Medtronic

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	Evaluation of BIS™ and Levels of Sedation with Common Inhalational Anesthetics in Healthy Volunteers (OLIVER)
Clinical Investigation Plan Identifier	MDT19053OLIVER
Study Product Name	BIS™ Complete Monitoring System
Sponsor/Local Sponsor	Medtronic, Medical Surgical Portfolio Patient Monitoring OU 6135 Gunbarrel Avenue, Boulder, CO 80301 U.S.A.
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Table of Contents

Table of Tables

Table of Figures

2. Glossary

Term	Definition/Acronyms
ADE	Adverse Device Effect
AE	Adverse Event
AEAC	Adverse Events Advisory Committee
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
BMI	Body Mass Index
bpm	Beats per minute
CA	Competent Authority
CBC	Complete Blood Count
CIP	Clinical Investigational Plan
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 a 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
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
DD	Device Deviation

Term	Definition/Acronyms
DMC	Data Monitoring Committee
DMP	Data Management Plan
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
EMR	Electronic Medical Record. Digital version of a patient's medical record within a single facility.
ET	End-tidal concentration
ET_{DES}	End-tidal concentration of Desflurane
ET_{SEVO}	End-tidal concentration of Sevoflurane
$EtCO_2$	End-tidal Carbon Dioxide. The value of exhaled carbon dioxide displayed by the capnograph device
FD	Financial Disclosure
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
Hz	Hertz
ICF	Informed Consent Form
IFU	Instructions for Use
IV	Intravenous
IPPV	Intermittent positive pressure ventilation
IRB	Institutional Review Board
ISF	Investigator Site File. Regulatory binder supplied by the sponsor

Term	Definition/Acronyms
LMA	Laryngeal mask
LOC	Level of consciousness
MAC	Minimum alveolar concentration
MOAA/S	Modified Observer's Assessment of Alertness/Sedation
NSR	Non-significant Rsik
PI	Principal Investigator. The person responsible for overseeing the study and assuring study completion in compliance with applicable regulations.
PIC	Patient Interface Cable
PK/PD	Pharmacokinetics and pharmacodynamics
POC	Point of Care
RA	Regulatory Authority
SpO2	A non-invasive spectroscopic estimate of arterial oxygen saturation measured transcutaneously by a pulse oximeter
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedures
TES	Tetanic Electrical Stimulation
TCI	Target-controlled infusion
TIVA	Total Intravenous Anesthesia
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect

3. Synopsis

Title	Evaluation of BIS™ and Levels of Sedation with Common Inhalational Anesthetics in Healthy Volunteers (OLIVER)
Product Name	Bispectral Index Sensor (BIS™) Complete Monitoring System
Sponsor	Medtronic Medical Surgical Portfolio Patient Monitoring OU 6135 Gunbarrel Avenue Boulder, CO 80301
Indication under investigation	Validation of the BIS™ index, one of the Complete Monitor output parameters, as an aid in monitoring the effects of desflurane, isoflurane and sevoflurane with balanced anesthetic techniques for adult patients.
Investigation Purpose	To investigate the relationship between BIS™ and inhaled anesthetics across a wide range of anesthetic concentration and hypnotic states, and to provide evidence to support BIS™ performance in use with isoflurane, sevoflurane and desflurane in combination with opioids.
Product Status	BIS™ is commercially available in the United States
Primary Objective	To determine BIS_{50} (BIS™ value at which 50% of patients will be unresponsive at a given drug concentration)
Secondary Objective(s)	To determine BIS_{95} (BIS™ value at which 95% of patients will be unresponsive at a given drug concentration) To determine Prediction Probability (P_K) for correctly predicting if the subject was responsive or unresponsive.
Study Design	This is a prospective, randomized study to collect data to evaluate the relationship between BIS™ and inhaled anesthetics without and with opioids. Five groups of anesthetics regimens will be studied as follow: 1. Sevoflurane alone 2. Sevoflurane with Remifentanil 3. Sevoflurane with Fentanyl 4. Desflurane alone 5. Isoflurane alone

	Healthy Volunteer Subjects will be randomized to one of the anesthetic regimen groups. The BIS™ bilateral sensor will be placed on the subject's forehead to study the effects of these drugs on the brain. Each subject will be given a sequence of dose ranges of the target drug to achieve targeted drug concentration. If required, a training group, comprising of the first 2 - 4 subjects at each site will be enrolled to train the site team on the technology and to determine the quality of data collection, as required, prior to randomization. Afterward, randomization will proceed based on the Sponsor's assessment of data quality. The Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale will be used at each steady-state step to measure the level of alertness in sedated subjects. Subjects will then be assessed using a Picture Recall assessment with a standardized set of pictures. Tetanic Electrical Stimulation (TES) will be used once the patient is unresponsive to painful stimuli (e.g., MOAA/S = 0, BIS™ < 40). TES will then be initiated once the subject reaches a MOAA/S = 0, BIS™ value < 40 at the highest concentration of anesthesia anticipated, with an increasing stimulation starting at 20mA, 50 Hz delivered for 1-5 seconds. If the subject does not purposefully (i.e. attempting to push the stimulus away) respond, the stimulation will increase to 30mA, 50Hz for 1-5 seconds, then 40mA, 50 hertz (Hz) for 1-5 seconds and finally to 50mA, 50Hz for 1-5 seconds. If there is still no purposeful response, the subject will be considered a non-purposeful responder (i.e. exhibiting a reflex withdrawal, facial grimace, or groan) and their response such as withdrawal of extremity, facial grimace or other will be recorded along with the BIS™ value prior to stimulation, at the end of all stimulation and approximately 2 minutes later, to allow for equilibration, following stimulation. If the subject does respond to any of the stimulations with a purposeful response, the TES will be ended, the response will be noted and the BIS™ value will be recorded at the time TES is ended and at approximately 2 minutes following the stimulation. Anesthesia will then be decreased in the same steps until subject is conscious.
Randomization	Once enrolled, subjects will be equally randomized to one of the anesthetic regimen groups.
Sample Size	A two-stage adaptive design is used in this study. For each regimen group, 10 subjects will be enrolled in stage 1, and upon evaluation, up to 20 additional subjects will be enrolled in stage 2. With 5 regimen groups, a maximum of 150 subjects will be enrolled. Based on the dose-response equation (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.

Duration	Study duration is expected to be up to approximately 9 months. The expected duration of each subject's participation is approximately 6 hours for both enrollment and procedure. The Enrollment Visit should take approximately 2 hours to complete, and the 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	Three to four investigational sites in the US
Inclusion/Exclusion Criteria	Inclusion Criteria: 1) Healthy (American Society of Anesthesiology (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 beats per minute (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 (PI) or designee will verify the eligibility of each subject with out-of-range vital signs and document approval before dosing]. Exclusion Criteria: 1) Has severe contact allergies that may cause a reaction to standard adhesive materials found in pulse oximetry sensors, electrocardiogram (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) Use of psychoactive medication within the past 60 days (e.g., benzodiazepines, antiepileptic drugs, 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 [point of care (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 pulmonary function test via spirometry [assessment by PI or delegate]; 13) Pregnant or lactating women [assessed by urine test and self-reported]; 14) Subjects with tattooed skin specific to the sensor placement areas (forehead, fingers, chest) [self-reported and assessment by PI or delegate]; 15) 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 Food and Drug Administration (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	Pre-Screening: • Online or phone call pre-screening Enrollment Visit (Visit 1): • Informed Consent Process • 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 subjects able to bear children 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. 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. Execution Visit (Visit 2): Prior to Randomization: • Inclusion/Exclusion Assessment • Vital Signs • Urine Testing for presence of: • Cotinine (nicotine metabolite) • Pregnancy- for subjects of childbearing potential • Alcohol Breathalyzer **Randomization** Procedure: • BIS™ sensor application and connection to BIS™ Monitor • TES sensor application to the calf with a stimulation of 5mA, 5Hz for 1-5 seconds or per device Instructions for Use (IFU) provided to ensure proper application • Safety Management • Intravenous Catheter Insertion for fluid and drug administration • Blood pressure monitoring • Electroencephalogram (EEG), Pulse Oximeter for saturation pulse oxygen (SpO_2), Capnography (or another system) for respiratory rate, and end-tidal carbon dioxide ($EtCO_2$)

	• BIS™, Picture Recall Test (for the sevoflurane, sevoflurane with remifentanil and sevoflurane with fentanyl groups), Modified Observer's Assessment of Alertness/Sedation (MOAA/S) Assessments TES assessment as described above. 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 carbon dioxide (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 oxygen (O_2) delivery. Any study procedures may be discontinued for the subject's safety. The opioids (remifentanil and fentanyl) will be administered via the target-controlled infusion (TCI) pump using either the preprogrammed pump protocols or computer-controlled program, e.g., Total Intravenous Anesthesia (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. Remifentanil and Fentanyl 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 target effect-site concentration of remifentanil and fentanyl. For remifentanil, Minto pharmacokinetics/pharmacodynamics (PK/PD) model will be used. [1] The kinetic model for fentanyl will not be weight-adjusted.[2] Inhalation anesthetic drugs will be administered via a tight-fitting face mask or a laryngeal mask (LMA). Volunteers will be connected to a circular breathing system of an anesthesia machine. After the volunteer loses responsiveness, LMA may be inserted as needed to facilitate airway control at deeper levels of anesthesia. Once emergence is started, LMA should be removed at the earliest point while ensuring subject safety. Inhalation agents will be administered with O_2 to maintain saturation of greater than 90%. Lidocaine can be administered per Investigator discretion as a bolus over 3-5 seconds at a maximum concentration of 100mg to aid in the infusion of propofol for subject's comfort. Phenylephrine may be used prophylactically on all subjects at a concentration of 100 mcg/mL for the prevention of hypotension as a result of inhaled anesthetics. Antiemetic / anti-nausea medication (i.e. Ondansetron) may be used prophylactically on all subjects for the prevention of nausea and vomiting at the investigator's discretion.

	Each subject will receive one of the anesthetic groups. The subject will rest for at least 12 minutes before starting any regimen. **Sevoflurane Group**, following approximately 2 minutes of baseline measurement, sevoflurane will be administered via a tight-face mask in steps to achieve a loss of consciousness by increasing the end-tidal concentration of sevoflurane (ET_{SEVO}). Targeted concentration for ET_{SEVO} are 0.2, 0.5, 0.7, 1, 2, 3, 4, 5% or higher until a BIS™ value not less than 30 is reached or per Investigator's discretion. The BIS™ value should be taken to at least 40, but not intentionally below 30. The equilibration time for each targeted concentration will be approximately 12 minutes to maintain a constant ET_{SEVO}. The BIS™ value, MOAA/S score and Picture Recall test will be assessed when the patient is awake and prior to the induction of any anesthetic and at each ET_{SEVO} concentrations. TES will then be initiated once the subject reaches a MOAA/S = 0, BIS™ value < 40 at the highest concentration of anesthesia anticipated. The BIS™ value will be recorded at the immediate end of the assessment and approximately 2 minutes following the TES assessment. ET_{SEVO} is decreased by the same steps until consciousness is regained. **Sevoflurane with Remifentanil Group**, approximately 2 minutes prior to starting sevoflurane, to attain an effect-site targeted concentration of remifentanil of 4 ng/ml, an initial IV bolus of remifentanil will be given followed by the start of an 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. Sevoflurane will be administered via a tight-face mask in steps to achieve a loss of consciousness by increasing the end-tidal concentration of sevoflurane (ET_{SEVO}). Targeted concentration for ET_{SEVO} are 0.2, 0.5, 0.7, 1, 2, 3, 4, 5% or higher until a BIS™ value not less than 30 is reached or per Investigator's discretion. The BIS™ value should be taken to at least 40, but not intentionally below 30. The equilibration time for each targeted plateau will be approximately 12 minutes. The BIS™ value, MOAA/S score and Picture Recall test will be assessed when the patient is awake and prior to the induction of any anesthetic and at each ET_{SEVO} concentrations with the exception of the Picture Recall test, which will just be completed at the first three steps. TES will then be initiated once the subject reaches a MOAA/S = 0, BIS™ value < 40 at the highest concentration of anesthesia anticipated. The BIS™ value will be recorded at the immediate end of the assessment and approximately 2 minutes following the TES assessment. ET_{SEVO} is decreased by the same steps until consciousness is regained. **Sevoflurane with Fentanyl Group**, approximately 2 minutes before starting sevoflurane, to attain an effect-site targeted concentration of fentanyl of 2

	ng/mL, an initial IV bolus of fentanyl will be given followed by the start of an infusion. Approximately within 10 minutes, the infusion rate of fentanyl may be adjusted to maintain the effect-site concentration of fentanyl of 2 ng/ml. Sevoflurane will be administered via a tight-face mask in steps to achieve a loss of consciousness by increasing the end-tidal concentration of sevoflurane (ET_{SEVO}). Targeted concentration for ET_{SEVO} are 0.2, 0.5, 0.7, 1, 2, 3, 4, 5% or higher until a BIS™ value not less than 30 is reached or per Investigator's discretion. The BIS™ value should be taken to at least 40, but not intentionally below 30. The equilibration time for each targeted plateau will be at least 12 minutes. The BIS™ value, MOAA/S score and Picture Recall test will be assessed when the patient is awake and prior to the induction of any anesthetic and at each ET_{SEVO} concentrations with the exception of the Picture Recall test, which will just be completed at the first three steps. TES will then be initiated once the subject reaches a MOAA/S = 0, BIS™ value <40 at the highest concentration of anesthesia anticipated. The BIS™ value will be recorded at the time of subject's response and approximately 2 minutes following the TES assessment. ET_{SEVO} is decreased by the same steps until consciousness is regained. The cardiac output will be monitored, and subjects could be discontinued per PIs discretion. The respiratory rate of 4 breaths/minute or less will be considered evidence of fentanyl-induced respiratory depression, and fentanyl will be discontinued. **Desflurane Group**, Due to desflurane being a volatile agent and not well tolerated as an induction agent, an initial intravenous IV bolus of 1% propofol provided at 2mg/kg, with supplemental boluses given at the investigator's discretion, in order to achieve LMA insertion. Propofol will be administered 0-15 minutes prior to desflurane. Desflurane will then be administered via a tight-face mask or LMA at the targeted end-tidal concentration of desflurane (ET_{DES}) of 2, 5, 7, 8, 9, 10 %, or higher until a BIS™ value not less than 30 is reached or per Investigator's discretion. The BIS™ value should be taken to at least 40, not intentionally below 30. The equilibration time for each targeted plateau will be approximately 12 minutes. The BIS™ value and MOAA/S score will be assessed when the patient is awake and at the different ET_{DES} concentrations. TES will then be initiated once the subject reaches a MOAA/S = 0, BIS™ value < 40 at the highest concentration of anesthesia anticipated. The BIS™ value will be recorded at the immediate end of the assessment and approximately 2 minutes following the TES assessment. The BIS™ value will be correlated with desflurane ET_{DES} concentration. LMA should be removed at the highest level of sedation while maintaining subject's

	safety in order to allow for a gradual emergence from anesthesia. ET_{DES} is decreased by the same steps until consciousness is regained. **Isoflurane Group:** Due to isoflurane being a volatile agent and not well tolerated as an induction agent, an initial IV bolus of 1% propofol provided at 2mg/kg, with supplemental boluses given at the investigators discretion in order to achieve LMA insertion, will be administered 0-15 minutes prior to isoflurane. Isoflurane will be administered via a tight-face mask or LMA in steps to achieve a loss of consciousness (MOAA/S of 0 or 1) by increasing the end-tidal concentration of Isoflurane (ET_{ISO}). Targeted concentration for ET_{ISO} are 0.2, 0.5, 0.7, 1, 1.5% or higher until a BIS™ value not less than 30 is reached or per Investigator's discretion. The BIS™ value should not be taken to at least 40, not intentionally be taken below 30. . The equilibration time for each targeted concentration will be approximately 12 minutes to maintain a constant ET_{ISO}. The BIS™ value and MOAA/S score will be assessed when the patient is awake and at each ET_{ISO} concentrations. TES will then be initiated once the subject reaches a MOAA/S 0, BIS™ value < 40 at the highest concentration of anesthesia anticipated. The BIS™ value will be recorded at the immediate end of the assessment and approximately 2 minutes following the TES assessment. The BIS™ value will be correlated with the isoflurane ET_{ISO} concentration. LMA should be removed at the highest level of sedation while maintaining subject's safety in order to allow for a gradual emergence from anesthesia. ET_{ISO} is decreased by the same steps until consciousness is regained. The start time of any drug infusion, target effect-site concentrations, infusion rate, the start and end time of the assessment including BIS™ value prior to MOAA/S assessment, Picture Recall test and TES 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. Also, the device data (raw signals), including Heart Rate, Blood Pressure, Respiration Rate, $EtCO_2$, SpO_2, BIS™, TCI 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 Assessments	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 (AE) , Serious Adverse Events (SAE), and Device-Related Adverse Events from the BIS™ sensor application throughout the study and through 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, 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. All randomized subjects will be included in the analysis. For those subjects who do not complete a follow-up call, the analysis will include all data up to the last collected point or follow-up call. Subjects who completed the procedure phase will not be replaced. If the subject discontinues before randomization or during the procedure phase, she/he will be replaced. 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 0 and 1 will be considered unresponsive. The data will be analyzed for each regimen. The logistic model (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% confidence 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. An **interim review** will be performed by MDT at the end of stage 1, when all (50 subjects with 10 subjects per group) have completed the evaluation. Both the primary and secondary objectives will be evaluated during the interim review. One or more groups may be dropped upon interim results for safety concern (unacceptable safety events per clinical judgment).

4. Introduction

4.1. Background

4.1.2 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 is the absence of a response, 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, it's vital that the anesthesiologist know when a patient has reached a depth of anesthesia commensurate with an impending stimulus. Superficial or deep depth levels can be disastrous in both the short and long run when a patient expects a surgical procedure to be safe and painless, assured that throughout the procedure, they are asleep, without any perception or memory 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.

This critical concentration aids in comparing the neurophysiologic effects of different drugs, both within and between different species. Inhalational anesthetics, including Isoflurane, Sevoflurane, and Desflurane, similarly have a designation for standardizing each agent's concentration/effect relationship. The minimum alveolar concentration (MAC) is the concentration of volatile anesthetic that prevents movement in response to a standard skin incision in 50% of patients. 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.[3]

4.1.2 EEG Monitoring in Anesthesia

Since 1939, anesthesiologists have known about changes in the electroencephalogram (EEG) that are produced by anesthetic agents.[4] 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. [5, 6] 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 prevent intraoperative awareness and help to ensure that an exact dose of anesthetic drugs is given. The lightness of anesthesia can result in the recall of events that happen in the operation room. Anesthesia that is too deep 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 [7]. There is no objective scale that measures "too light" or "too deep" anesthesia. Bispectral Index (BIS) technology monitoring measures sedation depth based on changes in EEG signals and allows anesthesia providers to titrate general anesthesia to achieve the desired LOC on the brain [7, 8]. The BIS™ technology consists of a sensor placed on the patient's forehead to measure the electrical signals from the cerebral cortex (the EEG), a digital signal converter to digitize the EEG, and derive the necessary processed EEG parameters, and a monitor to display the resultant BIS and EEG signal. BIS™ values quantify changes in the electrophysiologic state of the brain during anesthesia. BIS™ is a continuously processed EEG parameter that correlates to the patient's level of hypnosis, where 100 = awake and 0 = isoelectric 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. Overall, a BIS™ value below 60 is associated with a low probability of response to commands.[5, 9] Figure 1 reflects a general association between clinical state and BIS™ values. Ranges are based on results from a multi-center study [8] 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.

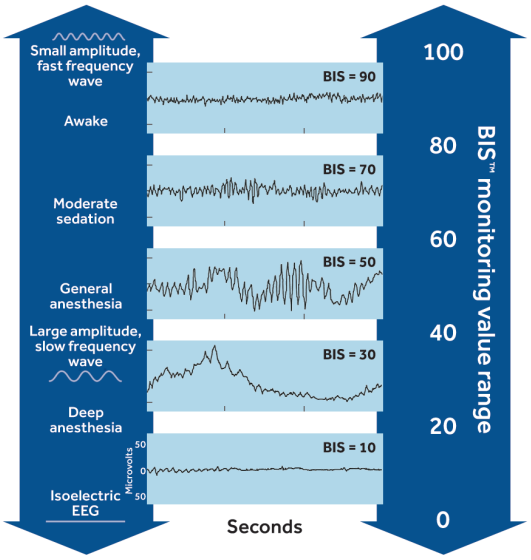

Figure 1: BIS™ Range Guidelines; a general association between clinical state and BIS values

4.1.2 Clinical Summary

The BIS™ system has been on the market for approximately 25 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 performance and safety of the BIS™ system in the published clinical literature carried out from May 2013 to September 2018. The safety clinical literature reviews accounted for 7,627 patients and performance data for 43,247 patients. 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 [10-41]	43,247	11 publications with safety data [11, 14, 20, 26, 27, 29, 35-37, 42, 43]	7,627

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, **Table 1,** did not reveal any new complications directly related to the use of the devices.

4.2. Purpose

To investigate the relationship between BIS™ and inhaled anesthetics across a wide range of anesthetic concentration and hypnotic states, and to provide evidence to support BIS™ performance in use with sevoflurane, isoflurane and desflurane in combination with opioids.

5. Objectives

5.1. Objectives

Primary Objective(s)

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

Secondary Objective(s)

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

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

6. Study Design

This is a prospective, randomized study to collect data to evaluate the relationship between BIS™ and inhaled anesthetics without and with opioids. Five groups of anesthetic regimens will be studied as follow:

1. Sevoflurane alone
2. Sevoflurane with Remifentanil
3. Sevoflurane with Fentanyl
4. Desflurane alone
5. Isoflurane alone

Healthy Volunteers Subjects will be randomized to an anesthetic group. The BIS™ bilateral sensor will be placed on the subject's forehead to study the effects of these drugs on the brain. Each subject will be given a sequential dose range of the target drug to achieve targeted drug concentration. At each steady-state step, and after at least 12 minutes to achieve equilibrium, the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale will be used to perform sedation/loss of consciousness assessment, with the Picture Recall test being used in the sevoflurane, sevoflurane with remifentanil and sevoflurane with fentanyl regimens to assess the subject's level of anesthesia awareness, and Tetanic Electrical Stimulation (TES) being used if the patient is unresponsive to tactile stimuli (e.g., MOAA/S = 0, BIS™ value

< 40 at the highest concentration of anesthesia anticipated). The loss of tactile response will be defined according to the MOAA/S score value < 2 (0-1) and the presence of verbal response at values >2 (2-5).

A training group, comprising of the first 2 - 4 subjects at each site will be enrolled to train the site team on the technology and to determine the quality of data collection, as required, before randomization. Afterward, randomization will proceed based on the Sponsor's assessment of data quality.

Subjects will have the effect of noxious electrical stimulation on the sedation state assessed for each arm once they achieve an MOAA/S score = 0, BIS™ value <40 at the highest concentration of anesthesia anticipated. The baseline BIS™ value will be recorded, followed by the MOAA/S assessment. Once TES is initiation, stimulation will start at 20mA, 50 Hz delivered for 1-5 seconds. If the subject does not purposefully (i.e. attempting to push the stimulus away) respond, the stimulation will increase to 30mA, 50Hz for 1-5 seconds, then 40mA, 50Hz for 1-5 seconds and finally to 50mA, 50Hz for 1-5 seconds. If there is still no purposeful response, the subject will be considered a non-purposeful responder (i.e. exhibiting a reflex withdrawal, facial grimace, or groan) and their response such as withdrawal of extremity, facial grimace or other will be recorded along with the BIS™ value prior to stimulation, at the time of each stimulation and approximately 2 minutes following each stimulation. If the subject does respond to any of the stimulations with a purposeful response, the TES will be ended, the response will be noted and the BIS™ value will be recorded at the time TES is ended and at approximately 2 minutes following the stimulation. LMA should be removed at this point, if allowed per Investigator's assessment without risk to subject. Anesthesia will then be decreased in the same steps until subject is conscious. 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 and 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 functions. Subjects will be continuously monitored throughout the study.

A two-stage design is used in this study. For each regimen group, 10 subjects will be enrolled in stage 1, and 20 subjects will be enrolled in stage 2. With 5 regimens, there will be a maximum of 150 subjects. An interim review will take place at the end of stage 1 (50 subjects and 10 subjects per regimen). Both the primary and secondary objectives will be evaluated during the interim review, and a particular group(s) may be dropped upon interim results for safety concerns (unacceptable safety events per clinical judgment) (refer to *Section 12*.)

6.1. Duration

Study duration is expected to be up to approximately 9 months. The expected duration of each subject's participation is approximately 6 hours for both enrollment and procedure. The Enrollment Visit should

take approximately 2 hours to complete, and the Study Visit will be approximately 4 hours per subject. Each subject will be contacted by phone within 48 hours of the study participation.

6.2. Rationale

This clinical study is designed to capture the performance of BIS™ with anesthetic agents across a wide range of anesthetic concentrations and hypnotic states. The study design is deemed appropriate in this setting and will provide more information to confirm the performance and safety of the BIS™ monitoring system.

The anesthetic regimens are selected based on clinical relevance. Inhalational anesthetics (e.g., isoflurane, sevoflurane and desflurane) can be used for the induction and maintenance of general anesthesia. Often inhaled anesthetics are used alone or in combination with other central nervous system depressants such as intravenous sedatives (e.g., propofol) and opioids (e.g., remifentanil and fentanyl.) During anesthesia, isoflurane, sevoflurane and desflurane can be maintained at end-tidal concentrations of 0.5 – 8% and 2.5 - 16%, respectively, in combination with opioids.

Intravenous (IV) opioids (e.g., remifentanil and fentanyl) are commonly used to provide analgesia and supplement sedation during general anesthesia. Opioids are often used in conjunction with volatile anesthetic agents and are typically not used alone during induction and maintenance of general anesthesia. The titration of the opioid doses can be facilitated by target-controlled infusion (TCI) pumps with the benefit that the recovery time from anesthetic doses can be appropriate for the individual patient and procedure. The TCI pump contains a microprocessor programmed with pharmacokinetic and pharmacodynamic models for relevant drugs. The user selects the drug and model to be used by that TCI pump and inputs the patient characteristics such as body weight and age, and the target plasma or 'brain' (effect-site) concentration, with the pump determining the initial bolus and subsequent infusion rates. The commonly used adult model remifentanil is Minto. For remifentanil, the induction levels of 4 ng/ml are commonly used, but the levels generally vary between 2-8 ng/ml. [44] For this study, the selected target effect-site concentration of remifentanil is 4 ng/ml to account for subject safety. During surgery, the effect-site concentration of fentanyl can vary. The effect-site concentrations of fentanyl between 0.8 and 1.4 ng/ml are associated with numerous complaints of postoperative pain, and concentrations 3.0 ng/ml and higher are associated with respiratory and cardiac depression. The optimal fentanyl effect-site concentration appears to be near 2 ng/ml [45].

A two-stage design will be implemented, given the benefits of patient protection and sample size savings for more details, refer to Section 13.

The de-identified data collected in this study also may be used for future product development.

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 are to extract characteristic features from the complex signal that the BIS™ algorithm can utilize to ultimately derive BIS™.

Table 2: System product/component information for the United States

Product Number	Component (Manufacturer)	Investigational or Market-released
185-0151	BIS™ Complete Monitor (Medtronic)	Market-released
185-1014-AMS	BIS™ BISx4 (Medtronic)	Market-released
186-0107	BIS™ Patient Interface Cable (Medtronic)	Market-released
N/A	BIS™ Sensor (Medtronic)	Market-released
N/A	BIS™ Detachable Power Cord (Medtronic)	Market-released

7.2. Manufacturer

BIS™ Complete Monitoring System by (15 Hampshire St, Mansfield MA) Medtronic Inc.

7.3. Packaging

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

All 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

BIS™ Complete Monitoring System Indications for Use

The BIS™ EEG complete monitoring 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 its associated parameters are intended for use on adult 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 Alfentanil, Desflurane, Fentanyl, Isoflurane, Midazolam, Nitrous Oxide, Propofol, Remifentanil, Sevoflurane and its usage with these 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.

Currently under investigation in this study is the validation of the BIS™ index as an aid in monitoring the effects of desflurane, isoflurane, propofol and sevoflurane with balanced anesthetic techniques for adult patients.

7.5. Equipment

BIS™ Complete Monitoring System

The BIS™ Complete Monitor is an easy-to-use microprocessor-based EEG monitor. The BIS™ Complete Monitor reports a BIS value by acquiring up to two channels of EEG from sensors attached to the patient's head and performing the computations necessary to produce the BIS index. The BIS index is then numerically displayed for the clinician's use. The BIS Complete Monitoring System consists of the following components (Figure 2):

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

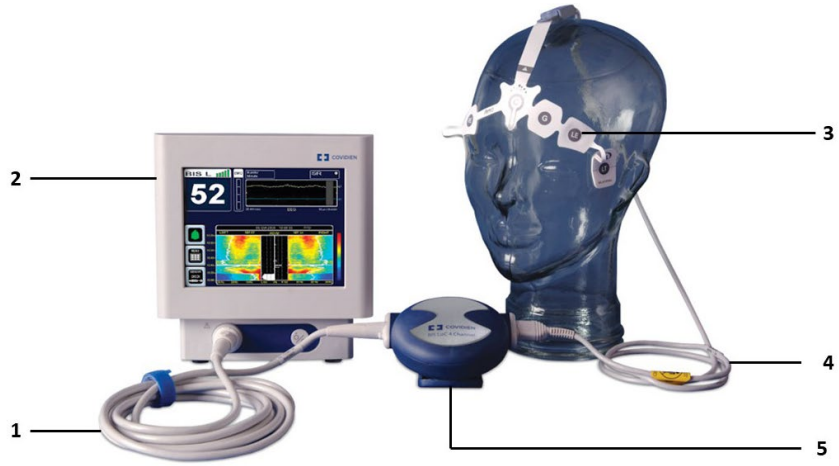

Figure 2: The BIS™ Complete Monitoring System. 1 - Monitor Interface Cable; 2 - BIS™ Monitor; 3- BIS™ bilateral sensor will be used; 4- Patient Interface Cable (PIC); 5- BISx4™ (LoC 4 Channel)

BISx4™

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.

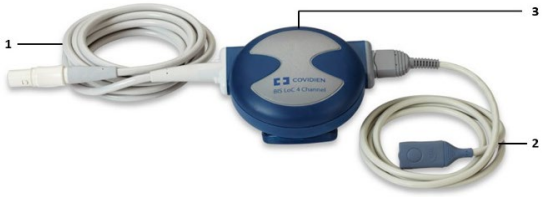

Figure 3: BISx4 - 1- Monitor Interface Cable connects to Monitor; 2- Patient Interface Cable connects to BIS sensor; 3- BISx4™ (BIS LoC 4 Channel)

Patient Interface Cable

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

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.

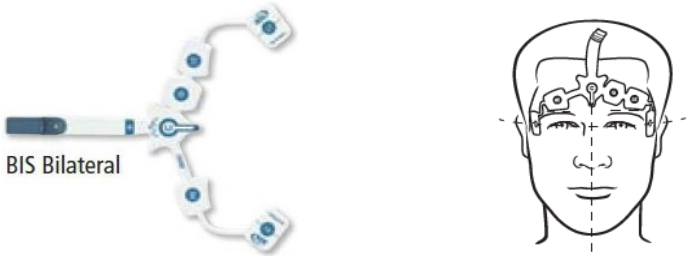

Figure 4: BIS™ Bilateral Sensor

Other Equipment

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

Site's Equipment/Supplies

Sevoflurane, isoflurane, desflurane, propofol, phenylephrine, ondansetron or other antiemetic / anti-nausea medication, lidocaine, remifentanil, and fentanyl will be provided by the site. The remifentanil and fentanyl 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. Other 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 Requirements

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 ensure any staff performing tasks related to the clinical trial (e.g., Study Coordinators, Study Nurses, Sub-Investigators, etc.) have been appropriately trained, their 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 provided by Medtronic free of charge delivery 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 outlined in this Clinical Investigation Plan. In addition, all information for the use, storage, and handling of the device/product as indicated in the Instructions for Use (IFU) and User Manual must be taken into account.

Product Return

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

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 dates of the investigational devices/products and subject identification shall be documented. At the end of the clinical study, the principal investigator must sign and date the original Product Accountability Log.

8. Study Site Requirements

8.1 Investigator / Investigation Study Site Selection

All investigators managing the subject's anesthesia must be qualified practitioners and experienced in the diagnosis and treatment of subjects undergoing anesthesia. All investigators must be 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:

- Institutional Review Board (IRB) approval (and voting list, as required by local law) of the current version of the Clinical Investigational Plan (CIP) and Informed Consent Form (ICF)
- Regulatory Authority (RA) approval or notification (as required per local law)
- Fully executed Clinical Trial Agreement (CTA)
- Financial disclosure
- Curriculum Vitae (CV) of investigators and key members of the investigation study site team

- 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

9. Selection of Subjects

9.1. Study Population

Up to 150 healthy, non-smoking (or has refrained from smoking for 2 days) volunteers, ages 18 to 60 years, will be selected for this study. In each group, subjects will be distributed across genders 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 9.3, 9.4, and 10, 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 with out-of-range vital signs and document approval 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) Use of psychoactive medication within the past 60 days (e.g., benzodiazepines, antiepileptic drugs, 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 pulmonary function test via spirometry [assessment by PI or delegate];

13) Pregnant or lactating women [assessed by urine test and self-reported];
14) Subjects with tattooed skin specific to the sensor placement areas (forehead, fingers, chest) [self-reported and assessment by PI or delegate];
15) 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 3, summarizes the intervals and data collection procedures.

Table 3: Schedule of Events

Study Tasks	Pre-Screening Phone Visit	Enrollment Visit 1	Execution Visit 2			Follow- up Phone Visit
			Pre-Procedure	Randomization	Procedure	
Eligibility Assessments						
Online or phone call pre-screening	x					
Informed Consent [1]		x				
Demographics		x				
Medical History		x				
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 signs		x	x			
Concomitant Medication		x	x			
Urine drug screen and alcohol breathalyzer			x			
Randomization to regimen group				x		
Safety Monitoring					x	
Sensors application					x	
Patient monitoring including raw data collection					x	

Procedure with drug administration					x	
BIS™, Picture Recall Test[4], MOAA/S, TES assessments					x	
Safety Assessments and Compensation						
Adverse Event Assessment [2]		x	x		x	x
Device Deficiency [3]					x	
Participant stipend			x		x	

1. Written informed consent must be obtained prior to any study-specific evaluations; for more details, refer to *Section 10.3*
2. All Adverse Events, regardless of relatedness or outcome, will be collected and reported from the time of BIS™ sensor application through 48 hours following procedure; for more details, refer to *Section 12*
3. Device Deficiency will be collected and reported; for more details, refer to *Section 12.*
4. Picture Recall Assessment will only be performed in the sevoflurane, sevoflurane with remifentanil, and sevoflurane with fentanyl groups.

10.2. Subject Pre-Screening/Screening

Patients will be pre-screened for potential enrollment in the clinical study based on prior medical history and records.

All subjects that are considered for the study should be included on the study screening log. The reason for non-eligibility, as determined by the Investigator should also be recorded on the study screening log. The screening log serves as a method for Medtronic to assess selection bias in the trial.

10.3. Subject Consent

At the enrollment visit, subjects will be approached to obtain written informed consent prior to any data collection. Once the signed and dated 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 the Institutional Review Board (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. A sample copy of the ICF will be maintained under separate cover.

The Investigator or authorized 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 authorized 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. 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;
- 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;
- Subjects able to bear children will have to attest to birth control methods;
- Adverse event review will be completed to assess events at baseline, and that occur after enrollment.

The **Enrollment** results and informed consent will stay valid for **60 days**.

10.5. Execution – Visit 2

Pre-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 volunteers will fast for at least 6 hours 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.
- Subjects of child-bearing potential will also have a urine pregnancy test done.
- Review Inclusion and Exclusion Criteria re-checked based on additional information.
- Enrollment Pass is based upon successful inclusion /exclusion criteria during Visits 1 and 2 with investigator sign-off.

Randomization

At Visit 2, all subjects who satisfy all the entry criteria will be equally randomized to each group of anesthetics regimens, stratifying by site. Randomization schedules will be created by an independent statistician, and randomization assignments will be automatically populated on the Randomization e-CRF. Once subjects are assigned to a study group, they are considered randomized. All randomized subjects should be encouraged to comply with the study procedures until the end of the study.

Procedure

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 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.

All subjects will be monitored during procedure using an electrocardiogram (ECG), Pulse Oximeter for SpO_2, and capnography (or another system) for Respiration Rate and $EtCO_2$. 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 (PI).

Regimen Set-Up

The opioids (remifentanil or fentanyl) will be administered via the target-controlled infusion (TCI) pump using either the preprogrammed pump protocols or 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 or fentanyl diluted to a single concentration of 50 µg/ml will be used in this study. The infusion rate between 0 and 1200 ml/hr will be used to achieve a targeted concentration of remifentanil and fentanyl. For remifentanil, Minto [1, 46] PK/PD model will be used. The kinetic model for fentanyl will not be weight-adjusted [2]. Phenylephrine may be provided at a concentration of 100 mcg/mL and lidocaine can be administered per Investigator discretion as a bolus over 3-5 seconds at a maximum concentration of 100mg. Antiemetic / anti-nausea medication (i.e. Ondansetron) may be used prophylactically on all subjects at the investigator's discretion.

Inhalation anesthetic drugs will be administered via a tight-fitting face mask or a laryngeal mask (LMA). Subjects will be connected to a circular breathing system of an anesthesia machine. After the subject loses responsiveness, a laryngeal mask airway (LMA) may be inserted as needed to facilitate airway control at

deeper levels of anesthesia. Inhalation agents will be administered with O_2 to maintain saturation of greater than 90%.

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. A stimulation of 2-5mA, 5 Hz for 1-5 seconds or per IFU will be provided to ensure proper application

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

MOAA/S, Picture Recall Test and Tetanic Electrical Stimulation (TES)

At each steady-state step and after equilibration, the MOAA/S assessment will be administered by an anesthesiologist. The same anesthesiologist, trained and delegated to perform the MOAA/S assessment on the Delegation of Tasks Log must perform all MOAA/S assessments for a specific subject, refer to **Appendix A.** The maximum number of delegated Anesthesiologists per site to perform the MOAA/S assessment is two in order to ensure consistency across physicians.

Subjects in the sevoflurane, sevoflurane with remifentanil and sevoflurane with fentanyl regimens will then be assessed using a Picture Recall test consisting of showing each subject a standard set of 10 pictures form the OASIS image set at each steady state and after equilibrium. The first set of control pictures will be shown prior to the administration of any anesthetics and following the initial MOAA/S assessment. The second set of control pictures will be shown at the second steady-state step following the MOAA/S assessment and the third set of control pictures will be shown at the third steady-state step following the MOAA/S assessment. If the subject is still awake at the fourth step, they will be shown a fourth set of control pictures following the MOAA/S assessment. At each step, the subject will be asked to confirm that they can see the pictures and if they are unable to open their eyes, the pictures will be shown and it will be noted that the pictures were not seen. Once the subject is deemed ready for discharge, they will be shown the 30-40 control pictures from the procedure in addition to 30 distractor pictures. It will be noted which pictures the subject was able to identify and whether they were control or distractor pictures.

Each site will be provided with 7 standardized sets of pictures. Three (3) to 4 control sets will be shown during the procedure and 3 will serve as distractors. These control and distractor sets of pictures should be switched for every other subject.

Subjects will receive noxious electrical stimulation using Tetanic Electrical Stimulation (TES) once they achieve a MOAA/S score = 0, BIS™ value < 40 at the highest concentration of anesthesia anticipated and have concluded the Picture Recall Test. 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. TES will then be initiated once the subject reaches a MOAA/S 0, BIS™ value <40 at the highest concentration of anesthesia anticipated., Stimulation will start at 20mA, 50 Hz delivered for 1-5 seconds. If the subject does not purposefully (i.e. attempting to push the stimulus away) respond, the stimulation will increase to 30mA, 50Hz for 1-5 seconds, then 40mA, 50Hz for 1-5 seconds and finally to 50mA, 50Hz for 1-5 seconds. If there is still no purposeful response, the subject will be considered a non-purposeful responder (i.e. exhibiting a reflex withdrawal, facial grimace, or groan) and their response such as withdrawal of extremity, facial grimace or other will be recorded along with the BIS™ value prior to stimulation, at the end of all assessments and approximately 2 minutes following all assessments. If the subject does respond to any of the stimulations with a purposeful response, the TES will be ended, the response will be noted and the BIS™ value will be recorded at the time TES is ended at approximately 2 minutes following the stimulation. Anesthesia will then be decreased in the same steps until subject is conscious.

Sevoflurane Group

After approximately 2 minutes of baseline measurement, sevoflurane will be administered in steps to achieve a loss of consciousness via a tight-face mask by increasing the end-tidal concentration of Sevoflurane (ET_{SEVO}). Targeted concentration for ET_{SEVO} are 0.2, 0.5, 0.7, 1, 2, 3, 4, 5% or higher until a BIS™ value not less than 30 is reached or per Investigator's discretion. The BIS™ value should

be taken to at least 40, but not intentionally below 30.. The equilibration time for each targeted concentration will be approximately 12 minutes to maintain a constant ET_{SEVO}.

The BIS™ value, MOAA/S score and picture recall test will be assessed when the patient is awake and prior to the induction of anesthetic and at the different ET_{SEVO} concentrations. TES will then be initiated once the subject reaches a MOAA/S =0 and the BIS™ value <40 at the highest concentration of anesthesia anticipated. The BIS™ value will be recorded at the time of subject's response and approximately 2 minutes following the TES assessment.

ET_{SEVO} is decreased by the same steps until consciousness is regained.

Sevoflurane with Remifentanil Group

Approximately 2 minutes prior to starting sevoflurane, to attain an effect-site targeted concentration of remifentanil of 4 ng/ml, an initial IV bolus of remifentanil will be given followed by the start of an 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.

Sevoflurane will be administered via a tight-face mask in steps to achieve a loss of consciousness by increasing the end-tidal concentration of sevoflurane (ET_{SEVO}). Targeted concentration for ET_{SEVO} are 0.2,

0.5, 0.7, 1, 2, 3, 4, 5% or higher until a BIS™ value not less than 30 is reached or per Investigator's discretion. The BIS™ value should be taken to at least 40, not intentionally below 30.

The equilibration time for each targeted plateau will be approximately 12 minutes. The BIS™ value, MOAA/S score and picture recall test will be assessed when the patient is awake and at the different ET_{SEVO} concentrations. TES will then be initiated once the subject reaches a MOAA/S = 0 and the BIS™ value < 40 at the highest concentration of anesthesia anticipated. The BIS™ value will be recorded at the time of subject's response and approximately 2 minutes following the TES assessment.

ET_{SEVO} is decreased by the same steps until consciousness is regained.

The cardiac output will be monitored, and subjects could be discontinued per PIs discretion. The respiratory rate of 4 breaths/min or less will be considered evidence of remifentanil-induced respiratory depression, and remifentanil will be discontinued.

Sevoflurane with Fentanyl Group

Approximately 2 minutes prior to starting sevoflurane, to attain an effect-site targeted concentration of fentanyl of 2 ng/mL, an initial IV bolus of fentanyl will be given followed by the start of an infusion. Approximately within 10 minutes, the infusion rate of fentanyl may be adjusted to maintain the effect-site concentration of fentanyl of 2 ng/ml.

Sevoflurane will be administered via a tight-face mask in steps to achieve a loss of consciousness by increasing the end-tidal concentration of sevoflurane (ET_{SEVO}). Targeted concentration for ET_{SEVO} are 0.2, 0.5, 0.7, 1, 2, 3, 4, 5% or higher until a BIS™ value not less than 30 is reached or per Investigator's discretion. The BIS™ value should be taken to at least 40, but not intentionally below 30.

The equilibration time for each targeted plateau will be at least 12 minutes.

The BIS™ value, MOAA/S score and picture recall test will be assessed when the patient is awake and at the different ET_{SEVO} concentrations. TES will then be initiated once the subject reaches a MOAA/S = 0 and the BIS™ value < 40 at the highest concentration of anesthesia anticipated. The BIS™ value will be recorded at the time of subject's response and approximately 2 minutes following the TES assessment. ET_{SEVO} is decreased by the same steps until consciousness is regained.

The cardiac output will be monitored, and subjects could be discontinued per PIs discretion. The respiratory rate of 4 breaths/minute or less will be considered evidence of fentanyl-induced respiratory depression, and fentanyl will be discontinued.

Desflurane Group

Due to desflurane being a volatile agent and not well tolerated as an induction agent, an initial IV bolus of 1% propofol provided at 2mg/kg, with supplemental boluses given at the investigators discretion in

order to achieve LMA insertion, will be administered 0-15 minutes prior to desflurane. Per Investigator's discretion and allowed by subject safety, once correct LMA placement has been confirmed, there will be an equilibrium time of approximately 15-20 minutes to allow the effect site concentration of propofol to reach a level consistent with a pharmacodynamic effect of consciousness as measured by a MOAA/S score of 2 or 3. Desflurane will then be administered via a tight-face mask at the targeted end-tidal concentration (ET_{DES}) of 2, 5, 7, 8, 9, 10 %, or higher 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 plateau will be approximately 12 minutes. The BIS™ value and MOAA/S score will be assessed when the patient is awake and at the different ET_{DES} concentrations. TES will then be initiated once the subject reaches a MOAA/S = 0 and the BIS™ value < 40 at the highest concentration of anesthesia anticipated. The BIS™ value will be recorded at the time of subject's response and approximately 2 minutes following the TES assessment.

The BIS™ value will be correlated with desflurane ET_{DES} concentration. LMA should be removed at the highest level of sedation while maintaining subject's safety in order to allow for a gradual emergence from anesthesia. ET_{DES} is decreased by the same steps until consciousness is regained.

Isoflurane Group

Due to isoflurane being a volatile agent and not well tolerated as an induction agent, an initial IV bolus of 1% propofol provided at 2mg/kg, with supplemental boluses given at the investigators discretion in order to achieve LMA insertion, will be administered 15-20 minutes prior to isoflurane. Per Investigator's discretion and allowed by subject safety, once correct LMA placement has been confirmed, there will be an equilibrium time of approximately 15-20 minutes to allow the effect site concentration of propofol to reach a level consistent with a pharmacodynamic effect of consciousness as measured by a MOAA/S score of 2 or 3. Isoflurane will be administered via a tight-face mask in steps to achieve a loss of consciousness (MOAA/S of 0,1) by increasing the end-tidal concentration of Isoflurane (ET_{ISO}). Targeted concentration for ET_{ISO} are 0.25, 0.5, 0.75, 1, 1.5% or higher until a BIS™ value not less than 30 is reached or per Investigator's discretion. The BIS™ value should be taken to at least 40, but not intentionally below 30.

The equilibration time for each targeted concentration will be approximately 12 minutes to maintain a constant ET_{ISO}. The BIS™ value and MOAA/S score will be assessed when the patient is awake and at the different ET_{ISO} concentrations. TES will then be initiated once the subject reaches a MOAA/S = 0 and the BIS™ value < 40 at the highest concentration of anesthesia anticipated. The BIS™ value will be recorded at the time of subject's response and approximately 2 minutes following the TES assessment.

The BIS™ value will be correlated with desflurane ET_{ISO} concentration. LMA should be removed at the highest level of sedation while maintaining subject's safety in order to allow for a gradual emergence from anesthesia. ET_{ISO} is decreased by the same steps until consciousness is regained.

eCRF Data Collection

The start time of any drug infusion, target effect-site concentrations, infusion rate, the start and end times of the assessments including BIS™ value prior to and after MOAA/S and TES assessments 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.

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

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, phone, email or text, should be made to contact 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. For device-related events refer to *Section 12* . Adverse events occurring from the time of BIS™ sensor application to 48 hours after the procedure will be recorded. For AEs and AE reporting requirements, refer to *Section 12*.

10.9. Recording Data

The study will utilize the electronic Case Report Forms (eCRFs) in a database provided by the Sponsor. All eCRFs will be completed using the assigned subject identification number.

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. 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;
- Serious Adverse Event/Serious Adverse Device Effect/Unanticipated Adverse Device Effect /Unanticipated Serious Adverse Device Effect reporting (*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.

10.11. Subject Exit, Withdrawal or Discontinuation

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) refer to *Section 9.6*.

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.

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.

11.2. 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.
- 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.

11.3. BIS™ Monitoring System Risks

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.

11.4. XAVANT STIMPOD™ Quantitative NMT Monitor

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.

11.5. Nellcor™ Pulse Oximeter

Nellcor™ Pulse Oximetry will be used per IFU. Some warnings are listed below, for more information on warnings and cautions refer to IFU.

- 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.

11.6. General Anesthesia Risks

There are some risks associated with general anesthetics, but the anesthetics under study 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, and difficulty passing urine. These may occur despite the best efforts to avoid them. For additional information related to potential medication, risks refer to **Table 4**.

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 anesthesiologist will be present to minimize all risks related to anesthesia.

Table 4: Possible Side Effects using Medication

Possible side effects of remifentanil but not limited to:	Less common side effects of 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	• Bluish lips or skin • Chills • Decreased cardiac output • Fast, pounding, or heartbeat or pulse • Feeling of warmth • Fever • Headache • Nausea or vomiting

• 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 • Itchiness	• 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
Possible side effects of fentanyl but not limited to: • Black, tarry stools • Blurred vision • Chest pain • Confusion • Convulsions • Cough • Decreased urine • Difficult or labored breathing • Dizziness • Dry mouth • Fainting • Fever or chills • Increased thirst • Irregular heartbeat • Lightheadedness • Loss of appetite • Lower back or side pain • Mood changes • Headache • Muscle pain or cramps • Nausea or vomiting • Nervousness • Numbness or tingling in the hands, feet, or lips • Painful or difficult urination • Pale skin • Pounding in the ears • Rapid breathing • Sneezing • Sore throat • Sunken eyes • Swelling of the hands, ankles, feet, or lower legs • Tightness in the chest • Troubled breathing with exertion • Ulcers, sores, or white spots in the mouth	Less common side effects of fentanyl but not limited to: • Abdominal or stomach pain • Change in walking and balance • Clumsiness or unsteadiness • Decreased awareness or responsiveness • Decreased frequency of urination • Headache • Muscle twitching or jerking • Pounding in the ears • Rhythmic movement of the muscles • Seeing, hearing, or feeling things that are not there • Seizures • Severe constipation • Severe sleepiness • Shakiness in the legs, arms, hands, or feet • Slow or fast heartbeat • Thinking abnormalities • Trembling or shaking of the hands or feet

• Unusual tiredness or weakness • Wrinkled skin	
Possible side effects of sevoflurane but not limited to: • cough • Dizziness • Drowsiness • Increased amount of saliva • Nausea /vomiting • Shivering • Laryngospasm • Airway obstruction • Breath holding • Apnea • Respiratory disorder • Headache • Hypotension • Hypertension • Agitation • Bradycardia • Hypotension • Bradycardia • Tachycardia • Malignant hyperthermia	Less common side effects of sevoflurane but not limited to: • Dry mouth • Arrhythmia, ventricular extrasystoles, supraventricular extrasystoles, complete AV block, bigeminy, inverted T wave, atrial fibrillation, atrial arrhythmia, second degree AV block, S-T depressed, extrasystoles • Sputum increased, hypoxia, wheezing, bronchospasm, hyperventilation, pharyngitis, hiccup, hypoventilation, dyspnea, stridor, hypoxia, asthma • Pulmonary edema • Increases in LDH, alkaline phosphatase, hypophosphatemia, acidosis, hyperglycemia • Blood glucose abnormal • Urination impaired, urine abnormality, urinary retention, oliguria • Rash • Muscle twitching • Syncope, hypertonia, taste perversion • Seizures, dystonia • Asthenia, pain, fluorosis • Allergic reactions
Possible side effects of desflurane but not limited to: • Bluish lips or skin • Body aches or pain • Congestion • Cough • Dryness or soreness of the throat • Fever • Hoarseness • Not breathing • Runny nose • Tender, swollen glands in the neck • Tightness in the chest • Trouble breathing • Trouble swallowing • Voice changes	Less common side effects of desflurane but not limited to: • Blurred vision • Chest pain or discomfort • Dizziness • Fast, pounding, or irregular heartbeat or pulse • Headache • Lightheadedness, dizziness, or fainting • Nervousness • Pounding in the ears • Slow or irregular heartbeat • Unusual tiredness • Allergic reactions
Possible side effects of isoflurane but not limited to: • Nausea • Vomiting • Shivering	Less common side effects of isoflurane but not limited to: • Dose-dependent hypotension • Arrhythmias • Malignant hyperthermia • Elevations in white blood cells • Decrease in creatinine and increase BUN

	• Ileus, severe • Hepatic dysfunction • Respiratory depression
Possible side effects of 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 • Hypertriglyceridemia • Hypertension • Rash • Pruritus • Arrhythmia • Bradycardia • Cardiac output decreased concurrent opioid use increases incidence) • Tachycardia	Less common side effects of propofol but not limited to • Arterial hypotension • Anaphylaxis • Asystole • Bronchospasm • Cardiac arrest • Seizures • Opisthotic rxn • Pancreatitis • Pulmonary edema • Phlebitis • Thrombosis • Renal tubular toxicity • Allergic reactions
Possible side effects of lidocaine but not limited to • Hypotension • Edema • Injection site burning/stinging/pain • Small purple or red spots on skin • Skin irritation • Constipation • Nausea • Vomiting • Confusion • Dizziness • Headache • Numbness and tingling • Drowsiness • Tremor •	Less common side effects of lidocaine but not limited to • Cardiac Arrest • Abnormal Heartbeat • Methemoglobinemia • Seizures • Severe allergic reaction • Malignant hyperthermia
Possible side effects of phenylepherine but not limited to • Blurred vision • Chest pain or discomfort • Difficult or labored breathing • Dizziness • Fainting • Fast, slow or irregular heartbeat • Headache • Nausea or vomiting • Nervousness • Pain in shoulders, arms, jaws or neck • Pounding in the ears	Less common side effects of phenylepherine but not limited to • Feeling of fullness in the head • Pounding or rapid pulse • Tingling in the arms or legs • Vomiting

• Sweating • Tightness in the chest • Unusual tiredness	
Possible side effects of ondansetron but not limited to • headache • constipation • weakness • tiredness • chills • drowsiness	Less common side effects of ondansetron but not limited to • blurred vision or vision loss • rash • hives • itching • swelling of the eyes, face, lips, tongue, throat, hands, feet, ankles, or lower legs • hoarseness • difficulty breathing or swallowing • chest pain • shortness of breath • dizziness, light-headedness, or fainting • fast, slow or irregular heartbeat • agitation • hallucinations (seeing things or hearing voices that do not exist) • fever • excessive sweating • confusion • nausea, vomiting, or diarrhea • loss of coordination • stiff or twitching muscles • seizures • coma (loss of consciousness)

11.7. 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.

11.8. 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 investigational device 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 investigational device 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;

[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 investigational device 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 investigational device does not otherwise present a potential for serious risk to the health, safety, or welfare of a subject.

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 definitions are provided in **Table 5**. AEs will be collected throughout the study from the BIS™ sensor application through 48 hours following procedure. A list of anticipated adverse events and risks that are expected in nature is included in Section 11.

Adverse Event 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.
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 6), initial reporting may be done by phone, fax, or on the CRF completing as much information as possible. The completed AE CRF must be submitted to Medtronic as soon as possible.

Any medication/treatment associated with the treatment of an AE must be reported.
Subject deaths are also required to be reported.

12.2. Device Deficiency

The DD definition is provided in **Table 5**. DD information will be collected throughout the study and reported to Medtronic. Note that DD that result in an AE to the subject should be captured as an AE only.

DD that did not lead to an AE but could have led to a SADE (i.e., if suitable action had not been taken, if intervention had not been made, or if the circumstances had been less fortunate) require immediate reporting (see **Table 5**).

12.3. Processing Updates and Resolution

For any changes in status of a previously reported adverse event or DD (i.e. change in actions taken, change in outcome, change in relatedness), information needs to be updated on, or added to the original AE or DD form. All AEs must be followed until the AE has been resolved, is unresolved with no further actions planned, the subject exits the study, or until study closure, whichever occurs first.

In the event that a subject is exited from the study prior to study completion, all efforts should be made to continue following the subject until all unresolved system or procedure related AEs, as classified by the investigator, are resolved, unresolved with no further actions planned, or 30 days post follow up phone call.

At the time of study exit, all collected adverse events that are unresolved must be reviewed and an update to the original AE must be reported.

12.4. Definitions/Classifications

Table 5: Adverse Event and Device Deficiency Definitions

General	
Adverse Event (AE)	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 and whether anticipated or unanticipated 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. (ISO 14155:2020, 3.2)
Adverse Device Effect (ADE)	AE related to the use of an investigational medical device NOTE 1: This definition includes AEs 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 an error use or from intentional misuse of the investigational medical device. NOTE 3: this includes 'comparator' if the comparator is a medical device. (ISO 14155:2020, 3.1)
Device Deficiency (DD)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance. NOTE 1: DD include malfunctions, use errors and inadequacy in the information supplied by the manufacturer including labeling.

	NOTE2: This definition includes device deficiencies related to the investigational medical device or the comparator. (ISO 14155:2020, 3.19)
Relatedness	
Procedure Related	An AE that occurs due to any procedure.
Seriousness	
Serious Adverse Event (SAE)	AE that led to any of the following a) death, b) serious deterioration in the health of the subject, users or other persons as defined by one or more of the following: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, including chronic disease, or 3) in-patient 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) fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered an SAE. (ISO 14155:2020, 3.45)
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. (ISO 14155:2020, 3.44)

12.5. Reporting of Adverse Events

12.5.1 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 7** 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 6: Adverse Event Classification Responsibilities

What is classified?	Who classifies?	Classification Parameters
Relatedness	Investigator	Device, Procedure
	Sponsor	Device, Procedure
Seriousness	Investigator	SAE, DD with SADE potential
	Sponsor	SAE, UADE/USADE, Complication or Observation (for all system or 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

12.5.2 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 7: Reporting Requirements

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.

Study Contact Information:

Clinical Affairs	Medical Affairs

Ami Stuart, PhD Clinical Study Manager Medtronic 6135 Gunbarrel Avenue Boulder, CO 80301 Phone: (801) 793-4800 ami.stuart@medtronic.com	Sam Ajizian, MD Chief Medical Officer-Patient Monitoring Medtronic 350 Cedar Trail Winston-Salem, NC 27104 Phone: (336) 749-8557 sam.ajizian@medtronic.com

12.6 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.

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

Neither a Data Monitoring Committee (DMC) nor an Adverse Events Advisory Committee (AEAC) will 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

The 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

A two-stage adaptive design is used in this study. For each regimen, 10 subjects will be enrolled in stage 1, and upon evaluation, up to 20 additional subjects will be enrolled in stage 2. With 5 regimens, a maximum of 150 subjects will be expected. 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

All randomized subjects will be included in the analysis. For those subjects who do not complete a follow-up call, the analysis will include all data up to the last collected point or follow-up call. Subjects who completed the procedure phase will not be replaced. If the subject discontinues prior to randomization or during the procedure phase, she/he will be replaced, but will count toward the total sample size if they were randomized.

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 scores of 2, 3, 4, and 5 will be considered as responsive. Subjects with MOAA/S assessment scores of 0 and 1 will be considered unresponsive. Tetanic Electrical Stimulation (TES) will be employed with an MOAA/S assessment score of ≤2 for the first two subjects in each group and <2 for all other subjects.

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 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.

14.4. Interim Review

The interim review will be performed at the end of stage 1, when all (50 subjects 10 subjects per regimen group) subjects have completed the evaluation. BIS™ values will be estimated using the Hill equation. One or more regimens may be dropped upon interim results for safety concerns (unacceptable safety events per clinical judgment).

For the final analysis, data from stage 1 and stage 2 will be combined by further taking into account pool-ability across sites and the adaptive nature of the 2-stage design (e.g., Bayesian integration with power prior and discounting function). Technical details will be specified in the SAP.

15. Ethics

15.1. Statement(s) of Compliance

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

- The Declaration of Helsinki (2013) and local laws and regulations of the countries in which the clinical study is conducted, including data protection laws, the Clinical Trial Agreement, Good Clinical Practice (GCP) E6 and regulatory requirement(s), including 21 CFR 803, 21 CFR 812.2, 21 CFR 50, 21 CFR 56. FDA Financial Disclosure regulations, 21 CFR 54, and this Clinical Investigational Plan.
- All principles of the Declaration of Helsinki have been implemented in this clinical study by means of the informed consent process, IRB approval, clinical study training.
- 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 or regulatory authority (if applicable) approval/ notification is received. Written IRB approval and any conditions of approval imposed by the IRB must be submitted to the Sponsor.

- If the IRB or other regulatory authorities impose any additional requirements (e.g., safety reports, progress reports, etc.), Medtronic will prepare the required documents and send them to the respective authority.

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 onsite or remotely to ensure:

- Overall compliance with the protocol, GCP, and the applicable regulations.
- Accurate records are being maintained.
- 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.
- Informed consent has been obtained for all study subjects.
- Adverse events and protocol deviations are documented and reported.
- 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.

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.

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 the study sponsor and authorized sponsor's representatives, 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

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 a CRF, 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.

16.3. Direct Access to Source Data/Documents

The principal investigator(s), his/her delegate(s), and the study coordinator(s) shall be accessible to Medtronic field personnel and the Clinical Study Manager. This accessibility is of particular importance for reviewing data on the electronic Case Report Form (eCRF). Direct or remote access to subject medical files for source data verification will need to be granted and prepared prior to any monitoring visits.

16.4. Confidentiality

All records and other information about subjects participating in this study will be treated as confidential. The identity of a subject will never be disclosed in the event that study data are published.

Subject confidentiality will be maintained throughout the clinical study in a way that ensures the information can always be traced back to the source data. For this purpose, a unique subject identification code will be assigned and used to allow identification of all data reported for each subject.

Regulatory authorities and the IRB may also be granted direct access to the medical history records in order to comply with legal and regulatory requirements. Investigators are to instruct their staff in the methods and importance of maintaining subject confidentiality according to local and national regulations and institutional requirements.

16.5. 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.

16.6. 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.

16.7. Record Retention

16.7.1 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 ICF
  - Observations of AEs/ADEs/DDs
  - Medical history
  - Documentation of the dates and rationale for any deviation from the protocol
- Randomization list
- List of investigation study sites
- Financial Disclosure (FD)
- Subject screening log & ID log
- Normal value(s)/range(s) for clinical laboratory test (if applicable)
- Lab certificate
- Device Disposition Logs containing Model and serial numbers of devices delivered to the study site, subject IDs of the subjects implanted, received dates of devices, implant/used dates, explant dates, returned-to-sponsor dates and reasons, initials of all persons who received, used or disposed each device, and method of disposal/destruction.
- All approved versions of the CIP, ICF
- Signed and dated CTA.
- 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.
- Regulatory Authority (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.

16.7.2 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
- All approved ICF templates, and other information provided to the subjects and advertisements, including translations
- Randomization records
- 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, IB/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.

16.8. Reporting Requirements

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. The investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in this section.

Table 8: Investigator reports applicable for all geographies per Medtronic requirements

Report	Submit to	Description/Constraints
UADE	Sponsor	An investigator shall submit to the sponsor and to the reviewing IRB a report of any UADE occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. (21 CFR 812.150(a))
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.

Sponsor Reports

Medtronic shall prepare and submit the following complete, accurate, and timely reports (by geography). Medtronic shall, upon request of the reviewing IRB, RA or FDA, provide accurate, complete and current information about any aspect of the investigation. Safety data Medtronic reporting requirements are listed in Section 12.

16.9. 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.

While study results are owned by the Sponsor, all data on which a publication is based will be made available to all authors as required for their participation in the publication processes. Furthermore, 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.

The number of authors will be dependent on the regulations of the concerning journal. 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 relevant intellectual content and final approval of the version to be published. Names of all participating investigators will appear in the Acknowledgment of the paper.

The publication of sub-studies, post-hoc analyses, regional results, or single-center experiences based on multicenter clinical studies should not precede that of the primary multicenter publication and should cite the primary publication whenever possible, as required by specific journal and scientific meeting guidelines.

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.

16.10. Suspension or Early Termination

The Sponsor reserves the right to discontinue the study at any stage, with written notice to all investigators, all reviewing IRBs. 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.)

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 Observer Assessment of Alertness/Sedation (OAA/S) Scale [47]	
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 prodding or shaking	2
Responds only after painful trapezius squeeze	1

Does not respond to painful trapezius squeeze	0

Appendix B – Open Affective Standardized Image Set (OASIS)

Pictures attached as zip file due to size.

Appendix C – NCM Sub-Study – Non-Contact Depth-Sensing Respiratory Monitoring

All subjects enrolled in MDT19053OLIVER Study (Main Study) may be invited to participate in the product development sub-part of the study. The purpose of this non-contact monitoring sub-study (NCM Sub-Study) is to collect data for further exploration of a non-contact physiological monitoring system based on depth-sensing camera technology.

Medtronic is continuously improving its monitoring devices to improve performance and widen the range of capabilities. In order to develop and assess a newly developed technology, the NCM Sub-Study is executed to collect data to show early feasibility and proof of concept for novel non-contact monitoring technology.

Background
Recently, Medtronic has worked on depth-sensing technologies where the distance from the camera to objects within the field of view is captured and used to produce physiological information, including airway resistance, heart rate, respiratory rate, volume change, and apnea events. Depth sensing cameras produce grayscale images where the intensity of pixels corresponds to the distance from the camera. Color mapping can be used to create false color images where the colors correspond to the distance from the camera, an example of which is contained in Figure 5.

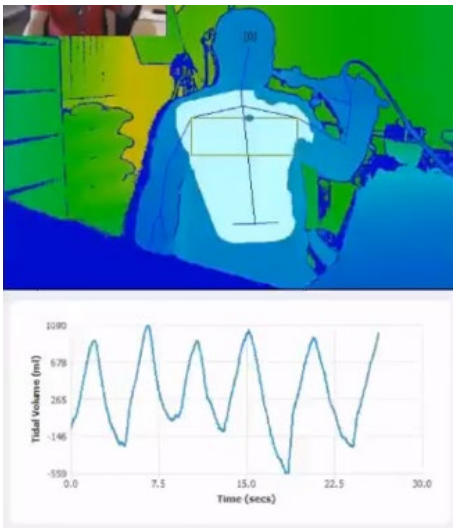

Figure 5: A false color depth image where a subject can be identified. A light blue mask indicates the torso region of interest (ROI) from where the volume change signal is computed. The volume change signal is shown in the lower part of the figure.

From this image, we have developed a technology to automatically superimpose a mask on the torso of the subject (as shown in Figure 5) from which we can measure distances from the camera over time. By integrating the change in the distance on the torso region of interest (ROI) over time, we can provide a real-time estimate of tidal volume change as the lungs expand and contract during inhalation and exhalation, respectively. An example of this calculated volume change signal is shown at the bottom of Figure 5. The volume change signal can then be converted to a tidal volume per breath and a respiratory rate (and hence minute volume).

From the volume change signal, we can extract a variety of physiological parameters, including tidal volume (peak-to-trough amplitude of the volume change signal), respiratory rate (frequency of volume change signal modulations), individual breath period and corresponding inhalation/exhalation (I/E) ratio, minute volume, etc. We can also extract a volume change signal from the chest and abdomen regions separately from which an indication of out of phase breathing, indicative of obstructive apnea, can be derived (as shown in Figure 6). The technology also detects cessation of breathing, talking, and coughing.

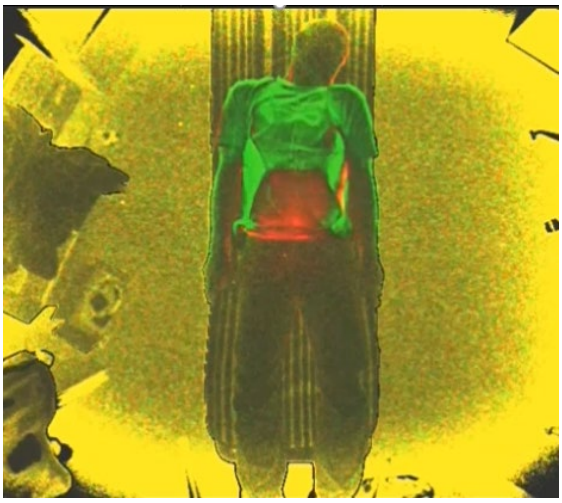

Figure 6: Paradoxical breathing shown on a subject's torso. Green indicates regions where the subject torso is moving towards the camera. Red indicates regions where the subject torso is moving away from the camera. Yellow/black indicates non-moving regions.

Objective

To collect depth-sensing video and respiration waveform signal data to explore the feasibility of non-contact respiratory monitoring technology.

Product Description

The RealSense D415 depth camera system (manufactured by INTEL™) is a non-contact camera technology for determining distances of objects in a scene using infrared sensing technology. It is a consumer product developed by INTEL™. Other commercially available depth-sensing systems may be employed in the study, (for example, the Microsoft™ Kinect Azure or Microsoft™ Kinect V2, INTEL RealSense D435, INTEL™ RealSense L515, Stereolabs™ ZED depth-sensing cameras or similar). Cameras may be used off-the-shelf, and no modifications to the actual product are required.

Study Visit (Main Study Visit 2)

For the subject who enrolled in the main study and consented to participate in NCM Sub-Study:

- Non-contact monitoring (NCM) camera will be placed 1.0 – 2.5 m from the subject (on a tripod or attached to the trolley, etc.) prior to the administration of any drugs and assessment for the Main Study.
- Make sure the subject is in view of the NCM camera and start recording.
- If non-contact monitoring equipment malfunctions, the Main Study will continue without stopping or interference from the NCM sub-part.
- Exact placement and distance of the cameras should be documented on the paper CRF.

- Raw non-contact monitoring data will be provided to Medtronic.

Analysis

The collected data from a pulse oximeter, capnography, and depth-sensing camera equipment will be used to develop a real-time non-contact respiratory monitoring system. Data will be analyzed and post-processed for this purpose. Additional analysis may be performed as necessary.

19. Version History

Version	Summary of Changes	Author(s)/Title
1.0	Not Applicable, New Document	Julia Katilius, Ph.D./ Sr. Clinical Program Manager Stephanie Monza, BS, CCRC Sr. Clinical Research Specialist
2.0	• Addition of Picture Recall Test • Changed TES assessment from one stimulation to 4 graduated stimulations • Added UADE reporting requirements to address GAP identified in versioning • Clarification of Adverse Events collection time period • Clarification of Anesthesiologists permitted to perform MOAA/S assessment	Stephanie Monza, BS, CCRC Sr. Clinical Research Specialist
3.0	• Change of procedure to increase anesthesia until a BIS™ value of 30 is reach or per Investigator's discretion • Clarification of Statistical Plan • Pictures used in Picture Recall Test changed to OASIS	Stephanie Monza, BS, CCRC Sr. Clinical Research Specialist
4.0	• Clarification of Picture Recall Assessment • Change of Anesthesia amounts to align to anesthesia device delivery amounts • Additional step of sevoflurane due to incidence of hypotension • Addition of use of lidocaine to decrease discomfort to subjects • Change of timing of TES assessment to ensure adequate sedation • Addition of phenylephrine to prevent hypotension • Addition of NCM sub-study	Stephanie Monza, BS, CCRC Sr. Clinical Research Specialist
5.0	• Change in administration of phenylephrine to be at the investigator's discretion	Ami Stuart, PhD, MSCI Sr. Clinical Research Specialist

	• Addition of ondansetron to prevent emesis / nausea administered at the investigator's discretion • Update of contact information for Clinical Affairs	