinations, with at least a 1-week washout period between regimens. Subjects will be sequentially assigned to start with either Propofol (P) or Propofol with 4 ng/ml of Remifentanil (R) regimens while BIS™ bilateral sensor placed on the subject's forehead. The Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale, refer to Appendix A, will be used to measure the level of alertness in sedated subjects with Tetanic Electrical Stimulation (TES) being used once subjects reach a MOAA/S score <2 and a BIS™ value of not below 30 or per Investigator's discretion.

An anesthesiologist authorized to administer sedation drugs will be responsible for administering any procedural drugs for the sedation and monitoring of subject safety and physical state. All other personnel involved with the safety monitoring of subjects must be trained in and familiar with the management of recovery of sedated patients. The study site should utilize a setting that is fully equipped for the monitoring and support of the subject's respiratory and cardiovascular function. Subjects will be continuously monitored throughout the study.

[redacted]

6.1. Duration

The study duration is expected to be up to approximately 4 months. The expected duration of each subject will be approximately (~) 10 hours. The Enrollment Visit should take approximately 2 hours to complete, and each Study Visit will be approximately 4 hours per subject. Each subject will be contacted by phone within 48 hours of the study participation.[6]

6.2. Rationale

This clinical study design is formulated in order to capture the performance of BIS™ with anesthetic agents across a wide range of hypnotic states. The study design is a non-randomized prospective healthy volunteer is deemed appropriate in this setting and will provide more information to confirm the performance and safety of the BIS™.

[redacted]

Propofol and Remifentanil will be administered as part of an anesthesia technique called total intravenous anesthesia (TIVA) that uses computer-controlled infusion pumps in a process called target-controlled infusion (TCI). [48] A target effect-site concentration is entered as ng/ml into the pump, which calculates its infusion rate according to the appropriate pharmacokinetic and pharmacodynamic model, which is derived from various patients for model refer to *Section 9.5*. For remifentanil, the induction levels of 4 ng/ml are commonly used in surgeries, but the levels generally vary between 2-8 ng/ml.[48, 49] For purposes of this study, the selected target effect-site concentration of 4 ng/ml of remifentanil will be reasonable and not associated with an increased risk of adverse events. This concentration deemed to be appropriate for concentration-based drug effects for remifentanil in healthy volunteers.

7. Product Description

7.1. General

The BIS™ complete monitoring system is a user-configurable patient monitoring system designed to monitor the hypnotic state of the brain based on the acquisition and processing of EEG signals. The BIS™ complete system processes raw EEG signals to produce a single number, called the BIS™ index, which correlates with the patient's level of hypnosis. A sensor placed on the patient's head transmits EEG signals to the BISx4™ unit. The BISx4™ unit filters and digitizes the signal, analyzes it for the artifact, and processes it using digital signal processing techniques to derive processed EEG parameters like BIS™, and finally sends the processed data to the monitor for display. The purpose of processing the EEG waveform data is to extract characteristic features from the complex signal that the BIS algorithm can utilize to derive BIS™.

7.2. Manufacturer

BIS™ Complete Monitoring System, BISx4™, Patient Interface Cable (PIC) and BIS™ Sensor by (15 Hampshire St, Mansfield MA) Medtronic Inc.

7.3. Packaging

The Sponsor is responsible for the packaging and labeling of the device for shipment to the study site. Research conducted for this study will utilize investigational devices and devices cleared through the 510(k) regulatory process. FDA cleared devices are being used within the FDA-cleared indications for use (IFU) and do not require special labeling.

While exempt from Investigational Device Exemption (IDE) submission as a non-significant risk device under 12 CFR 812.2, Investigational devices used for research on humans in the United States are provided under regulation, meaning there are no regulatory approvals in place for marketing the device (e.g., 510(k)). The device will be labeled with the following:

"CAUTION - Investigational Device. Limited by Federal (or the United States) Law to investigational use."

It is the investigator's responsibility to ensure the appropriate labeling is visible and remains intact throughout the life of the study.

All FDA-cleared equipment associated with the clinical study will be identified with visible markings stating, "For clinical trial use only." Labeling of devices will be provided in accordance with local language requirements.

7.4. Intended Population

7.4.1. BIS™ Complete Monitoring System

The BIS™ EEG complete monitor system is intended for use under the direct supervision of a licensed healthcare practitioner or by personnel trained in its proper use. The system and all its associated parameters are intended for use on adult and pediatric patients within a hospital or medical facility, providing patient care to monitor the state of the brain by data acquisition of EEG signals. The BIS™ index, one of the Complete Monitor output parameters, may be used as an aid in monitoring the effects of certain anesthetic agents; and its usage with certain anesthetic agents may be associated with a reduction in primary anesthetic use and a reduction in emergency and recovery time. Use of the BIS™ index for monitoring to help guide anesthetic administration may be associated with the reduction of incidence of awareness with recall in adults during general anesthesia and sedation. The BIS™ Complete Monitoring System includes:

- BIS™ Complete Monitor
- BISx4™ (BISx4™ will be used in this study)
- Patient Interface Cable (PIC)
- BIS™ Sensor

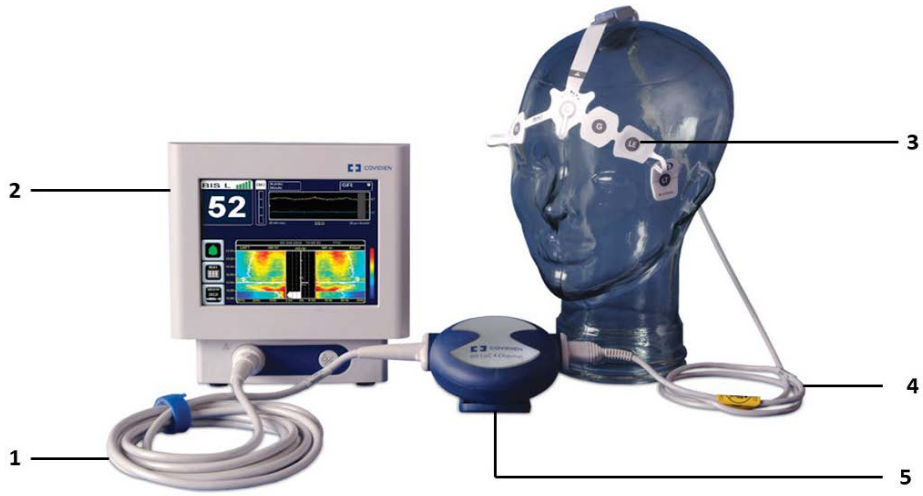


Figure 2: The BIS™ Complete Monitoring System. 1 - Monitor Interface Cable; 2 - BIS™ Monitor; 3- BIS™ bilateral sensor; 4- Patient Interface Cable (PIC); 5- BISx4™ (LoC 4 Channel)

7.4.2. BISx4™ Modules

The BISx4™ receives, filters, digitizes, and processes patient EEG signals. It is located close to the patient's head, where the EEG signal is less subject to interference from other medical equipment. The BISx4™ is shown in Figure 3**.** Its long flexible Monitor Interface Cable connects to the front of the monitor. The Patient Interface Cable (PIC) connects the BIS™ sensor to the BISx4™. The attachment clip on the BISx4™ is used to secure it in a convenient location near the patient's head. The BISx4™ Module is a variant of the BISx™ Module, and it processes up to four channels of EEG data. In this study, BISx4™ Module will be used with Bilateral Sensor.

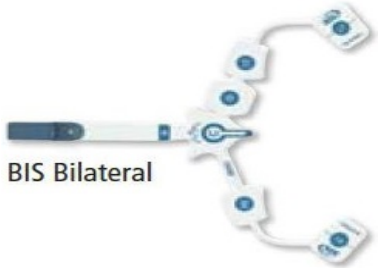
Figure 3: BISx4™ - 1- Monitor Interface Cable connects to Monitor; 2- Patient Interface Cable connects to BIS™ sensor; 3- BISx4™ (BIS™ LoC 4 Channel)

7.4.3. Patient Interface Cable

Covidien BIS™ Sensor Patient Interface Cable (PIC) connects the BISx4™ to the BIS™ Sensor, refer to **Figure 3.**

7.4.4. BIS Bilateral Sensor

The sensor is the single-use component of the BIS™ Monitoring System and should be replaced after each use. BIS™ Bilateral Sensors are designed with a 6 electrode pre-gelled EEG electrode array that is applied directly to the patient's forehead to transmit EEG signals to the BISx4™ Module. When the System is connected to a BISx4™ module and a BIS™ Bilateral Sensor, the monitor displays four channels of EEG. The sensor will be applied per IFU.



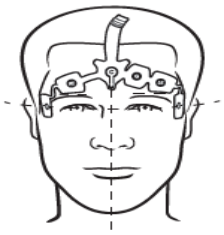


Figure 4: BIS™ Bilateral Sensor

7.5. Equipment

7.5.1. Other Equipment

Additional equipment such as FDA-cleared Pulse Oximeter (SpO_2 sensors and N600x monitors or other), capnography devices, a STIMPOD™ NMS450X nerve stimulator and TOF monitor may be provided by the sponsor to the study site.

[redacted]

7.5.3. Site's Equipment/Supplies

Propofol and remifentanil will be provided by the site. The remifentanil and propofol will be administered using the target-controlled infusion (TCI) computer-controlled program, e.g., TIVA Trainer, or another computer-controlled program/pump. In addition, the four monitors (Nexfin, Covidien Capnostream, ADInstruments Bio Amp FE132 & Oximeter Pod ML320/F) are integrated into ADInstruments PowerLab. This is connected to a Mac computer on which the software program, ADInstruments LabChart v8, is used to collect the data output from the PowerLab. Any additional monitors may be used as needed. All monitors will be used per site's guidance or practice.

7.6. Product Use

A member of the Medtronic team will set up the BIS™ system at each participating research site or will guide the site in set up remotely in order to ensure all equipment is fully functional. Specific instructions for the Site Investigator and staff on system set up, use sensor application, and data transfer will be provided before subject enrollment.

7.7. Product Training Materials

Prior to site activation or subsequent involvement in clinical study activities, Medtronic will provide clinical study training relevant and pertinent to the involvement of personnel conducting clinical study activities and investigator responsibilities. Principal Investigators participating in the clinical study and the associated clinical study staff will receive training on the device and system (including but not limited to device characteristics, storage requirements, warnings, precautions, and contraindications.)

It is the responsibility of the Principal Investigator at each participating site to assure any staff performing tasks related to the clinical trial (e.g., Study Coordinators, Study Nurses, Sub-Investigators, etc.) have been appropriately trained, training documented and included on the Delegation of Authority Log.

7.8. Product Receipt and Tracking

The investigator or designee will maintain records of devices/products or products provided by Medtronic free of charge delivered to the study site, e.g., device shipping forms. The following records will be maintained at a minimum for product delivery, receipt, and tracking at the site: dates, quantities received, lot/serial numbers, and expiration dates, as applicable.

7.9. Product Storage

Devices/products or products provided by Medtronic free of charge must be stored in a secured area. The method of storage shall prevent the use of devices/products for other applications than mentioned in this Clinical Investigation Plan. In addition, all information for the use, storage, and handling of the device/product as indicated in the IFU and User Manual must be taken into account.

7.10. Product Return

Any devices provided by Medtronic free of charge, and all monitors and accessories should be returned to Medtronic and documentation of return should be maintained. Non-functioning investigational devices must be returned to Medtronic as soon as possible for investigation. Instructions for returning the device will be provided.

7.11. Product Accountability

Devices/products will be traced during the clinical study by specific serial numbers (or lot numbers) assigned to each device/product. The investigator is responsible for the maintenance of a Product Accountability Log in the Investigator Site File. On this log, the receipt, use, return, and disposal of the investigational devices/products shall be documented. At the end of the clinical study, the principal investigator or delegate must sign and date the original Device Tracking Log.

8. Study Site Requirements

8.1. Investigator/Investigation Site Selection

All investigators managing the subject's anesthesia must be qualified practitioners and experienced in the diagnosis and treatment of subjects undergoing general anesthesia. All physicians must be experienced and/or trained in the handling of BIS™ Complete Monitoring System.

The role of the principal investigator is to implement and manage the day-to-day conduct of the clinical investigation as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical investigation.

The principal investigator shall:

- Be qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation
- Be experienced in the field of application and training in the use of BIS™ Complete Monitoring System
- Disclose potential conflicts of interest, including financial, that interfere with the conduct of the clinical investigation or interpretation of results
- Be able to demonstrate that the proposed investigational study site:
  - Has the required number of eligible subjects needed within the recruitment period
  - Has one or more qualified investigators, a qualified investigational study site team and adequate facilities for the foreseen duration of the clinical investigation

Study site personnel training will be completed and documented prior to participation in this study.

8.2. Study Site Activation

During the activation process (prior to subject enrollment), Medtronic will train study site personnel on the clinical investigation plan, on relevant standards and regulations, informed consent, and on data collection and reporting tools. If new members join the study site team, they will receive training on the applicable study requirements relevant to their role before contributing to the study.

Prior to performing study related activities, all regulatory requirements shall be fulfilled, including, but not limited to the following:

- IRB approval (and voting list, as required by local law) of the current version of the CIP and IC
- RA approval or notification (as required per local law)
- Fully executed CTA
- Financial disclosure (if applicable)
- CV of investigators and key members of the investigation study site team (as required)

- Documentation of delegated tasks
- Documentation of study training.
- Additional requirements imposed by local regulations, the IRB and RA shall be followed, if appropriate.

In addition, all participating study site staff must be trained on the current version of the CIP as well as on the applicable study requirements depending on their role and must be delegated by the principal investigator to perform study related activities.

Medtronic will provide each study site with documentation of study site/investigator readiness; this letter must be received prior to performing study related activities.

8.3. Role of the Sponsor Representatives

Sponsor representatives may provide support at the study site as required for the study under supervision of the Principal Investigator, including:

- Provide study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities
- Technical support under the supervision of a study investigator, but no data entry, shall be performed by Medtronic personnel or their representatives at study sites
- Monitoring and auditing activities

In addition, for this study, sponsor representatives may be authorized by the principal investigator to perform the following significant trial related duties:

- Support study investigators in performing the study procedure
- Support data collection during the procedure

9. Selection of Subjects

9.1. Study Population

Up to 30 healthy, non-smoking (or has refrained from smoking for 2 days) subjects, ages 18 to 60 years, will be enrolled for this study. The subjects will be distributed across both sexes as equally as practical.

9.2. Subject Enrollment

Subjects will be enrolled in the study once all eligibility requirements for the study have been met. Subjects who give informed consent for the protocol in order to undergo screening for eligibility are not considered enrolled and should not be enrolled until the screening is completed as indicated in *Sections*

8.3, 8.4, and 9, and they are determined to meet all eligibility criteria. Study enrollment is accomplished by signing of the informed consent and successfully passing the study inclusion /exclusion criteria and health screening evaluation. Subjects who sign informed consent, but are not enrolled, are considered screen failures.

9.3. Inclusion Criteria

1. Healthy (ASA physical status 1), male or female subjects between the ages of 18 to 60 years;
2. Completion of a health screening for a medical history by a licensed physician, nurse practitioner or physician assistant;
3. Vital signs must be within the following ranges to be included: Vital signs measured sitting after 3 minutes rest; heart rate: 45-90 bpm; systolic blood pressure: 110-140; diastolic blood pressure: 50-90. Out-of-range vital signs may be repeated once. [Pre-dose vital signs will be assessed by the Principal Investigator or designee (e.g., a medically qualified sub-investigator) before study drug administration. The Principal Investigator or designee will verify the eligibility of each subject before dosing];

9.4. Exclusion Criteria

1. Has severe contact allergies that may cause a reaction to standard adhesive materials found in pulse oximetry sensors, ECG electrodes, respiration monitor electrodes, or other medical sensors [self-reported];
2. Known neurological disorder (e.g., epilepsy, the presence of a brain tumor, a history of brain surgery, hydrocephalic disorders, depression needing treatment with anti-depressive drugs, a history of brain trauma) [self-reported and assessment by PI or delegate];
3. Known cardiovascular disease (e.g., hypertension, coronary artery disease, prior acute myocardial infarction, any valvular and/or myocardial disease involving a decrease in ejection fraction, arrhythmias, which are either symptomatic or require continuous medication/ pacemaker/ automatic internal cardioverter defibrillator), current implanted pacemaker or automatic internal cardioverter defibrillator [self-reported and assessment by PI or delegate];
4. Has a clinically significant abnormal finding on medical history, physical examination, clinical laboratory tests, or ECG at the screening [self-reported and assessment by PI or delegate];
5. Recent use of psychoactive medication (e.g., benzodiazepines, antiepileptic drugs, Parkinson medication, anti-depressant drugs, opioids) [self-reported and assessment by PI or delegate];
6. Subjects with known gastric diseases [self-reported and assessment by PI or delegate];

7. Has a positive urine cotinine test or urine drug screen or oral ethanol test [POC testing];
8. Known history of allergic or adverse response to drugs to be administered [self-reported];
9. Known history of complications relating to previous general anesthesia or conscious sedation [self-reported and assessment by PI or delegate];
10. Known history of malignant hyperthermia [self-reported and assessment by PI or delegate];
11. Has a room air saturation less than 95% by pulse oximetry [measurement by PI or delegate];
12. Has a clinically significant abnormal ECG [assessment by PI or delegate];
13. Has a clinically significant abnormal pulmonary function test via spirometry [assessment by PI or delegate];
14. Pregnant or lactating women [assessed by urine test and self-reported];
15. Subjects with tattooed skin specific to the sensor placement areas (forehead, fingers, chest) [self-reported and assessment by PI or delegate];
16. The subject must not take any prescription medication, except female hormonal contraceptives or hormone replacement therapy, from 14 days before the dosing until the end-of-study visit without evaluation and approval by the Investigator. Subjects who participated in a previous clinical trial who received a required FDA approved concomitant medication, for example, naltrexone, but were not randomized may be considered for participation in this study if they meet the washout requirement [assessment by PI or delegate];

10. Study Procedures

10.1. Schedule of Events

The Schedule of Events, Table 2, summarizes the intervals and data collection procedures.

Table 2: Schedule of Events

Study Tasks	Pre-screening	Enrollment	Execution				
	No visit	Visit 1	Prior to Procedure	Procedure Visit 2	Phone Call	Procedure Visit 3	Phone Call
Eligibility Assessments							
Online or phone call pre-screening survey	x						
Informed Consent [1]		x					
Demographics		x					
Medical History		x					

Study Tasks	Pre-screening	Enrollment	Execution				
	No visit	Visit 1	Prior to Procedure	Procedure Visit 2	Phone Call	Procedure Visit 3	Phone Call
Physical Exam		x					
Pulmonary function test		x					
Single 12-lead ECG		x					
Urine sample for the presence of cotinine		x	x				
Urine pregnancy test (Female)		x	x				
Complete blood count		x					
Inclusion/exclusion assessment		x	x				
Vital monitoring		x	x	x		x	
Concomitant Medication		x	x				
Urine drug screen and alcohol breathalyzer			x				
Safety Monitoring				x		x	
Sensor application				x		x	
Propofol or Propofol with Remifentanil administration				x		x	
BIS™, MOAA/S, TES assessments				x		x	
[redacted]				[redacted]		[redacted]	
Safety Assessments and Compensation							
Adverse Event Assessment [3]		x	x	x	x	x	x
Device Deficiency [4]				x			
Participant stipend [5]		x		x			

1. Written informed consent must be obtained prior to any study-specific evaluations; for more details, refer to *Section 9.2*

[redacted]

3. All Adverse Events, regardless of relatedness or outcome, will be collected and reported; for more details, refer to *Section 11*
4. Device Deficiency will be collected and reported; for more details, refer to *Section 11.*
5. For more details regarding the subject compensation, refer to *Section 15.6*.

10.2. Pre-Screening

Prior to the Baseline/ Enrollment Visit, interested subjects will complete an online REDCap screening survey and have the opportunity to review the Informed Consent Forms (ICFs). After the successful

completion of the screening survey, the study staff will review the survey, and qualified subjects will be invited to attend a study Visit 1.

10.3. Subject Consent

At the enrollment visit, subjects will be approached to obtain written informed consent prior to any data collection. Once the Informed Consent Form (ICF) is collected, the screening of the subject will follow. The purpose of the study and the benefits and risks of the procedures will be explained to the subject, and the consent process must be documented. Subjects who agree to study participation must sign IRB- approved ICF. Consent to participate in this study must be given in writing. Subjects that are unable to give consent will not be included in the study.

The Investigator or designee must obtain written informed consent before any clinical study related activity takes place. Prior to entry into the study, the IRB and Medtronic-approved ICF form, and the Health Insurance Portability and Accountability Act (HIPAA) Authorization Form (if not included within the ICF) (the US only) will be given to each subject.

The Investigator or designee will fully inform the subject of all aspects of the clinical study that are relevant to the subject's decision to participate in the clinical study (e.g., purpose and duration of the study, requirements of the subject during the study, potential risks and possible benefits associated with participation in this study). All items addressed in the ICF must be explained. The language used shall be as non-technical as possible and must be understandable to the subjects. The subject must have ample time and opportunity to read and understand the ICF, to inquire about the details of the clinical study, and to decide whether or not to participate in the clinical study. All questions about the clinical study should be answered to the satisfaction of the subject. In the case that a subject is unable to read, an impartial witness must also be present and sign the informed consent to confirm that the research has been clearly explained and all of the subject's questions have been answered.

Neither the Investigator nor the investigation site staff shall coerce or unduly influence a subject to participate or to continue to participate in the clinical study. The informed consent process shall not waive or appear to waive the subject's rights. When the subject decides to participate in the clinical study, the HIPAA Form (if applicable) and the ICF must be personally signed and dated by the subject.

After the subject has signed and dated the ICF, the Investigator must provide the subject with a copy.

Medtronic will inform the Investigators whenever information becomes available that may be relevant to the subject's confirmed participation in the clinical study. The Investigator or his/her authorized designee should inform the subject in a timely manner.

Medtronic will revise the written ICF whenever new information becomes available that may be relevant to the subject's confirmed participation in the clinical study. The revised information will be sent to the Investigator for approval by the IRB. After approval by the IRB, a copy of this information must be provided to the participating subjects, and the informed consent process, as described above, needs to be repeated.

10.4. Baseline/ Enrollment - Visit 1

After successful completion of the pre-screening, qualified subjects will be invited to attend Visit 1 to complete the ICF. The Investigator or designee will inform the prospective subjects on the study procedures and explain the consenting process. Once ICF is signed, the following will be performed during the screening:

- Demographics (race, ethnicity, sex, height, weight, skin tone, calculated body mass index (BMI)) will be recorded on the eCRFs;
- Medical History will be evaluated and documented to evaluate for prior or existing medical conditions and/or procedures that would exclude subjects from participation in the study;
- Physical examination including an evaluation of general appearance, cardiovascular, respiratory musculoskeletal system, skin, neurologic function, and head, eyes, ears, nose, and throat; The American Society of Anesthesiologist (ASA) physical status classification system is used to evaluate the degree of a patient's "sickness" or "physical state." Only subjects with ASA Physical status 1 will be enrolled;
- Concomitant Medications, including the history of prescription and over the counter medication, will be carefully noted and recorded. Medication name, indication for use, dose, frequency, route of administration start/stop date will be recorded on the eCRFs;
- Vital signs - Heart Rate, Systolic, and Diastolic Blood Pressures, Respiratory Rate and Oxygen Saturation (SpO_2) will be evaluated and recorded;
- Single 12-lead ECG;
- Complete blood count (CBC);
- Urinary pregnancy test;
- A urine sample will be tested for the presence of cotinine (nicotine metabolite) to exclude smokers;
- Female subjects will have to attest to birth control methods;

- Adverse event review will be completed to assess events the baseline, and that occur after enrollment.

The **Baseline/ Enrollment** results will stay valid for **60 days**.

10.5. Execution – Visit 2

10.5.1. Prior to Procedure

On the study day, subjects will arrive at the clinical research unit with appropriate fluid and solid intake as directed by study staff. The subject will be instructed not to consume beverages and foods containing alcohol, grapefruit, or caffeine/xanthine from 48 hours before dosing until the end-of-study visit. All subjects will fast as it will be instructed by the Investigator or designee before the start of the drug administration. The per dosing instructions will be provided to the subject.

- Any significant change in health status since Visit 1 will be recorded.
- Concomitant Medication and adverse events will be checked.
- All subjects will have urine drug screen and alcohol breathalyzer (Oral Ethanol) tests done.
- Female subjects, childbearing age, will also have a urine pregnancy test done.
- Review Inclusion and Exclusion Criteria based on additional information.
- Enrollment is based upon successful inclusion /exclusion criteria during Visits 1 and 2.

10.5.2. Procedure – Visit 2 and Visit 3

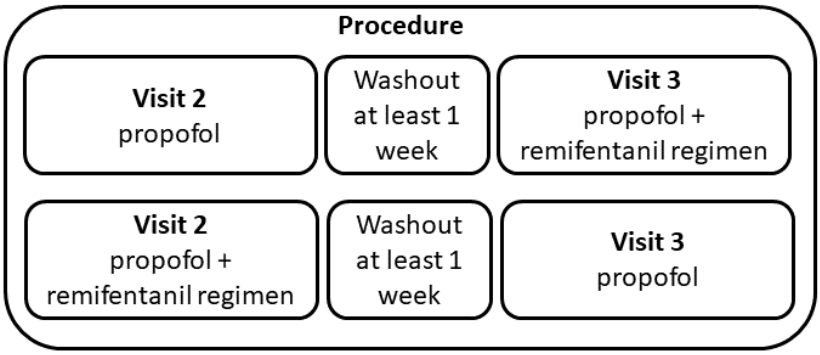


Figure 5: Schematic Representation of Procedure Schedule

The subjects will receive two regimens of anesthesia with different drug combinations, with at least a 1-week washout period between regimens. Once the pre-procedure part completed, the subject will be sequentially assigned to start with either Propofol (P) or Propofol with 4 ng/ml of Remifentanil (R) regimens, as shown in Figure 5.

10.5.2.1. Safety Monitoring

For the subject's safety, an anesthesiologist authorized to administer sedation drugs will be responsible for administering any procedural drugs for the sedation and monitoring of subject safety and physical state. All other personnel involved with the safety monitoring of subjects must be trained in and familiar with the management of recovery of sedated patients. The study site should have a setting that is fully equipped for the monitoring and support of the respiratory and cardiovascular function. Subjects will be continuously monitored throughout the study. All subjects will be monitored using an electrocardiogram (ECG), Pulse Oximeter for SpO_2, $EtCO_2$. A clinician will be monitoring respiratory and cardiac functions to determine if interventions are needed to maintain an adequate airway. The respiration support will be provided to ensure an unobstructed airway, adequate oxygenation (SpO_2 >92%), and CO_2 homeostasis throughout the study. As needed for airway support, the anesthesiologist may gently lift chin or jaw thrust (with or without manually assisted breathing), insertion of an airway device (oropharyngeal airway or laryngeal mask airway) and/or intermittent positive pressure ventilation (IPPV). Mask or nasal cannula will be used for supplemental O_2 delivery.

Any study procedures may be discontinued for the subject's safety. For patient safety, modifications to the procedure steps will be left to the judgment of the Principal Investigator.

10.5.2.2. Regimen Set-Up

The propofol and remifentanil will be administered using the Total Intravenous Anesthesia (TIVA) method via the target-controlled infusion (TCI) computer-controlled program, e.g., TIVA Trainer, or another computer-controlled program, to ensure that the targeted effect-site concentration of a drug is reached and maintained at each drug concentration plateau. 1% propofol and remifentanil diluted to a single concentration of 50 µg/ml will be used for this study. The infusion rate between 0 and 1200 ml/hr will be used to achieve a targeted concentration of propofol and remifentanil. For propofol, the effect-site concentration for propofol will be predicted using Schneider pharmacokinetics and pharmacodynamics (PK/PD) model [45, 46]. For remifentanil, Minto [47, 50] PK/PD model will be used. The assisted ventilation of the subject with either facemask, LMA or intermittent positive pressure ventilation (IPPV) may be used.

Subjects will have an intravenous catheter inserted for fluid and drug administration. Blood pressure will be monitored using an automated blood pressure cuff.

10.5.2.3. Sensor Application

The BIS™ sensor will be applied per its IFU. Subjects will have an intravenous catheter inserted for fluid and drug administration. The TES sensor will be applied per its IFU to the calf with a stimulation of 2mA, 2Hz for 1-5 seconds provided to ensure proper application.

The subject will rest for ~12 minutes before starting any regimen.

MOAA/S and Tetanic Electrical Stimulation (TES)

At each steady-state step and after equilibration, the MOAA/S assessment will be administered by an anesthesiologist. It is preferred that the same anesthesiologist performs the MOAA/S assessment for all subjects, refer to **Appendix A.**

Subjects will receive noxious electrical stimulation using Tetanic Electrical Stimulation (TES) once they achieve a MOAA/S score <2. The instructions for testing the sensor placement are listed above. The BIS™ value will be recorded, followed by the MOAA/S assessment. Then, TES will be initiated following the Instructions for Use (IFU) for the XAVANT STIMPOD™ NMS 410/450X device. The subject will receive one stimulation of 50mA, 50 Hz for 5 seconds. Their response, such as withdrawal of the extremity, a facial grimace, or a verbal groan will be recorded. Approximately 2 minutes after this assessment, the BIS™ value will be recorded.

[redacted]

10.5.2.4. Propofol Group

The initial target effect-site concentrations of propofol will be 0.5 µg/ml followed by incremental increases in the target effect-site concentrations of 1.5, 2, 2.5, 3, 4, 6, to a maximum of 8 µg/ml until a BIS™ value of not lower than 30 is intentionally reached or per Investigator's discretion. The BIS™ value should not intentionally be taken below 30. The equilibration time for each targeted plateau will be at least 12 minutes. The BIS™ value and MOAA/S score will be assessed and recorded when the patient is awake and at the different targeted propofol concentrations. Tetanic Electrical Stimulation (TES) will be used following the MOAA/S assessment when the subject reaches a MOAA/S score of <2. The BIS™ value will be recorded at the time of subject's response and approximately 2 minutes following the TES assessment. The propofol concentration will be decreased by the same steps until consciousness occurred.

10.5.2.5. Propofol with Remifentanil Group

Where remifentanil is administered with propofol, approximately 2 minutes before starting propofol, to attain an effect-site targeted concentration of remifentanil of 4 ng/ml, remifentanil will be given by a continuous infusion. Approximately within 7 minutes, the infusion rate of Remifentanil may be adjusted to maintain the effect-site concentration of remifentanil of 4 ng/ml throughout the study.

The initial target effect-site concentrations of propofol will be 0.5 µg/ml followed by incremental increases in the target effect-site concentrations of 1.5, 2, 2.5, 3, 4, 6, to a maximum of 8 µg/ml until a BIS™ value of not lower than 30 is intentionally reached or per Investigator's discretion. The BIS™ value should not intentionally be taken below 30. The equilibration time for each targeted plateau will be approximately 12 minutes. The BIS™ value and MOAA/S score will be assessed and recorded when the patient is awake

and at the different effect-site concentration of propofol. Tetanic Electrical Stimulation (TES) will be used following the MOAA/S assessment when the subject reaches a MOAA/S score of <2. The BIS™ value will be recorded at the time of subject's response and approximately 2 minutes following the TES assessment. The propofol concentration will be decreased by the same steps until consciousness occurred.

10.5.2.6. CRF Data Collection

The start time of any drug infusion, target effect-site concentrations, infusion rate, the start time of the assessments including BIS™ value prior to MOAA/S assessment, Tetanic Electrical Stimulation (TES) and the end time of assessment as well at the BIS™ value at the time of subject's response and approximately 2 minutes following the TES assessment will be recorded in the electronic Case Report Forms (eCRFs). Any adjustments to the infusion rate and time of adjustment will be recorded, and any changes to subject management during the procedure will be noted on the eCRFs.

10.5.2.7. Raw Device Data Collection

The device data (raw signals), including Heart Rate, Blood Pressure, Respiration Rate, $EtCO_2$, SpO_2, BIS™, TCI, if available, will be collected in real-time during the procedure. The BIS™ data will be recorded with a USB memory stick connected to the monitor. Periodically, the raw device data will be transferred directly to the Medtronic secure server for data quality review and analysis. The instructions on the secure data transfer will be provided by Medtronic.

10.6. Follow-up

10.6.1. Phone Call

The site will attempt to contact each subject by phone within 48 hours after completion of the procedure to perform a safety assessment. At least three attempts should be made to the subject. Each attempt should be clearly documented in the source documents, and the response or lack thereof should be captured. The safety assessment will include asking the subject the following questions:

- Have you had any medical problems since your discharge from the clinical research unit?
- Have you taken any medications (either prescribed or self-medicated) since discharge from the clinical research unit?

10.7. Assessment of Efficacy

Refer to *Section 14.*

10.8. Assessment of Safety

For safety analyses, adverse events will be summarized using frequency counts and percentages, refer to *Section 14.* Descriptive statistics will be provided by event type, severity, and relationship to study

procedures and devices. Individual listings of adverse events, including event type, start date, duration, severity, and device-relatedness, will be provided as appropriate. Adverse events occurring during the procedure or 48 hours after the procedure will be recorded. For AEs and AE reporting requirements, refer to *Section 11*.

10.9. Recording Data

The study will utilize the electronic Case Report Forms (eCRFs) in a database provided by the Sponsor.

eCRF completion may be delegated by the Principal Investigator (documented on the Delegated Task List) to other study personnel, but the Principal Investigator remains responsible for the accuracy and integrity of all data entered in eCRFs. The Principal Investigator or delegated Sub-Investigator is required to approve all data on eCRFs via electronic signature.

Additional details regarding procedures used for data review, database cleaning, issuing and resolving data queries, and identification of steps for creation, modification, maintenance, archiving retrieval or transmission of source data via any computerized systems will be provided in the study-specific Data Management Plan (DMP).

10.10. Role of Sponsor's Representatives

The sponsor's representatives will provide support as required for the clinical study, including but not limited to technical support during the procedure and/or technical support during follow-up in order to ensure that all study requirements are met, and the procedure is performed according to the Instructions for Use. The sponsor's representatives providing technical support may be listed on the sponsor's technical support list.

10.11. Deviation Handling

The investigator is required to conduct this study in accordance with the protocol, Good Clinical Practice (GCP), Institutional Review Board (IRB) requirements, and applicable regulations. The investigator is not allowed to deviate from the above-mentioned documents except under emergency circumstances to protect the rights, safety, and well-being of human subjects.

A study deviation is defined as an event when the investigator or site personnel did not conduct the study according to the protocol or the clinical trial agreement.

The investigator is required to obtain prior approval from the sponsor and IRB *before* initiating deviations from the Clinical Investigation Plan, except where necessary to protect the life or safety and physical well-

being of a subject in an emergency. Such approval will be documented in writing and maintained in the study investigator files.

Major deviations are defined as deviations with respect to:

- Patient informed consent procedure;
- Patient eligibility criteria;
- Study data collection and reporting (e.g., missing raw BIS data);
- Serious Adverse Event /Serious Adverse Device Effect /Unanticipated Adverse Device Effect (*for reporting refer to Section 12*).

Deviations will be recorded at the site and reported to Medtronic on the eCRF. The deviation document shall be signed and dated by the investigator or his authorized designee. At a minimum, the following information will be recorded:

- identification of the investigator and site
- description of deviation
- date of occurrence
- reason for the deviation
- patient identifier, if associated with the event

Deviations will be entered into a database to allow a comprehensive review on a regular basis for identifying trends that warrant additional preventive or corrective actions to mitigate further occurrence. Clinical study management at Medtronic shall conduct this review. Repetitive or serious investigator compliance issues may result in the need to initiate a corrective action plan, and in some cases, freeze enrollment or ultimately terminate the investigator's participation in the clinical study.

Study deviations must be reported to Medtronic, regardless of whether medically justifiable, pre-approved by the study leader (see contact details section) or taken to protect the subject in an emergency.

In the case that the deviation involves a failure to obtain a subject's informed consent or is made to protect the life or physical well-being of a subject in an emergency, the deviation must be reported to the IRB as well as the study leader as soon as possible after the occurrence of the event. Reporting of all other study deviations should comply with IRB policies and/or local laws.

The investigator shall adhere to IRB requirements and procedures for reporting study deviations.

All deviations from the CIP shall be included in the final report.

10.12. Subject Exit, Withdrawal or Discontinuation

It is the subject's right to withdraw from the study at any time and for any reason without sanction, penalty or loss of benefits to which the subject is otherwise entitled, and without jeopardizing their future medical care. The investigator may withdraw the subject at any time to protect the health, safety, or welfare of the subject. Every effort should be made to collect the status of any ongoing adverse events, at a minimum. All subjects will be encouraged to remain in the study through the follow-up phone call.

If the subject discontinues participating in the study prior to completing the study requirements, the reason for withdrawal will be recorded in the subject's study records and eCRF.

If withdrawal from the study is due to problems related to the investigational device safety or performance, the investigator shall ask for the subject's permission to follow his/her status outside the clinical study.

10.12.1. Subject Exit From Study

There are many scenarios in which a subject may exit the study. The following terms are used for withdrawal and completion:

- Screen Failure: Did not meet the study inclusion/exclusion criteria;
- Study Withdrawal: Removal from the study after Enrollment by either subject, PI, or Sponsor, or technical problems;
- Study Complete: Completion of all study related activity by the subject;
- Lost to Follow up: Subjects lost to follow-up will be documented. The investigator should make every attempt to contact the subject to have the subject complete the follow-up phone call within 48 hours or to determine the occurrence/resolution of adverse events (if any).

11. Risks and Benefits

11.1. Potential Risks

Risks to participation are primarily physical. There are no social, economic, legal, long-term psychological, or other risks that have been identified. Risks under this protocol relate to both study devices and study procedures. We believe that the risks from the device(s) are in keeping with the definition of non-significant risk devices (NSR). Further, the devices in this study are non-invasive, and the clinical protocol

design is minimal risk to the subject. No treatment or treatment decisions will be made during the course of this study. Following is a list detailing potential risks from study devices and the clinical protocol.

11.1.1. BIS™ Sensor Risks

The BIS™ Sensor is applied directly to the patient's skin to enable recordings of electrophysiological (such as EEG) signals. The sensor will be used as per IFU. The sensors used in this study may expose subjects to the following risks:

- Minor discomfort, allergic reaction, or skin irritation (such as redness, itching) at the sensor application site is probable but is usually self-limited within hours.
- Pressure points/ injury in application areas are possible but anticipated to be rare due to the short duration of the study. Care in the application and removal of the sensors is advised. Skin reactions will be observed during and after the study procedures.
- Electric shock is very rare, and the product design and testing ensure insulation and ground fault detection. No liquids should be used near the devices.
- Burn to the skin (due to a small amount of heat generated) is a rare unanticipated risk, and not likely due to the short duration of the study.

Some Sensor Warnings and Cautions are listed below, for more information on warnings and cautions, refer to Sensor IFU.

Warnings:

- To reduce the hazard of burns during use of brain-stimulating devices (e.g., transcranial electrical motor evoked potential), place stimulating electrodes as far as possible from the bis sensor and place sensor according to instructions.

Cautions:

- Patient position may increase the risk of skin irritation on the forehead. With patients in prone position, consider minimizing pressure on the sensor.
- Do not use if sensor is dry.
- To avoid dry out, do not open pack until ready for use.
- Due to intimate skin contact, reuse may pose risk of infection.
- If skin rash or other unusual symptoms develop, stop use and remove.
- Limited to short-term use (maximum 24 hours).
- Do not cut sensor, as this will result in improper operation.

- Upon removal, slight redness of skin may occur and typically resolves within a short period of time.

11.1.2. BIS™ Monitoring System Risks

BIS™ Monitoring System will be used per IFU. Some warnings are listed below, for more information on warnings and cautions refer to IFU.

Warnings:

- Explosion hazard: do not use the BIS™ complete system in a flammable atmosphere or where concentrations of flammable anesthetics may occur.
- Monitor is not designed for use in MRI environment.
- Use only the power cord supplied by the manufacturer. Never adapt the plug from the monitor to fit a non-standard outlet.
- U.S.A. requirement: for proper grounding, the power receptacle must be a three-wire grounded outlet. A hospital grade outlet is required. Never adapt the three-prong plug from the monitor to fit a two-slot outlet. If the outlet has only two slots, make sure that it is replaced with a three-slot grounded outlet before attempting to operate the monitor.
- If the integrity of the external protective earth ground is in doubt, the BIS™ complete system shall be operated from its internal battery power source only.
- Be sure the monitor is mounted securely in place to avoid personal or patient injury.
- The BIS™ complete monitor should not be used adjacent to or stacked with other equipment. If adjacent or stacked use is necessary, the BIS™ complete monitor should be observed to verify normal operation in the configuration in which it will be used.
- When connecting external equipment (e.g., data capture computer), the system leakage current must be checked and must be less than the IEC 60601-1-1 limit.
- Using accessories other than those specified may result in increased electromagnetic emissions or decreased electromagnetic immunity of the BIS™ complete monitoring System.
- The use of accessory equipment not complying with the equivalent safety requirements of this equipment may lead to a reduced level of safety of the resulting system. Consideration relating to the choice shall include: Use of the accessory in the patient vicinity. Evidence that the safety certification of the accessory has been performed in accordance to the appropriate IEC 60601-1 and/or IEC 60601-1-1 harmonized national standard.
- Due to elevated surface temperature, do not place the BISX™ unit in prolonged direct contact with patient's skin, as it may cause discomfort.

- The conductive parts of electrodes or sensor and connectors should not contact other conductive parts, including earth.
- To reduce the hazard of burns during use of high-frequency surgical equipment, the sensor or electrodes should not be located between the surgical site and the electro-surgical unit return electrode.
- To reduce the hazard of burns during use of brain-stimulating devices (e.g., transcranial electrical motor evoked potential), place stimulating electrodes as far as possible from the BIS™ sensor and make certain that sensor is placed according to package instructions. The sensor must not be located between defibrillator pads when a defibrillator is used on a patient connected to the BIS™ complete system.
- To minimize the risk of patient strangulation, the patient interface cable (PIC) must be carefully placed and secured.
- Shock Hazard: Do not attempt to disconnect the power cord with wet hands. Make certain that your hands are clean and dry before touching the power cord.
- Universal precautions shall be observed to prevent contact with blood or other potentially infectious materials. Place contaminated materials in regulated waste container.
- Do not mix disinfecting solutions (e.g., bleach and ammonia), as hazardous gases may result.
- Electrical Shock Hazard: Do not remove monitor covers during operation or while power is connected to monitor.
- Electrical Shock Hazard: The manufacturer's inspection of this apparatus verified that the ground leakage current and the patient safety current were less than the specified limits established by the applicable safety standards. As a matter of safe practice, the institution should conduct periodic tests to verify these currents.
- Whenever an event such as spillage of blood or solutions occurs, re-test ground leakage current before further use.
- Leakage current must be checked by a qualified biomedical engineering technician whenever instrument case is opened.
- Power supply is internally fused. Replace power supply only with Covidien BIS™ Complete power supply.
- Portable RF communications equipment (including peripherals such as antenna cables and external antennas) should be used no closer than 30 cm (12 inches) to any part of the BIS™ complete monitoring system, including cables specified by the manufacturer. Otherwise, degradation of the performance of this equipment could result.

- Check Target Range alarm limits to ensure they are appropriate for the patient being monitored with each use. Ensure Target Range alarm limits do not exceed the standard thresholds set by the institution.
- Do not decrease the adjustable alarm volume below ambient sound levels. Decreasing the alarm volume below ambient levels may compromise patient safety.
- Explosion hazard: do not use the BIS™ complete system in a flammable atmosphere or where concentrations of flammable anesthetics may occur.
- Use only the power cord supplied by the manufacturer. Never adapt the plug from the monitor to fit a non-standard outlet.
- If the integrity of the external protective earth ground is in doubt, the BIS™ complete monitor shall be operated from its internal battery power source only.
- Due to elevated surface temperature, do not place BISX™ unit in prolonged direct contact with patient's skin, as it may cause discomfort.
- The conductive parts of electrodes or sensor and connectors should not contact other conductive parts, including earth.
- To reduce the hazard of burns during use of high-frequency surgical equipment, the sensor or electrodes should not be located between the surgical site and the electro-surgical unit return electrode.
- The sensor must not be located between defibrillator pads when a defibrillator is used on a patient connected to the BIS™ complete system.
- Check Target Range alarm limits to ensure they are appropriate for the patient being monitored with each use. Ensure Target Range alarm limits do not exceed the standard thresholds set by the institution.
- Universal precautions shall be observed to prevent contact with blood or other potentially infectious materials. Contaminated materials should be disposed of in accordance with national and local waste disposal legislation and requirements.
- Do not mix disinfecting solutions (e.g., bleach and ammonia) as hazardous gases may result.
- Leakage current must be checked by a qualified biomedical engineering technician whenever an instrument case is opened.
- A power supply is internally fused. Replace power supply only with Covidien BIS™ complete power supply.

- Electrical Shock Hazard: The manufacturer's inspection of this apparatus verified that the ground leakage current and the patient safety current were less than the specified limits established by the applicable safety standards. As a matter of safe practice, the institution should conduct periodic tests to verify these currents. Whenever an event such as spillage of blood or solutions occurs, re-test before further use.
- Using accessories other than those specified may result in increased electromagnetic emissions or decreased electromagnetic immunity of the BIS™ complete monitoring system.

The BIS™ complete system should not be used adjacent to or stacked with other equipment. If adjacent or stacked use is necessary, the BIS™ complete monitor should be observed to verify normal operation in the configuration in which it will be used.

11.1.3. Nellcor™ Pulse Oximeter

- Pulse and Tissue Oximetry Sensor placement involves positioning pulse and tissue oximetry sensors on the subject in the same manner that is used on hospitalized subjects.
- The sensors may be warm to the touch. Under normal operating conditions, (no fault conditions), the sensors are not expected to overheat. If the sensors are too warm, they will be removed immediately.
- The sensors exert a minimal amount of pressure. Sensors may leave minor impressions at the sensor application site, which should fade and resolve within the day. They should not cause discomfort. If the sensors are too uncomfortable, they will be removed.
- Adhesive sensors may cause some irritations to the skin in some subjects. Typical skin irritations present with redness of the skin and in some cases of sensitivity, an allergic reaction can occur.
- Removal of the sensor may cause pulling of the skin or hair, and this can be felt as pain.
- The risk in the use of oximetry sensors is believed to be minor.
- A heating pad or hot water bottles may be used on the hands to improve circulation. The subject may experience some mild discomfort if the water is too warm. To minimize the discomfort, the subject will be asked if the heating is too warm, it will be turned on the lowest level possible for comfort, removed or additional separation will be used between the heater and the site for comfort.

11.1.4. XAVANT STIMPOD™ Quantitative NMT Monitor Risks

STIMPOD™ Quantitative NMT monitor will be used per IFU. Some warnings are listed below, for more information on warnings and cautions refer to the IFU.

Warnings:

- Use of cables or accessories other than those supplied with the STIMPOD may result in serious injury.
- Maintenance on this device may only be performed by the manufacturer or persons explicitly authorized by the manufacturer.
- Do not use the STIMPOD in close proximity to equipment that produces strong electromagnetic fields, such as high frequency surgical equipment. The cable leads could act as an antennae and dangerous currents could be induced as a result.
- Do not apply the STIMPOD to patients with implanted electrical devices, such as cardiac pacemakers, without first consulting with an appropriate medical specialist.
- The device should not be used adjacent to or stacked with other equipment and that if adjacent or stacked use is necessary, the device should be observed to verify normal operation in the configuration in which it will be used.
- The patient should avoid contact with metallic objects that are grounded, produce an electrical conductive connection with other equipment and/or enable capacitive coupling.
- The cables should be positioned in such a way that they do not contact either the patient or other cables.
- Simultaneous connection of a patient to high frequency surgical ME equipment and the STIMPOD may result in burns and possible damage to the stimulator.
- Operation in close proximity (e.g. 1m) to a shortwave or microwave therapy ME equipment may produce instability in the stimulator output.
- Application of electrodes near the thorax may increase the risk of cardiac fibrillation.
- No modification of the equipment is allowed.
- Do not modify this equipment without authorization of the manufacturer.
- If this equipment is modified, appropriate inspection and testing must be conducted to ensure continued safe use of the equipment.

11.1.5. General Anesthesia Risks

There are some risks associated with taking general anesthetics, but they are relatively safe when administered correctly. Although not all of these side effects may occur, if they do occur, they may need medical attention. All Subjects will be monitored by health care professionals closely for the effects. The most common side effects of general anesthesia include sore throat due to the breathing tube, nausea, vomiting, dizziness, bruising, or soreness from the IV drip, shivering and feeling cold, difficulty passing urine. These may occur despite the best efforts to avoid them. For additional information related to potential medication, risks refer to Table 3.

Also, when placing a breathing tube, there is a small risk that the anesthesia provider can damage the subject's teeth. This risk increases if the subject has loose teeth or other dental problems. With any medication given, the Subject could have an allergic reaction. Although rare, unexpected severe

complications with anesthesia can occur and include, but not limited to, the remote possibility of infection, bleeding, drug reactions, blood clots, loss of sensation, loss of limb function, paralysis, stroke, brain damage, heart attack or death. The anthologist will be present to minimize all risks related to anesthesia.

Table 3: Possible Side Effects using Medication

Possible side effects using remifentanil but not limited to • blurred vision • chest pain or discomfort • confusion • difficult or troubled breathing • dizziness, faintness, or lightheadedness when getting up suddenly from a lying or sitting position • irregular, fast or slow, or shallow breathing • lightheadedness, dizziness, or fainting • muscle stiffness or tightness • pale or blue lips, fingernails, or skin • shortness of breath • slow or irregular heartbeat • sweating • unusual tiredness or weakness	Less common side effects of remifentanil but not limited to • bluish lips or skin • chills • decrease in cardiac output • fast, pounding, or heartbeat or pulse • feeling of warmth • fever • headache • nausea or vomiting • nervousness • not breathing • pain after surgery • pain in the shoulders, arms, jaw, or neck • pounding in the ears • problems with bleeding or clotting • redness of the face, neck, arms, and occasionally, upper chest • shivering • allergic reactions • other side effects may occur
Possible side effects using Propofol but not limited to • hypotension • apnea lasting 30-60 sec • apnea lasting >60 sec • movement • injection site burning/stinging/pain • respiratory acidosis during weaning	Less common side effects of Propofol but not limited to • arterial hypotension • anaphylaxis • asystole • bronchospasm • cardiac arrest

• hypertriglyceridemia • hypertension • rash • pruritus • arrhythmia • bradycardia • cardiac output decreased concurrent opioid use increases incidence) • tachycardia	• seizures • opisthotic reaction • pancreatitis • pulmonary edema • phlebitis • thrombosis • renal tubular toxicity • allergic reactions • other side effects may occur

11.2. Potential Benefits

There are no medical benefits to the subjects who participate in this study. There is, however, the potential for benefiting future subjects should this study enable the development of improved medical monitoring devices.

11.3. Risk-Benefit Rationale

Medtronic has determined that this is a study of a "non-significant risk device" due to the nature of the devices being tested. Utilizing the FDA criteria[1,2] listed below to distinguish between significant and non-significant risk devices, Medtronic has determined that:

- The device under investigation is not intended as an implant and does not present a potential for serious risk to the health, safety, or welfare of a subject;
- The device under investigation is not purported or represented to be for use supporting or sustaining human life and does not present a potential for serious risk to the health, safety, or welfare of a subject;
- The device under investigation is not for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health, and does not present a potential for serious risk to the health, safety, or welfare of a subject; and
- The device under investigation does not otherwise present a potential for serious risk to the health, safety, or welfare of a subject.

[1] 21CFR812.2 (b)(1)(ii) and 21CFR812.3(m)

[2] Information Sheet Guidance For IRB/EC , Clinical Investigators, and Sponsor. Significant Risk and Non-significant Risk Medical Device Studies/ January 2006/UMC126418

The potential risks of these devices have been assessed and are not greater than those of currently approved and marketed devices of the same type (e.g., pulse and tissue oximeters, $EtCO_2$ monitors, non-invasive blood pressure monitors, ECG or respiration monitors). Society may benefit from more accurate medical monitors.

Medtronic requests that the reviewing IRB indicates its agreement with this determination of non-significant risk device in its letter of approval for this study.

12. Adverse Events and Device Deficiencies

12.1. Adverse Events

AE (Adverse Event) definitions are provided in **Table 4**. AE information will be collected throughout the study from the BIS™ sensor application until the follow-up phone call. A list of anticipated adverse events and risks that are expected in nature is included in *Section 10*.

Reporting of these events to Medtronic will occur on an AE Form. Each event must be reported separately. Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened.

For AEs that require immediate reporting (see **Table 4**), initial reporting may be done by phone, fax, or on the eCRF completing as much information as possible. The completed AE eCRF must be submitted to Medtronic as soon as possible.

Any medication/treatment associated with the treatment of an AE must be reported

AE assessment for the purposes of this study will cease after the follow-up phone call within 48 hours after the procedure. All AEs considered at least possibly related to the study will be followed until resolved, stabilized, and/or returned to baseline.

Table 4: Definition of Adverse Events and Device Deficiencies

General	
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. *NOTE 1:* This definition includes events related to the investigational medical device or the comparator.

	NOTE 2: This definition includes events related to the procedures involved. *NOTE 3:* For users or other persons, this definition is restricted to events related to investigational medical devices.
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device. *NOTE 1:* This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. *NOTE 2:* This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
Device Deficiency (DD)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. *NOTE:* Device deficiencies include malfunctions, use errors, and inadequate labeling.
Relatedness	
Device Related	An AE that results from the presence or performance (intended or otherwise) of the device.
Procedure Related	An AE that occurs related to the procedure.
Seriousness	
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a Serious Adverse Event.
Serious Adverse Event (SAE)	An adverse event that a) led to death, b) led to serious deterioration in the health of the subject, that either resulted in 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-subject or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to fetal distress, fetal death or a congenital abnormality or birth defect. *NOTE:* Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.
Unanticipated Adverse Device Effect (UADE)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the CIP or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects.
Complication	An adverse event that includes the following is considered a complication: • Results in death, • Involves any termination of significant device function, or • Requires an invasive intervention Non-invasive (21 CFR 812.3 (k)): when applied to a diagnostic device or procedure, means one that does not by design or intention:

	• Penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra, or • Enter the ear beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or the vagina beyond the cervical os Where "penetrate" means: to pass, extend, pierce, or diffuse into or through something; to enter by overcoming resistance; to gain entrance to, and "pierce" means to force a way into or through something NOTE (FDA): Blood sampling that involves simple venipuncture is considered noninvasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for non-investigational purposes is also considered noninvasive.
Observation	Any AE that is not a complication. NOTE 1: Only system or procedure related Aes will be classified as "Complication" or "Observation"

12.2. Reporting of Adverse Events

Principal Investigator must report applicable events and product deficiencies to Medtronic and where appropriate an IRB or regulatory authority.

Study Contact Information:

Clinical Affairs	Medical Affairs
Stephanie Monza, BS, CCRC Senior Clinical Research Specialist/ Clinical Study Manager Medtronic 6135 Gunbarrel Avenue Boulder, CO 80301 [redacted]	Karen Phillips, MD Senior Medical Affairs Director Medtronic 2101 Faraday Avenue Carlsbad, CA 92008 [redacted]

12.2.1. Adverse Event and Device Deficiency Classification

All AE and DD will be reviewed by a Medtronic representative. AEs will be classified according to the definitions provided.

Upon receipt of AE at Medtronic, a Medtronic representative will review the AE/DD for completeness and accuracy and when necessary will request clarification and/or additional information from the Investigator. Medtronic will utilize MedDRA for Regulatory Activities, to assign a MedDRA term for each AE based on the information provided by the investigator.

Regulatory reporting of AEs and DDs will be completed according to local regulatory requirements. Refer to Table 5 for a list of required investigator and Medtronic reporting requirements and timeframes. It is the responsibility of both to abide by any additional AE reporting requirements stipulated by the EC responsible for oversight of the study.

For emergency contact regarding a UADE, USADE, SAE and/or SADE, contact a study representative immediately (refer to the study contact list provided in the study site's study documents binder/investigator site file or refer to the Sponsor contact information provided on the title page).

AEs and Deaths will be classified according to the standard definitions as outlined below:

Table 5: Adverse Event Classification Responsibilities

What is classified?	Who classifies?	Classification Parameters
Relatedness	Investigator	Device, Procedure
	Sponsor	Device, Procedure, BIS™ System components
Seriousness	Investigator	SAE, DD with SADE potential
	Sponsor	SAE, UADE/USADE, Complication or Observation (for all procedure related adverse events), DD with SADE potential
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Sponsor	MedDRA term assigned based on the data provided by Investigator

12.2.2. Adverse Event and Device Deficiency Reporting Requirements

Regulatory reporting of AEs and DDs will be recorded and reported according to local regulatory requirements. It is the responsibility of the Investigator and the sponsor to abide by the AE reporting requirements stipulated by local law and the study site's IRB.

Table 6: Reporting Requirements for Events

Serious Adverse Device Effects (SADE), including Unanticipated Adverse Device Effect (UADE):	
Investigator submits to:	
Medtronic	Within 24 hours after the investigator first learns of the event.
Regulatory Authority	As per local reporting requirements.
IRB	Submit to IRB per local reporting requirement.
Sponsor submits to:	
Regulatory Authorities	Reporting timeframe as per local requirement.
IRB	Submit to IRB per local reporting requirement.
Serious Adverse Events (SAE)	
Investigator submits to:	
Medtronic	Within 24 hours after the investigator first learns of the event.
Regulatory Authority	As per local reporting requirements.
IRB	Submit to IRB per local reporting requirement.
Sponsor submits to:	
Regulatory Authorities	Reporting timeframe as per local requirement.

IRB	Submit to IRB per local reporting requirement.
Adverse Device Effects (ADE)	
Investigator submits to:	
Medtronic	Within 24 hours after the investigator first learns of the event.
Sponsor submits to:	
Regulatory Authority	As per local reporting requirements.
IRB	Submit to IRB per local reporting requirement.
Sponsor submits to:	
Regulatory Authorities	Reporting timeframe as per local requirement
IRB	Submit to IRB per local reporting requirement.
All other AEs	
Investigator submits to:	
Medtronic	Submit as soon as possible, but no later than within 10 working days after the investigator first learns of the event.
Regulatory Authority	As per local reporting.
IRB	Submit to IRB per local reporting requirement.
Device Deficiency with SADE potential	
Investigator submits to:	
Medtronic	No later than 48 hours after the investigator first learns of the event.
Regulatory Authorities	As per local reporting requirements.
IRB	As per local reporting requirement.
Sponsor submits to:	
Regulatory Authorities	As per local reporting requirements.
IRB	As per local reporting requirement.
All other Device Deficiencies	
Investigator submits to	
Medtronic	No later than 48 hours after the investigator first learns of the event.
Regulatory Authorities	As per local reporting requirements.
IRB	As per local reporting requirement.
Sponsor submits to:	
Regulatory Authorities	As per local reporting requirements.
IRB	As per local reporting requirement.

12.3. Product Complaint Reporting

Product complaint reporting and vigilance reporting are applicable and AEs related to any market-released device during the study must be reported. The reporting of product complaints is not part of the study and should be done in addition to the AE reporting requirements. Refer to local regulations for reporting requirements.

Product Complaint: Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a medical device that has been placed on the market.

- Abuse: Abnormal use (definition acc. #4.1 of Meddev 2.12-1
- Misuse: Use error (definition acc. #4.20 of Meddev 2.12-1)

It is the responsibility of the investigator to report all product complaint(s) associated with a medical device distributed by Medtronic, regardless whether they are related to intended use, misuse or abuse of the product. Reporting must be done immediately and via the regular channels for market-released products. The reporting of product complaints by the clinical team must be done according to the local Standard Operating Procedures. Medtronic will notify the Ras (e.g. CA) as applicable for the following incidents immediately upon learning of them and is not limited to AEs and DDs only:

- Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or instructions for use which led or might have led to the death or serious deterioration in the state of health of a patient, user, or other person.
- Any technical or medical reason resulting in withdrawal of a device from the market by the manufacturer.
- Any serious deterioration in the state of health, including:
  - Life-threatening illness or injury
  - Permanent impairment of a body function or permanent damage to a body structure
  - A condition necessitating medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure

13. Data Review Committees

A Data Monitoring Committee (DMC), Adverse Events Advisory Committee (AEAC) will not be utilized for this clinical study as there are no safety concerns suggesting the need for a DMC. This study is considered a non-significant risk for study participants. Thus, the need for additional safety oversight beyond Medtronic's already rigorous safety monitoring processes is not required. A Medtronic Medical Advisor, as needed, will provide an independent medical review according to the study Safety and Complaint Management Plan. The Medical Advisor will not be affiliated with an investigative center.

14. Statistical Design and Methods

Statistical analyses will be conducted by Medtronic or its designee as outlined in the Statistical Analysis Plan (SAP.) Any changes in statistical methods will be detailed in the Clinical Study Report (CSR.) Data exclusion will be captured in the Data Management Plan.

14.1. Sample Size Justification

Up to 30 subjects will be enrolled to collect data from approximately 20 subjects and to account for anticipated screen failures and subject dropouts. Based on the dose-response relationship (logistic model) with an allowable error of ± 15% for BIS_{50} and a coefficient of variation of 25% at the alpha level of 0.05, the sample size will provide sufficient power (>80%) to evaluate the performance of anesthetic agents.

14.2. Analysis Populations

The primary effectiveness analysis will be based on all evaluable data from this study. Subjects who discontinue participation prematurely will be included in the analysis of results. Subjects who withdraw from the study prior to completing both regimens will be replaced by a new subject.

14.3. Statistical Methods

Standard demographic information and baseline characteristics will be summarized using descriptive statistics. For safety assessments, adverse events (AEs) will be summarized using frequency counts and percentages. Descriptive statistics will be provided by severity and relationship as needed.

Any subject who responds to any verbal command with MOAA/S assessment score of 2, 3, 4, and 5 will be considered as responsive. Subjects with MOAA/S assessment scores of <2 will be considered unresponsive. Tetanic Electrical Stimulation (TES) will be employed with an MOAA/S assessment score of <2.

The BIS™ index value collected from the left side of the brain will be used for primary analysis to reflect the typical operation of the device from this study. The BIS™ index value collected from the right side of the brain will be used for internal research purposes.

The value of BIS™ will be assessed at the different targeted-controlled drug concentrations or infusion rates. The logistic model (simplified Sigmoid E_{max} model) will be used to analyze the relationship between the BIS™ index and loss of responsiveness through the probability of response curves. The values of BIS™, at which 50% (BIS_{50}) and 95% (BIS_{95}) of subjects are unresponsive, and their 95% confidential intervals will

be derived. The systematic variance between groups will be evaluated. The Prediction Probability score (P_k) for correctly predicting if the subject was responsive or unresponsive will be assessed.

15. Ethics

15.1. Statement(s) of Compliance

The investigator is responsible for ensuring that the clinical study is conducted in accordance with:

- This Clinical Investigational Plan and Standard Operating Procedures (SOPs).
- Food and Drug Administration (FDA) Good Clinical Practice (GCP) guidelines and regulatory requirement(s), including 21 CFR 803, 21 CFR 812.2, 21 CFR 50, 21 CFR 56. FDA Financial Disclosure regulations, as well as the International Conference on Harmonization (ICH) guidelines and any other regional/national requirements for clinical trials, as applicable.
- If the IRB or other regulatory authority imposes any additional requirements (e.g., safety reports, progress reports, etc.), Medtronic will prepare the required documents and send them to the respective authority.
- Investigators must inform Medtronic of any change in the status of IRB approval once the investigation site has started enrollment. If any action is taken by an IRB with respect to the investigation, that information will be forwarded to Medtronic by the respective investigator.
- The clinical study will not begin until the IRB approval/ notification is received. Written IRB approval and any conditions of approval imposed by the IRB must be submitted to the Sponsor.

16. Study Administration

16.1. Monitoring

Site monitoring visits will be performed by the study monitor or other qualified sponsor staff per the monitoring plan to ensure:

a) Overall compliance with the protocol, GCP, and the applicable regulations.

b) Accurate records are being maintained.

c) Accurate and complete study data are being reported (comparing CRF to source documents.) In some cases, the CRF will also be the source documentation of some information.

d) Informed consent has been obtained for all study subjects.

e) Adverse events and protocol deviations are documented and reported.

f) Investigational and non-investigational device accountability and disposition are accurately documented.

Monitoring visits will be conducted at the start, during, and at the closure of the clinical study in accordance with Medtronic SOPs and the Monitoring Plan. An interim monitoring visit may be combined with the closing monitoring visit. Monitoring may be performed with in-person visits or remotely, when applicable. The quality of the device data obtained from the investigator and maintained by the Sponsor will be confirmed through an internal review of data quality. Prior to any device data quality checks, the ICF will be checked in person or remotely.

The frequency of monitoring visits will occur based on subject enrollment, duration of the study, study compliance, site performance, site adherence to the protocol, findings from previous monitoring visits, and any suspected inconsistency in data that requires investigation. The monitoring visit frequency may be changed based on study needs and subject enrollment rates. Specific monitoring requirements are detailed in the study-specific Monitoring Plan.

The Sponsor will provide updated contact lists, including the monitors' name and contact information to the investigational sites.

Medtronic or designee will conduct site monitoring visits to monitor compliance with the protocol, clinical study agreement, and applicable regulations, and adherence to the data collection procedures, to assess the accuracy and completeness of submitted clinical data, and to verify that records are being properly maintained for the duration of the study.

Monitoring activities will be documented and include a summary of what the monitor reviewed and the observations regarding the completion of previous action items, significant findings, facts, deviations, conclusions, and recommended actions to be taken to secure compliance.

If problems are encountered with the quality of the collected data, the study may be halted for the period of time until the problem has been assessed and corrected. The evaluation of the data quality will be the responsibility of the Medtronic Clinical Affairs personnel or designee.

The Investigator or authorized study personnel should be available at each monitoring visit. Direct access to the subject records and other source data must be provided to study eCRF, the Sponsor, regulatory authorities, auditors, IRB members, or inspectors.

Direct access to patient medical files for source data verification will need to be granted and prepared prior to any monitoring visits.
Raw device data will not be monitored.

16.2. Data Management

16.2.1. Data Collection

The investigator must ensure accuracy, completeness, and timeliness of the data reported in the eCRFs and all other required reports. Data reported on the eCRFs which are derived from source documents must be consistent with the source documents, and discrepancies need to be justified in a documented rationale, signed and dated by the (principal) investigator, and filed in the patient medical file.

Only authorized persons can complete eCRFs. All data requested on the eCRF are considered required. The Principal Investigator must ensure the accuracy and completeness of the recorded data and then provide his/her signature on the appropriate eCRFs. The Investigator's electronic signature for specific eCRFs will be documented in compliance with local regulations. Changes to data previously submitted to the sponsor will require a new electronic signature by the Investigator to acknowledge/approve the changes.

Medtronic will only consider eCRFs to be complete when all discrepancies have been resolved by the site and reviewed and closed by Medtronic. Also, specific eCRFs must be reviewed and electronically signed by the Investigator, indicating his/her agreement with the accuracy of all recorded data. It is expected that the Investigator and his/her staff will cooperate with the monitoring team and provide any missing data in a timely manner.

The Electronic Data Capture (EDC) system maintains an audit trail on entries, changes, or corrections in eCRFs. Upon completion of an eCRF, the investigator shall sign the eCRF in a timely manner, if a change to an already signed eCRF occurs, the investigator shall re-sign this eCRF.

16.2.2. Device Data

The raw data will be collected using BIS™ and other equipment, e.g., co-oximeter, blood pressure monitors, etc. The data will be exported to an encrypted flash memory device for each subject. The memory device will be stored at the investigation site. Periodically, the raw data will be transferred directly to the Medtronic secure server for data quality review and analysis.

16.2.3. Direct Access to Source Data/Documents

Data entered must be traceable to source documents. Source documentation is defined as the first-time data appear and may include original documents, data, and records (e.g., hospital records, clinical and office charts, procedure reports, laboratory records, or evaluation checklists, recorded data from

automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, subject files.)

The eCRFs (or paper copies) may not serve as source documents. Source documentation for data elements not routinely captured in medical records may vary from site to site; the site may use source document worksheets if identified as source documents and are signed and dated appropriately.

16.2.4. Time Windows for Completion of eCRFs

eCRFs are recommended to be entered into the RDC system within 10 days of the completion of the protocol-specified visit or sooner as requested by the sponsor.

16.2.5. Data Review and Processing

Data management will be done according to Medtronic SOPs and the Data Management Plan for this clinical study. These documents will be made available on request. All collected data will be reviewed for completeness, correctness, and consistency. In case of issues, queries will be sent to the investigator to complete, correct, or comment on the data.

Visual and/or computer data review will be performed to identify possible data discrepancies. Manual and/or automated queries will be created in the Oracle remote data capture (RDC) system and will be issued to the site for an appropriate response. The site staff will be responsible for resolving all queries in the database in a timely manner and as requested by Medtronic.

Automatic discrepancies will be issued in accordance with the Edit Check Document and the eCRF Database Question Specifications.
In the event of data discrepancies, investigational centers will be asked to resolve queries electronically in the RDC system; otherwise, irresolvable data-related issues will be routed to the Sponsor for review and final disposition.

16.3. Confidentiality

All information and data sent to parties involved in study conduct concerning subjects or their participation in this study will be considered confidential. Study sites will assign a unique SID to each subject. Records of the subject/SID relationship will be maintained by the study site. The SID number is to be recorded on all study documents to link them to the subject's medical records at the study site. Confidentiality of data will be observed by all parties involved at all times throughout the clinical investigation. All data shall be secured against unauthorized access. The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data. In the US, "Protected Health Information" (PHI) will be maintained in compliance with the HIPAA of 1996. To maintain confidentiality, the subject's name or any other PHI should not be recorded on any study

document other than the IC. This scenario will be covered in the IC. In the event a subject's name/PHI is included for any reason, it will be blinded as applicable. In the event of inability to blind the identification (e.g., digital media), it will be handled in a confidential manner by the authorized personnel. Data relating to the study might be made available to third parties (for example in case of an audit performed by RA), provided the data are treated as confidential and that the subject's privacy is guaranteed. No identifiable subject information will be published.

16.4. Audits and Investigation Site Inspections

In addition to regular monitoring visits, Medtronic may conduct audits at participating investigation sites. The purpose of an audit is to verify the adequate performance of the clinical study related activities. Regulatory authorities may also perform inspections at participating investigation sites. Any regulatory authority inspection announcements shall be forwarded immediately to the Medtronic per contact information above.

The investigator and/or institution shall permit Medtronic and regulatory bodies direct access to source data and documents, taking into account any restrictions due to local law, to perform clinical study related monitoring, audits, IRB review (if applicable), and regulatory inspections.

16.5. Subject Compensation

The study will incur no cost to the subject. The subject will be paid $500 in total compensation, $200 for completing the screening visit and the first regimen, and an additional $300 for completing the second regimen. Screen failures will be compensated $25.

16.6. Liability

Medtronic maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a clinical study insurance statement/certificate will be provided to the IRB.

16.7. CIP Amendments

The investigator may propose any appropriate modification(s) to the Clinical Investigation Plan or investigational device or investigational device use. Medtronic will review and decide whether the modification(s) will be implemented.

Medtronic will submit any amendment to the Clinical Investigation Plan, including a justification for such amendment, to the investigators to obtain approval from their IRB.

Any amendment to the protocol requires written approval by the IRB and regulatory authority (if applicable) prior to its implementation unless there are overriding safety reasons. In some instances, an amendment may require a change to the ICF.

The Sponsor and Investigator will obtain IRB approval concerning the revised ICF prior to the implementation of the change. The Investigator understands that subjects must be consented using the most current IRB approved version of the ICF. If the ICF is updated, subjects who have participated will be re-consented at the direction of the IRB.

16.8. Record Retention

16.8.1. Investigator Records

The investigator is responsible for the preparation and retention of the records cited below. All of the below records, with the exception of case history records and case report forms, should be kept in the Investigator Site File (i.e., the study binder provided to the investigator) or Subject Study Binder. CRFs must be maintained and signed electronically within the electronic data capture system during the study. The following records are subject to inspection and must be retained for a period of two years (or longer as local law or hospital administration requires) after product approval or the date on which the investigation is terminated.

- All correspondence between the IRB, sponsor, monitor, RA and the investigator that pertains to the investigation, including required reports.
- Subject's case history records, including:
  - Signed and dated IC (by subject)
  - Observations of AEs/ADEs/DDs
  - Documentation of the dates and rationale for any deviation from the protocol
- Subject screening log & ID log
- Normal value(s)/range(s) for clinical laboratory test
- Lab certificate
- Device Disposition Logs containing Model and serial numbers of devices delivered to the study site, subject IDs of the subjects
- All approved versions of the CIP, IC
- Signed and dated CTA.
- FD
- CV of principal investigators and key members of investigation study site team (as required by applicable regulations.

- Documentation of delegated tasks.
- IRB approval documentation. Written information that the investigator or other study staff, when member of the IRB, did not participate in the approval process. Approval documentation must include the IRBs composition, where required per local law.
- RA notification, correspondence and approval, where required per local law.
- Study training records for study site staff.
- Any other records that FDA and local regulatory agencies require to be maintained.
- Final Study Report including the statistical analysis.

An investigator may withdraw from the responsibility to maintain records for the period required, as indicated in the paragraph above and transfer custody of the records to any other person who will accept responsibility. An investigator must notify the Sponsor if prior records are being transferred.

16.8.2. Sponsor Records

Medtronic shall maintain the following accurate, complete, and current records:

- All correspondence which pertains to the investigation
- Investigational device traceability record containing Model and serial numbers of devices, shipping date and name and address of person that received shipped device, location (if different than person shipped to), transfer and receipt by Medtronic dates
- Sample of label attached to investigational device
- Signed Investigator Trial Agreements, FD and current signed CV of principal investigator and key members of the investigation study site team (as required by local law), delegated task list
- All signed and dated case report forms submitted by investigator, including reports of Aes, ADEs and DDs (for non-OC studies)
- All approved IC templates, and other information provided to the subjects and advertisements, including translations
- Copies of all IRB approval letters and relevant IRB correspondence and IRB voting list/roster/letter of assurance
- Names of the institutions in which the study will be conducted
- RA correspondence, notification and approval as required by national legislation
- Names/contact addresses of monitors
- Monitoring visit reports
- Statistical analyses and underlying supporting data
- Final report of the study
- The CIP, Report of Prior Investigations summary and study related reports, and revisions

- Study training records for study site personnel and Medtronic personnel involved in the study
- Any other records that local regulatory agencies require to be maintained.

Medtronic records and reports will be maintained in a password-protected document management system, and paper documents (where applicable) will be stored in stored in secured file cabinets at Medtronic during the course of this study.

After closure of the study Medtronic could archive records and reports indefinitely.

16.9. Reporting Requirements

16.9.1. Investigator Reports

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all case report forms, adverse events and adverse device effects (reported per the country-specific collection requirements), device deficiencies, deaths, and any deviations from the clinical investigation plan. If any action is taken by an IRB with respect to this study, copies of all pertinent documentation must be forwarded to Medtronic in a timely manner. Reports are subject to inspection and to the retention requirements as described above for investigator records.

Safety data investigator reporting requirements are listed in Section 12.1. The investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in this section.

Table 7: Investigator reports applicable for all geographies per Medtronic requirements

Report	Submit to	Description/Constraints
Withdrawal of IRB approval	Sponsor and Relevant Authorities	The investigator must report a withdrawal of approval by the reviewing IRB of the investigator's part of the investigation within 5 working days.
Study Deviations	Sponsor and IRB	Any deviation from the clinical investigational plan shall be recorded together with the explanation of the deviation. Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Except in such emergency, prior approval is required for changes in the plan or deviations.
Final Report	IRBs and Relevant Authorities	This report must be submitted within 12 months of study completion or termination.

16.10. Publication and Use of Information

The Medtronic Publication and Authorship Policy is aligned with the International Committee of Medical Journal Editors (ICMJE) recommendations (www.icmje.org). The Sponsor will seek to publish, in appropriate peer-reviewed journals and scientific conferences, results of clinical studies where human

subjects are involved, regardless of the outcome. The study will be recorded on www.clinicaltrials.gov before the first enrollment.

The data may be published or used by study investigators provided that such publication or use is in accordance with this protocol, the Medtronic Publication and Authorship Policy, and the Clinical Investigation Agreement. Investigators must submit a copy of all manuscripts and/or abstracts to the Sponsor for review and comment 30 days prior to planned submission. Medtronic acknowledges that its right to review and comment shall relate solely to the proprietary, licensing, and/or confidential rights Medtronic may have in such proposed publication, rather than whether such results and/or opinions are favorable to Medtronic. Authorship on any publication(s) resulting from this clinical study will be assigned according to substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content and final approval of the version to be published.

Medtronic involvement in a publication (e.g., funding of the study; sponsor of the study; collection, analysis, and interpretation of data; professional writing assistance) must be disclosed according to journal-specific policies, submission requirements, and prevailing editorial standards, in addition to those specified by International Committee of Medical Journal Editors. The authors must ensure that an acknowledgment/disclosure statement is included in the body of the manuscript for Medtronic to review for accuracy. All authors must also disclose financial or personal affiliations that could be considered conflicts of interest as per journal/conference requirements.

Medtronic, as the owner of the data, can use the data and/or any results derived from the data or publications based on that data for marketing purposes, further research, and development of devices or educational use. The study sponsor will collect data in such a way that no subject can be identified and monitor study records. Participating subjects will not be identified by name in any published reports about the clinical study.

16.11. Suspension or Early Termination

The Sponsor reserves the right to discontinue the study at any stage, with written notice to all investigators and reviewing IRB. Similarly, investigators may withdraw from the study at any time, subject to providing written notification to the Sponsor 30 days prior to the date they intend to withdraw.
The Sponsor and investigators will be bound by their obligation to complete the follow-up of subjects already participating in the study. If the study is terminated or suspended, no additional enrollment will be allowed unless otherwise informed by the sponsor. The current subjects will be followed according to the protocol, and information obtained during subject follow-up shall be reported to the Sponsor on the appropriate eCRF.

If the study is terminated prematurely or suspended by the sponsor, the sponsor will promptly inform the investigators and regulatory authorities (if required) of the termination and the reason(s). The IRB will also be promptly informed and provided with the reason(s) for termination or suspension by the sponsor or by the investigator. The investigator will promptly inform the subjects and assure appropriate therapy and follow-up for the subject, as needed.

If the investigator (or IRB) terminates or suspends the investigation without the prior agreement of the sponsor, the investigator will promptly inform the sponsor, the institution (if required), and the IRB and provide a detailed written explanation of the termination or suspension. The sponsor will inform the regulatory authorities (if required.)

In the case of early termination of the study, all study subjects should be followed until the resolution of any pending adverse event(s.)

Medtronic reserves the right to discontinue the study at any time for administrative or other reasons. Written notice of study termination will be submitted to the investigator in advance of such termination. Possible reasons for considering study suspension or termination of the study for all centers include but are not limited to:

- Failure to obtain initial IRB approval or annual renewal of the study;
- Consistent non-compliance to the CIP (e.g., failure to adhere to inclusion/exclusion criteria, failure to follow subjects per scheduled follow-ups, failure to implement required corrective and preventive actions, etc.);
- Lack of enrollment;
- Noncompliance to regulations and the terms of the Clinical Trial Agreement (e.g., failure to submit data in a timely manner, failure to follow-up on data queries and monitoring findings in a timely manner, etc.);
- IRB suspension of the center;
- Fraud or fraudulent misconduct (as defined by local law and regulations);
- Investigator request (e.g., no longer able to support the study).

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18. Appendices

Appendix A – Modified Observer's Assessment of Alertness/Sedation scale

The Modified Observer Assessment of Alertness/Sedation (MOAA/S) Scale [51]	
Response	**Score**
Responds readily to name spoken in normal tone	5
Responds lethargically to name spoken in normal tone	4
Responds only after name is called loudly, repeatedly, or both	3
Responds only after mild to moderate prodding or shaking	2
Responds only after painful trapezius squeeze	1
Does not respond to painful trapezius squeeze	0

[redacted]

19. Version History

Version	Summary of Changes	Author(s)/Title
1.0	Not Applicable, New Document	Julia Katilius, Ph.D./ Sr. Clinical Program Manager
2.0	Administrative Change Only 9.5.2.3	Julia Katilius, Ph.D./ Sr. Clinical Program Manager
3.0	Administrative Change Date Alignment pg.1 and pg. 2 / Table 2. Updated CBC to visit 1	Julia Katilius, Ph.D./ Sr. Clinical Program Manager
4.0	Revision change from CIP template vs A to vs B Addition of TES assessment Simplification of study procedures and assessments from paragraph form to bullet points Clarification of Study Products vs equipment Separate section of study site requirements for clarity Separate section of Adverse Events and Device Deficiencies for clarity Reformatting of tables for clarity Updated Sponsor contact information Addition of Subject Death reporting requirements for clarity Separation of investigator vs sponsor record retention requirements Addition of tables clarifying reporting requirements	Stephanie Monza, BS, CCRC Sr. Clinical Research Specialist
5.0	Change of procedure to increase anesthesia until a BIS™ value of 30 is reach or per Investigator's discretion Formatting changes Clarification of Statistical Plan	Stephanie Monza, BS CCRC Sr. Clinical Research Specialist