Medtronic

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	Bispectral Index and End-Tidal Anesthetic Gas Concentration in Pediatric Patients undergoing Sevoflurane Anesthesia (BTIGER)
Clinical Investigation Plan Identifier	MDT20032BTIGER
Study Product Name	BIS Complete Monitoring System
Sponsor/Local Sponsor	Medtronic Patient Monitoring & Respiratory Interventions 6135 Gunbarrel Avenue, Boulder, CO 80301 U.S.A.
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2. Glossary

Term	Definition
ADE	Adverse Device Effect
AE	Adverse Event
ASA	American Society of Anesthesiology
BIS™	Bispectral Index (BIS) technology monitoring uses processed EEG signals to measure sedation depth based on the level of consciousness
CFR	Code of Federal Regulation
CIP	Clinical Investigation Plan
CNS	Central Nervous System
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
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
DD	Device Deficiency
DoH	Declaration of Helsinki
DTL	Delegated Task List
ECG	Electrocardiogram. A diagnostic tool that measures and records the electrical activity of the heart
eCRF	Electronic Case Report Form
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

Term	Definition
ET	End-tidal concentration
EMR	Electronic Medical Record
$EtCO_2$	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
HR	Heart Rate
ICF	Informed Consent Form
IFU	Instructions for Use
IRB	Institutional Review Board
ISF	Investigator Site File
LMA	Laryngeal mask
LOC	Level of consciousness
NSR	Non-Significant Risk
PHI	Protected Health Information
PI	Principal Investigator
PIC	Patient Interface Cable
PK/PD	Pharmacokinetics and pharmacodynamics
RA	Regulatory Authority
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SpO_2	A non-invasive spectroscopic estimate of arterial oxygen saturation measured transcutaneously by a pulse oximeter

Term	Definition
SOC	Standard Of Care
SOP	Standard Operating Procedures
SQI	Signal Quality Index
UADE	Unanticipated Adverse Device Effect

3. Synopsis

Title	Bispectral Index and End Tidal Anesthetic Gas Concentration in Pediatric Patients undergoing Sevoflurane Anesthesia (BTIGER)
Clinical Study Type	Post-Market Pivotal /IDE Study
Product Name	BIS™ Complete Monitoring System
Sponsor	Medtronic, Patient Monitoring & Respiratory Interventions 6135 Gunbarrel Avenue Boulder, CO 80301
Indication under investigation	Intended for use in pediatric patients (4 years old and above)
Investigation Purpose	The purpose of this study is to investigate the relationship between BIS™ values including EEG profile and anesthetic agents in the pediatric population
Product Status	BIS™ is commercially available in the United States
Primary Objective(s) and/or Endpoint(s)s	Primary objective: To characterize BIS™ performance with the anesthetic agent in pediatric patients ages 4 to 18 years Primary endpoint: The end-tidal sevoflurane concentration in both patient groups acquired during maintenance of anesthesia. The study will be considered a success if the primary objective, achieving statistical and clinical significance in obtaining the end-tidal sevoflurane concentration during maintenance in both patient groups, is achieved.
Secondary Objective(s) and/or Endpoint(s)	Secondary endpoint(s): • Recovery assessments in patients receiving monitoring compared to standard anesthetic practice (instructions for collection contained in **Study Procedures and Assessments**):

	• Emergence
	• Emergence is defined as the time when any of the following first occurred:
	• Eyes open spontaneously
	• Crying or phonating
	• Purposeful movements
	• PACU discharge readiness using Modified Aldrete Score [15,16]
	• Anesthesia Airway Management (AAM) will be noted:
	  ○ Awake and Deep Extubation (endotracheal tube (EET) vs. laryngeal mask airway (LMA)
	  ○ Airway reflexes (e.g., coughing, choking, laryngospasm)
	Additional/Exploratory Endpoints:
	• Clinical Anesthesia Assessment, recorded as the incidence of movements, grimacing, eye opening, tearing, sweating, mydriasis and cardiovascular changes while undergoing anesthesia
	• Pediatric Anesthesia Emergence Delirium (PAED)
	• Wong-Baker FACES Pain Rating Score

Study Design	This is a multi-center, prospective, observational, non-invasive, randomized controlled study to collect data to compare the performance of standard practice (SP) group with the BIS™ monitoring (BIS) group. Pediatric patients between the ages of 4 to 18 years undergoing routine sevoflurane general anesthesia with an expected maintenance duration of greater than 30 minutes will be recruited. If the maintenance duration is less than 25 minutes, the data will continue to be collected, but will not be included in the data analysis and the subject will be replaced with an additional subject. General surgeries including abdominal, urological, orthopedic, ophthalmological or other procedures approved by the Medtronic study team with an American Society of Anesthesiologists physical status of I - III. Children will be recruited from the preoperative clinic and will be divided into three age groups • 4 to 8 years • 9 to 12 years

	• 13 to 18 years A training group comprising of the first 2 - 4 subjects at each site will be enrolled to train the site team on the new technology and to determine the quality of data collection prior to randomization. Afterward, randomization will proceed based on the Sponsor's assessment of data quality. **For the BIS™ group**, sevoflurane will be titrated to achieve a target BIS™ value of 45 – 60 during maintenance of anesthesia and a target BIS™ value of 60 – 75 beginning at the start of skin closure. In order to protect against inadequate or excessive anesthesia in the BIS™ guided group, the subject will be assessed approximately every 5 minutes for signs of anesthesia. In the event of hypertension and/or tachycardia (>20% above baseline) unexplained by surgical manipulation and or signs of autonomic or somatic responses (e.g., diaphoresis, movement) an additional dose of opioid will be administered. If that does not resolve the situation, then the anesthesiologist may alter the anesthetic concentration outside the BIS™ guidelines to assure adequate anesthesia. In the event of hypotension and/or bradycardia (>20% below baseline), fluids and/or vasopressor will be administered. If that does not resolve the situation, then the anesthesiologist may alter the anesthetic concentration outside the BIS™ guidelines. Subjects with BIS™ values that are outside of the specified range of 45 – 60 during maintenance of anesthesia for >35% of the maintenance duration will be considered a protocol deviation and the subject will be excluded from the final data analysis. The subject will be replaced by an additional enrolled subject. The excluded subject will continue to be monitored for any safety events and the clinician will ensure medical care is provided for any safety event that occurs. Data from excluded subjects will be acknowledged in the final study report but will not be included in the primary statistical analysis. The exception to this exclusion is any data that is outside of the specified range of 45 – 60 as a result of the anesthesiologist titrating sevoflurane as a result of clinical signs or cardiovascular changes defined above. The end-tidal sevoflurane concentration will be continuously recorded. Fentanyl or morphine will be administered at the discretion of the anesthesiologist, for example, 1.5 mcg/kg at induction and 0.75 mcg/kg every 30 minutes in accordance with usual clinical indications. **For the SP group**, sevoflurane, fentanyl, propofol, and morphine will be administered at the discretion of the anesthesiologist for example, fentanyl and morphine at 1.5 mcg/kg at induction and 0.75 mcg/kg every 30 minutes in accordance with usual clinical indications.

Randomization	Subjects will be randomized 1:1 within each age group and each site to one of the two groups, standard practice (SP) or BIS™ (BIS) groups.
Sample Size	The first 2 - 4 subjects at each site will be enrolled to train the site team on the new technology and to determine the quality of data collection prior to randomization (n = 16-32). They will not be randomized and will not be included in the final analysis. For the analysis, a minimum of 36 subjects are required in each age group (18 per treatment group) for a minimum of 108 qualifying data sets. Subjects with non-qualifying data sets will be rejected and replaced with a newly randomized subject. This sample size was independently powered for each of the 3 age groups based on data from a previously published study conducted by Emory University.
Planned number of sites	Eight investigational sites in the US
Inclusion/Exclusion Criteria	Inclusion Criteria: 1) Pediatric Subjects (ASA PS I or II or III) aged: 4 years to 18 years scheduled for procedures with sedation where the process of assessment will not interfere with the procedure, progress, or patient care 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 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, hemiplegia, demyelinating disorders, cerebral palsy, congenital anomalies of the brain or spinal cord, or other known neurologic disorders) 3) Severe developmental delay per assessment of investigator or report of parent/guardian 4) Airway abnormalities 5) Pregnancy; subjects of childbearing potential will have a urine screen for pregnancy before surgery 6) If the process of assessment will interfere with the procedure or the progress of the procedure 7) Taking psychoactive medications

	8) Taking any medications that may have an impact on the Central Nervous System (CNS) 9) Planned use of any regional anesthesia; a local field block is not included in this exclusion and can be used at the discretion of the anesthesia provider 10) Planned use of dexmedetomidine (Precedex) 11) Refusal to participate in the study

Study Procedures and Assessments	**BIS™ Group:**
	Baseline/Enrollment Visit:
	• Informed Consent
	• Review of Inclusion/Exclusion
	• Demographics
	• Medical History
	• Pre-operative vitals obtained in pre-operative holding
	Procedure:
	• Randomization: Prior to Procedure
	• Induction and Maintenance:
	• BIS™ sensor positioning and validation of appropriate impedance of electrodes
	• Clinical Anesthesia Assessment including incidence of:
	  • Movement
	  • Grimacing
	  • Eye opening
	  • Tearing
	  • Sweating
	  • Mydriasis
	  • Cardiovascular changes
	• End of Procedure:
	  • Collection of BIS™ sensor placement, monitoring of cardiovascular variables, event markers and assessments
	• Recovery:

	• Anesthesia Airway management • Collection of incidents of post- op nausea • Pediatric Anesthesia Emergence Delirium (PAED) • Wong-Baker FACES Pain Rating Score when subject is awake • Time of PACU Discharge **SP Group:** Baseline/Enrollment Visit: • Informed Consent • Review of Inclusion/Exclusion • Demographics • Medical History • Pre-operative vitals obtained in pre-operative holding Procedure: • Randomization: Prior to Procedure • Induction and Maintenance: • BIS™ sensor positioning and validation of appropriate impedance of electrodes • Clinical Anesthesia Assessment including incidence of: • Movement • Grimacing • Eye opening • Tearing • Sweating • Mydriasis • Cardiovascular changes • BIS™ monitor concealing: done to ensure that the clinician is blinded to the BIS™ values and that the BIS™ value is not used to guide the conduct of the anesthetic. The signal quality index (SQI) number will be visible to the anesthesiologist during the case to capture a good quality signal. The details on SQI monitoring will be provided to the study site.

	• End of Procedure:
	  • Collection of BIS™ sensor placement, monitoring of cardiovascular variables, event markers and assessments
	• Recovery:
	  • Anesthesia Airway management
	  • Collection of incidents of post- op nausea
	  • Pediatric Anesthesia Emergence Delirium (PAED)
	  • Wong-Baker FACES Pain Rating Score when subject is awake
	  • Time of PACU Discharge
	
	<u>Prior to induction</u>
	The subjects will be taken into the operating room, and anesthesia delivery system will be applied per institutional guidance. Prior to the induction of anesthesia, all subjects will have an age-appropriate BIS™ sensor applied. The clinician will select the appropriate BIS™ pediatric or BIS™ QUATRO sensor based on the size and space available on the subject's forehead. The sensor will be placed on the forehead per the IFU recommendation. If the patient is not cooperative when awake, the BIS™ sensor will be placed after adequate sedation has been achieved with the use of pre-medication drugs. The choice of pre-medication, dose, and time of administration will be determined by the site anesthesiologist and will not be altered for this study, but the use of these drugs will be recorded on the eCRFs.
	
	In addition, an age-appropriate pulse oximeter sensor (reference 7.5.1) will be applied to the patient per sensor IFU. A left or right index finger is the preferred sensor site. Alternatively, the sensors can be applied to a smaller finger, thumb, or big toe. The sensor type, position, and side will be recorded on the eCRFs.
	
	<u>Monitoring and Cardiovascular Variables</u>
	Pulse oximeter, non-invasive blood pressure (NIBP), electrocardiography, and skin temperature will be collected per institutional guidance but are not mandated per the protocol. The standard monitoring procedures will be conducted per institutional recommendation. The de-identified digital copies of these files will be provided to Medtronic as available.

	Pre-surgical Cardiovascular variables (heart rate [HR]; systolic and diastolic blood pressure [BP] including hypotension; oxygen saturation; and temperature), and the BIS™ value (for the BIS™ group) will be recorded at baseline preferably before administering any pre-medication or sedatives. Cardiovascular variables will be monitored during the surgery, and any abnormal hemodynamic parameters and times will be noted. The de-identified digital copies of these files will be provided to Medtronic as available. Induction Anesthesia will be induced with sevoflurane alone, or a combination of sevoflurane and nitrous oxide (N_2O) in 100% oxygen for both groups. If nitrous oxide is used, it will be discontinued after the placement of a tracheal tube or laryngeal mask (LMA), or another airway management. If necessary, a neuromuscular blocking agent will be used to facilitate endotracheal intubation. The choice of induction medication, dose, and time of administration will be determined by the site anesthesiologist and will not be altered for this study, but the use of these drugs will be recorded on the eCRFs. If the subject is in need of a nerve block for pain management following the procedure, this block should be placed once skin closure is complete and prior to extubation. This block cannot be placed prior to skin closure. Subjects with the planned use of any regional anesthesia are excluded from this study, however if a caudal block becomes necessary for the subject during the course of the surgical procedure, data will continue to be collected on the subject, however the data will not be included in the data analysis and the subject will be replaced by an additional enrolled subject. The use of dexmedetomidine (Precedex) is prohibited from being used in this study. If it becomes necessary to use this medication during the course of the surgical procedure, data will continue to be collected on the subject, however the data will not be included in the data analysis and the subject will be replaced by an additional enrolled subject. Maintenance anesthesia **In the SP group**, sevoflurane, fentanyl, and morphine administration will be at the discretion of the anesthesiologist, for example, fentanyl

	and morphine 1.5 mcg/kg at induction and 0.75 mcg/kg every 30 minutes, using clinical signs and cardiovascular changes to adjust anesthetic concentration. **In the BIS™ group**, fentanyl and morphine administration will be at the discretion of the anesthesiologist, for example, fentanyl and morphine 1.5 mcg/kg at induction and 0.75 mcg/kg every 30 minutes, using clinical signs and cardiovascular changes, however sevoflurane will be adjusted to achieve a target BIS™ values of 45 – 60 during maintenance of anesthesia and BIS™ values of 60 – 75 beginning of skin closure. Subjects with BIS™ values that are outside of the specified range of 45 – 60 during maintenance of anesthesia for >35% of the maintenance duration will be considered a protocol deviation and the subject will be excluded from the final data analysis and will be replaced by an additional subject. The excluded subject will continue to be monitored for any safety events and the clinical will ensure that medical care is provided should a safety event occur. Data from the excluded subject will be acknowledged in the final study report but will not be included in the primary statistical analysis. The exception to this exclusion is any data that is outside of the specified range of 45 – 60 as a result of the anesthesiologist titrating medications as a result of clinical signs or cardiovascular changes defined above. Additionally, data points will be excluded if significant artifact is present or if the sevoflurane concentration or BIS™ value is missing. At the completion of the surgery, and after confirmation of the return of neuromuscular function, sevoflurane will be discontinued, and discontinuation time will be recorded, and as applicable, extubation will be performed when the patients demonstrate the purposeful movement, facial grimace, or eye-opening to jaw thrust. <u>Event Markers and Assessments</u> During the case, the time of events (for example start of induction, LOC, airway management /intubation (as applicable), the start of the procedure, incision, N_2O off (as applicable), sevoflurane off, extubation (as applicable), eye-opening, end of the procedure, move to PACU, and PACU discharge readiness) will be recorded.

	The end-tidal anesthetic gas concentration will be time-locked to the BIS™ system recordings. End-tidal sevoflurane, oxygen, and nitrous oxide concentrations will be downloaded from the anesthetic monitoring device, and de-identified digital copies will be provided to Medtronic. Time and values of BIS™, ET_{SEVO} concentration (%) and other medication, FiO2(%) and EtO2(%), EtCO2(%) will be recorded at the following time intervals: • Baseline • Study start • At IV placement, as applicable • Start of induction • Start of N2O, as applicable • Start of sevoflurane • Anesthesia Airway Management (AAM) • AAM change (including type of AAM) • At any airway reflex (coughing, choking, laryngospasm) • Every 15 min after airway management • At all medication administration (as applicable) • N_2O off (as applicable) • Start of the surgery/procedure • Skin incision, if applicable • End of surgery/procedure (or skin dressing or cast or splint applied or abdominal block) • Skin closure, if applicable • Sevoflurane off • Termination of all anesthesia • Extubation • Physician Awakening subject, if applicable • Time of emergence (if occurs in OR) • End of study (removal of device)

	• 15 min post dexmedetomidine administration, if applicable • Time moved to PACU Recovery Assessments Subject recovery will be observed continuously after the termination of anesthesia for presence of coughing, choking, laryngospasms, and emergence. Emergence is defined as the time when any of the following first occurred: • eyes open spontaneously, • crying or phonating, or • purposeful movements. The time of emergence, time subject moved to PACU, and time of readiness for discharge will be recorded. The time of these assessments will be captured in medical records, source, and recorded on the eCRFs. All subjects will be assessed at 15-minute intervals beginning at anesthesia termination: • Vitals Signs • Pediatric Anesthesia Emergence Delirium (PAED) • Wong-Baker FACES Pain Scale (when subject is awake) • PACU discharge readiness - Modified Aldrete Score
Safety Assessments	This is a prospective, randomized, controlled study where the only change in routine management is the placement of the BIS™ monitor probe on the forehead. The choice of sedative drugs, dose, and route of administration will be based on clinical indications as judged by the attending Anesthesiologist, and it will not be changed for the study. The BIS™ monitor will not be used in situations where the placement of the probe will interfere with a procedure, cause scan artifacts, or where the presence of a metal monitor is contraindicated (e.g., MRI scans). Therefore, we believe there is only a minimal increase in risks from participating in the study. This risk relates to the possibility of developing irritation to the skin at the site of placement.

	Subjects will be monitored for Adverse Events, Serious Adverse Events, and Device-Related Adverse Events from BIS™ sensor applications throughout the BIS™ sensor removal.
Statistics	Standard demographic information and baseline characteristics will be summarized using descriptive statistics. For safety assessments, adverse events (AEs) will be summarized using frequency counts and percentages. Descriptive statistics will be provided by severity and relationship as needed. The primary analysis will be based on all evaluable data (excluding training subjects). Normality of data will be tested using the Kolmogorov-Smirnov test. Depending on whether normality assumption hold, a two group t-test or Wilcoxon rank-sum test will be used to compare between the two treatment groups. A P-value of less than 0.05 is considered statistically significant unless otherwise specified. The secondary endpoints will be evaluated using the Holm-Bonferroni method to ensure the overall type I error rate is controlled at the 0.05 level. Cardiovascular Variables will be summarized for both groups. The incidence of hypotension will be summarized and compared to anesthesia sedation levels. The anesthetic requirements with the BIS™ value, the percentage of time during maintenance with BIS™ values within the specified ranges, and number of episodes and duration of burst suppression will be assessed for both treatment groups. Additional endpoints, including PAED scale, Pain Rating Score and a subgroup analysis for subjects requiring neuromuscular blockade, will be summarized using descriptive statistics for each group and groups combined.

4. Introduction

4.1. Background

4.1.1. Basics of Anesthesia & Anesthetics

General anesthesia (GA) is a reversible state of controlled unconsciousness that is achieved with drugs that prevent awareness, pain, recall, distress, and movement in patients during surgery. Two critical components of general anesthesia are hypnosis and analgesia. Maintaining an adequate level of anesthesia depth is essential to the attenuation of these responses. The analgesic component may be considered as the probability of tolerance to a painful stimulus. Tolerance means the absence of a response being either a somatic response (*e.g.*, movement, sweating, eye-opening) or a hemodynamic response (increase in heart rate or blood pressure). When the state of general anesthesia is inadequate for the level of nociceptive stimulation from surgery, the heart rate and blood pressure can increase dramatically, alerting the anesthesiology provider to the possibility of increased nociception and arousal. Higher doses of an anesthetic are necessary to prevent reactions to more intense surgical stimuli. This fact has suggested that different states of anesthesia fall along a continuum of depth, with deeper anesthesia eliminating reactions to stronger stimuli [2]. Thus, the anesthesiologist needs to know when a patient has reached a depth of anesthesia commensurate with an impending stimulus. The patient expects a surgical procedure to be safe and painless, with the assurance that throughout the procedure, s/he is asleep, without any perception or memory of what happened during that period.

4.1.2. EEG Monitoring in Anesthesia

Since 1939, anesthesiologists have known about changes in the electroencephalogram (EEG) that are produced by anesthetic agents [3]. 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 varying 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** [4, 5]. The first changes induced by barbiturates in the EEG are 20-30 Hz (initial rapid response) waves, followed by the superimposition of 5-12 Hz alpha waves. Loss of consciousness occurs just as the initial rapid response yields to the slower oscillations. Spindle bursts of 5-12 Hz become prominent, and in turn, decline as the EEG develops large polymorphic waves of 1-3 Hz. When this slow polymorphic activity becomes dominant, the patient tolerates skin incision. At still higher concentrations of barbiturates, the EEG displays periods of suppression, each terminating with "burst" of renewed activity, which contains high-frequency components. The burst gradually subsides as it leads into the next episode of suppression. This combination of alternating phases of high-amplitude and low-amplitude periods is called "burst suppression."

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

of anesthesia can result in awareness with a recall of events that happen in the operating 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 [3]. There is no objective scale that measures "too light" or "too deep" anesthesia. Bispectral Index (BIS™) technology monitoring uses processed EEG signals to measure sedation depth based on level of consciousness (LOC) signals. It allows anesthesia providers to titrate general anesthesia to achieve the desired LOC on the brain [3, 6]. BIS™ technology consists of a sensor, a digital signal converter, and a monitor. The sensor is placed on the patient's forehead to pick up the electrical signals from the cerebral cortex and transfer them to the digital signal converter. BIS™ values quantify changes in the electrophysiologic state of the brain during anesthesia. Overall, a BIS™ value below 60 is associated with a low probability of response to commands. The BIS™ is a continuously processed EEG parameter that correlates to the patient's level of hypnosis, where 100 = awake and 0 = flat-line EEG. The BIS™ parameter was designed to correlate with "hypnotic" clinical endpoints (sedation, lack of awareness, and memory) and to track changes in the effects of anesthetics on the brain. **Figure 1** reflects a general association between clinical state and BIS™ values. Ranges are based on results from a multi-center study [6] of the BIS™ system involving the administration of specific anesthetic agents. BIS™ values and ranges assume that the EEG is free of artifacts that can affect its performance. Titration of anesthetics to the BIS™ range should be dependent upon the individual goals established for each patient. These goals and associated BIS ranges may vary over time and in the context of patient status and treatment plan.

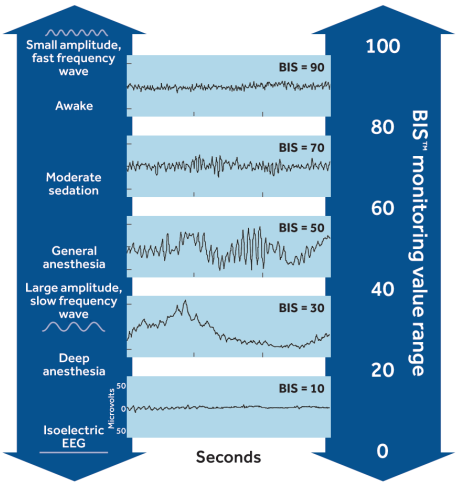


Figure 1: BIS™ Range Guidelines; a general association between clinical state and BIS™ values

4.1.3. BIS Monitoring in Pediatric Populations

Several studies demonstrate that BIS™ monitoring in children and infants provides a similar response to those achieved in the adult population [7-9]. Few selected published or sponsor supported studies have

demonstrated that using the Bispectral Index (BIS™) system correlates significantly with the level of responsiveness and the depth of anesthesia in pediatric patients.

4.1.3.1. Published Studies

A prospective study to investigate sedation with dual monitoring of Comfort Score (CS) and BIS™ module using BIS™ four-electrode or BIS™ pediatric sensors in open muscle biopsies in 30 children ages 1-18 was conducted by Tschiedel and colleagues [10]. The purpose of this study was to correlate and compare BIS™ and CS. None of the participants in the study experienced side effects related to the anesthesia or procedure. In 25 patients, sedatives were reduced according to low BIS™ values (<60). No unintended anesthesia awareness was noted during the study period. This study supported that Bispectral Index provides an additional helpful tool to guide sedation/analgesia in minor surgical procedures in children. BIS™ values </=60 correlated with sufficient depth of sedation and prevented unintended awareness. Additionally, BIS measurement allowed for distinct regulation of depth of sedation without prolonged sedation/analgesia due to unintended overdose.

A randomized, controlled trial aimed to determine if the depth of sevoflurane anesthesia impacts emergence agitation (EA) in children undergoing ophthalmic surgery was conducted [11]. Children, ages 2 to 8, were randomized into light sedation (BIS™ 55-60) or deep sedation (BIS™ 40-45) groups. EA was measured using the Pediatric Assessment of Emergence Delirium (PAED) scale. Peak PAED scores (light: 7.7 ± 4.6; deep: 8.6 ± 5.3, p= 0.45) and EA incidence (light: 1; deep: 2) were similar between groups. While there was a significant mean BIS™ score difference between groups, the relationship between BIS™ score and end-tidal sevoflurane concentration was weak (r= -.03).

The effects of Bispectral index monitoring on hemodynamics and recovery profile in developmentally delayed pediatric patients undergoing dental surgery were investigated in 40 patients by Fredrick and colleagues [11]. Participants were randomized into MAC-guided sevoflurane anesthesia (Group 1) or BIS™ guided anesthesia (Group 2). The impact of BIS™ monitoring on the recovery time of developmentally delayed children undergoing dental surgery was evaluated. The general anesthesia was maintained with 1-2 minimum alveolar concentration (MAC) of sevoflurane in oxygen by standard practice. The recovery profile, time to spontaneous ventilation, extubation, ability to open eyes, and PACU discharge were evaluated. The BIS™ guided group had improved recovery times. There were significant differences between recovery times and Non-communicating Children's Pain Checklist - Postoperative Version (NCCPC-PV) scores of two groups. Time to spontaneous ventilation [Difference in means (95% CI); 3.17 (1.79-4.54) P < 0.001], extubation [Difference in means (95% CI); 3.13 (1.66-4.60) P < 0.001], open eyes [Difference in means (95% CI); 3.97 (2.34-5.59) P < 0.001], and PACU stay time [Difference in means (95% CI); 23.55 (18.08-29.01) P < 0.001] were significantly shorter in Group 2. In conclusion, results suggest that routine BIS™ monitoring may be beneficial due to its favorable effects on the recovery profile in developmentally delayed pediatric patients.

Degoute and colleagues [8] conducted a prospective study to evaluate the correlation between BIS™ and the clinically assessed hypnotic component of anesthesia (CA score) in 27 pediatric and 27 adult patients when sevoflurane as the sole anesthetic was used. BIS™ and CA were compared at the loss of consciousness (LOC) and the recovery of consciousness (ROC), **Figure 2**. Mean (SD) BIS™ decreased significantly at LOC in children and adults from 94 (2.7) to 87.4 (4) and from 96.2 (2) to 86.7 (4.4), respectively, without any difference between groups. Correlation coefficients (p) between BIS™ and CA at LOC were -0.761 in children and -0.911 in adults. BIS™ index increased significantly at ROC in children and adults from 74.1 (4.2) to 86.7 (2) and from 80.2 (5) to 90.7 (3), respectively. Correlation coefficients between BIS™ and CA in ROC were -0.876 in children and -0.837 in adults.

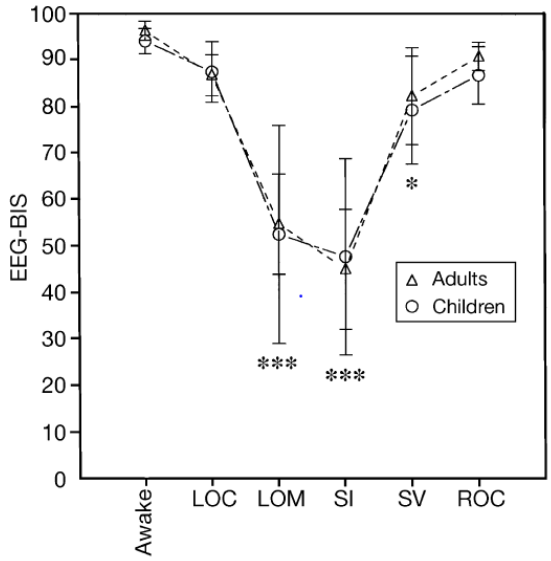


Figure 2: EEG BIS™ in child and adult patients (27 in each group). Abbreviations: Awake=baseline values, LOC - loss of consciousness; LOM - loss of movement; SI - skin incision; SV - spontaneous ventilation; ROC - recovery of consciousness. Data are post stimulus. Results are mean ± SD. ***Significantly different from baseline values within a group (P<0.001); one-way analysis of variance with Bonferroni's correction where indicated.

In conclusion, the study suggested that the BIS™ values at ROC were not different from those at LOC in either group. It was found that the correlation between the BIS™ index and end-tidal sevoflurane concentration in children to be similar to that observed in adults.

4.1.3.2. Sponsor Supported Studies

The Effect of Bispectral Index Monitoring on Anesthetic Use and Recovery in Children Anesthetized with Sevoflurane in Nitrous Oxide

A prospective, randomized, observer-blinded study was designed to evaluate the effect of BIS™ monitoring on anesthetic use and recovery characteristics in pediatric patients [12]. Two hundred forty (240) patients were enrolled in the study. During a baseline phase before starting randomization, data of

38 patients were collected "historical controls." These control patients were anesthetized according to standard institutional practice.

Two hundred two (202) patients age 0–18 years were randomized into one of two groups: standard practice (SP) and BIS™ guided (BIS™). Patients age 0–3 years, undergoing inguinal hernia repair (IH), and patients age 3–18 years, undergoing tonsillectomy and/or adenoidectomy (TA), were selected, **Table 1**. All patients were anesthetized with sevoflurane in 60% N_2O/O2.

In the BIS™ group, anesthetic delivery was adjusted to achieve a target BIS™ values of 45–60 during maintenance and 60–70 during the last 15 minutes of the procedure.

Table 1: Demographic Data (mean ± SD)

	Control	SP	BIS
Infants (age 0–6 mo), hernia repair			
Number	8	28	32
Sex (M/F)	5/3	23/5	27/5
Age (yr)	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1
Weight (kg)	4.8 ± 1.0	5.1 ± 1.6	5.5 ± 1.6
Duration of Surgery (min)	26.2 ± 7.4	32.0 ± 17.6	30.1 ± 14.5
Infants and small children (6 mo–3 yr), hernia repair			
Number	11	34	33
Sex (M/F)	7/4	29/5	28/5
Age (yr)	1.8 ± 1.1	1.9 ± 1.0	2.2 ± 1.0
Weight (kg)	11.5 ± 3.6	11.9 ± 2.8	13.3 ± 3.0
Duration of Surgery (min)	20.8 ± 12.0	25.7 ± 11.8	24.8 ± 14.9
Children (age 3–18 yr), tonsillectomy and/or adenoidectomy			
Number	19	35	40
Sex (M/F)	10/9	23/12	26/14
Age (yr)	5.9 ± 2.0	6.1 ± 2.6	6.7 ± 2.5
Weight (kg)	24.8 ± 9.5	27.7 ± 14.7	26.9 ± 10.6
Duration of Surgery (min)	28.1 ± 14.2	33.2 ± 20.3	27.7 ± 17.1
SP = Standard Practice group; BIS = Bispectral Index group			

In the patients 0–6 months of age undergoing IH, sevoflurane concentrations during maintenance (2.0 ± 0.4% SP, 0.9 ± 0.8 BIS™), during the last 15 minutes (1.6 ± 0.4% SP, 0.6 ± 0.6% BIS™), and at the end of the procedure (1.1 ± 0.6% SP, 0.3 ± 0.3% BIS™) were smaller in the BIS™ group, **Table** . Emergence and recovery measures, **Table** , were unaffected by BIS™ titration. In the children 6 months to 3 years of age, there were no significant differences between the SP and BIS™ groups in anesthetic use or recovery measures.

Table 2: Intraoperative Data for Control, Standard Practice (SP), and BIS Groups (mean ± SD)

	Control	SP	BIS
Infants (age 0–6 mo), hernia repair			
Average ET sevoflurane, maintenance (%)	2.2 ± 0.7	2.0 ± 0.4	0.9 ± 0.8*
Average ET sevoflurane, last 15 min (%)	2.0 ± 0.9	1.6 ± 0.4	0.6 ± 0.6*
Average ET sevoflurane, end of procedure (%)	1.5 ± 0.9	1.1 ± 0.6	0.3 ± 0.3*
BIS™ maintenance	34.9 ± 5.8	36.2 ± 11.8	35.7 ± 9.6
BIS™ last 15 min	34.9 ± 7.0	40.4 ± 12.5	41.0 ± 10.5
BIS™ end of procedure	37.7 ± 7.1	43.1 ± 17.5	48.3 ± 12.9
Infants and small children (6 mo–3 yr), hernia repair			
Average ET sevoflurane, maintenance (%)	1.8 ± 0.4	2.3 ± 0.6	2.2 ± 0.5
Average ET sevoflurane, last 15 min (%)	2.0 ± 0.7	2.0 ± 0.6	1.9 ± 0.5
Average ET sevoflurane, end of procedure (%)	1.5 ± 0.9	1.4 ± 0.8	1.2 ± 0.6
BIS™ maintenance	55.8 ± 15.2	50.0 ± 14.1	54.8 ± 9.1
BIS™ last 15 min	51.8 ± 14.4	54.5 ± 14.7	55.9 ± 10.4
BIS™ end of procedure	56.2 ± 18.4	61.4 ± 15.3	64.5 ± 10.1
Children (age 3–18 yr), tonsillectomy and/or adenoidectomy			
Average ET sevoflurane, maintenance (%)	2.4 ± 0.4	2.4 ± 0.6	1.8 ± 0.4*
Average ET sevoflurane, last 15 min (%)	2.2 ± 0.5	2.1 ± 0.7	1.6 ± 0.6*
Average ET sevoflurane, end of procedure (%)	1.6 ± 0.7	1.5 ± 0.7	1.1 ± 0.6
BIS™ maintenance	37.2 ± 7.5	39.6 ± 11.5	47.2 ± 10.1
BIS™ last 15 min	43.6 ± 11.2	44.8 ± 11.3	55.7 ± 7.9*
BIS™ end of procedure	50.1 ± 15.3	53.0 ± 16.0	63.0 ± 8.6*
ET = end-Tidal; SP = Standard Practice group; BIS = Bispectral Index group			
*** P < 0.05 versus SP group.**			

Table 3: Time from End of Procedure Needed to Achieve the Primary Recovery End Points for the Control, SP, and BIS groups (mean ± D)

	Control	SP	BIS
Infants (age 0–6 mo), hernia repair			
First response (min)	3.3 ± 1.8	4.3 ± 4.0	2.9 ± 2.6
Extubation (min)	10.9 ± 7.5	9.3 ± 8.9	5.0 ± 2.6
Ready to discharge (min)	29.0 ± 11.1	25.8 ± 19.7	18.3 ± 8.2
Infants and small children (6 mo–3 yr), hernia repair			
First response (min)	3.4 ± 1.9	4.1 ± 2.4	3.8 ± 2.5
Extubation (min)	4.2 ± 3.0	7.6 ± 4.1	6.5 ± 3.1
Ready to discharge (min)	21.1 ± 8.0	21.1 ± 9.7	20.3 ± 8.8
Children (age 3–18 yr), tonsillectomy and/or adenoidectomy			
First response (min)	6.7 ± 3.7	7.0 ± 3.9	4.2 ± 3.7*
Extubation (min)	11.3 ± 5.0	11.3 ± 5.9	7.1 ± 3.7*

Ready to discharge (min)	22.0 ± 9.2	26.7 ± 11.2	20.0 ± 7.9*

SP = Standard Practice group; BIS = Bispectral Index group

*** P < 0.05 versus SP group.**

In conclusion, in the TA age 3–18 year group, BIS™ monitoring was associated with a significant reduction in end-tidal sevoflurane concentration during maintenance (2.4 ± 0.6%, SP and 1.8 ± 0.4% BIS™, mean ± SD) and during the last 15 min of the procedure (2.1 ± 0.7, SP and 1.6 ± 0.6, BIS), refer to **Table** . Recovery times were 25%–40% faster in BIS-titrated patients, **Table** .

Pediatric Evaluation of the Bispectral Index (*BIS™*) Monitor and Correlation of BIS™ with End-tidal Sevoflurane Concentration in Infants and Children

Denman and colleagues conducted a prospective clinical study in children undergoing general anesthesia. Seventy-seven (77) pediatric patients were studied under the two protocols [9]. An initial group of 55 patients, observational protocol, had BIS recorded during routine general anesthetics. The anesthetist was not aware of the BIS™ value. Sedative-hypnotic drugs used included methohexital, propofol, sevoflurane, isoflurane, desflurane, nitrous oxide, and diazepam. For this group, BIS™ values were analyzed for three prospectively defined case milestones: before the induction of anesthesia, during maintenance, and at emergence from anesthesia. In addition, a "nadir BIS™," the lowest BIS™ value occurring within the 10-min period after the induction of anesthesia, was recorded. In addition, data from 26 adults collected previously at the same clinical endpoints were used to compare BIS, **Table 4** and **Figure 3**.

Table 4: BIS™ (Bispectral Index) Values at Case Milestones in Un-premedicated Children and Infants Versus Adults

	Awake	Nadir	Maintenance	Emergence
Pediatric				
n	26	49	44	32
Mean BIS™	94.12	16.36	42.39	83.51
SD	4.53	12.73	14.18	11.63
Adult				
n	57	20	20	58
Mean BIS™	96.60	36.30	44.90	80.19
SD	3.31	9.08	10.76	12.33
P	NS	0.00001	NS	NS
Power[a]	0.99	0.99	0.96	0.91

[a] Power to detect a difference of 10 or more BIS units between adults and children with $\alpha = 0.05$

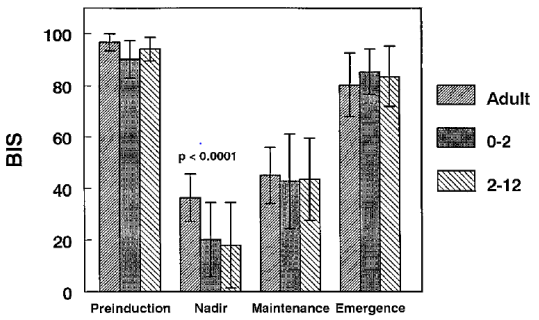


Figure 3: Bispectral index (BIS™) values at case milestones in adults, infants, and children. The nadir BIS™ for the combined pediatric groups was significantly lower than that for adults. Error bars represent sd.

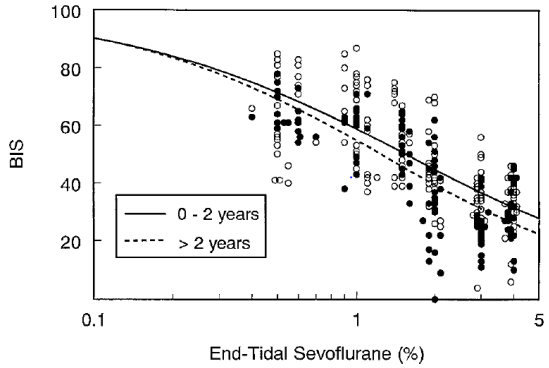


Figure 4: Bispectral index (BIS™) values versus end-tidal sevoflurane concentration. The difference between infants and children was statistically significant. The solid circles represent the children and the open circles represent the infants.

Twenty-two patients (11 infants and 11 children) were studied while receiving sevoflurane as the primary anesthetic, and BIS™ measurements were recorded at five steady-state end-tidal sevoflurane concentrations of 3.0%, 2.0%, 1.5%, 1.0%, and 0.5%. Mean BIS and standard deviation were determined at each concentration of sevoflurane, **Figure 4**.

BIS™ responses during general anesthesia were observed in infants and children and compared with values measured in adults. No difference between unpremeditated children and adults is seen in BIS™ values before the induction, during maintenance, or at emergence. BIS™ nadir is lower in children than adults, and this difference is statistically significant. The study demonstrated that BIS™ values in awake and anesthetized children and infants were comparable to values in adults.

The use of BIS™ during general anesthesia improves the titration of anesthetics in adults. The data from both of these pediatric studies suggest that the same methods may be applied to pediatric patients.

4.2. Purpose

The purpose of this study is to investigate the relationship between BIS™ and anesthetic agents in pediatric patients ages 4-18.

5. Objectives and/or Endpoints

5.1. Objectives

5.1.1. Primary Objective(s)

The primary objective of this study is to characterize BIS™ performance with the anesthetic agent in pediatric patient ages 4 to 18 years.

5.2. Endpoints

5.2.1. Primary Endpoint(s)

The end-tidal sevoflurane concentration in both patient groups acquired during maintenance of anesthesia. The study will be considered a success if the primary objective, achieving statistical and

- Clinical Anesthesia Assessment, recorded as the incidence of movements, grimacing, eye opening, tearing, sweating, mydriasis and cardiovascular changes while undergoing anesthesia
- Pediatric Anesthesia Emergence Delirium (PAED)
- Wong-Baker FACES Pain Rating Score

clinical significance in obtaining the end-tidal sevoflurane concentration during maintenance in both patient groups, is achieved.

5.2.2. Secondary Endpoint(s)

Secondary endpoint(s):

Additional/Exploratory Endpoints:

- Recovery assessments in patients receiving monitoring compared to standard anesthetic practice (instructions for collection contained in **Study Procedures and Assessments**):
  - Emergence,
  - Emergence is defined as the time when any of the following first occurred:
  - Eyes open spontaneously
  - Crying or phonating
  - Purposeful movements
  - PACU discharge readiness using Modified Aldrete Score
  - Anesthesia Airway Management (AAM) will be noted:
    - Awake and Deep Extubation (endotracheal tube (EET) vs. laryngeal mask airway (LMA)
    - Airway reflexes (e.g., coughing, choking, laryngospasm)

6. Study Design

This is a multi-center, prospective, randomized controlled study to collect data to compare the performance of standard practice (SP) group with the BIS™ monitoring (BIS™) group. Pediatric patients between the ages of 4 to 18 years undergoing routine sevoflurane general anesthesia with an expected surgical procedure duration of 30 minutes or more will be recruited. General surgeries include abdominal, urological, orthopedic, ophthalmological, or other procedures approved by the Medtronic study team with an American Society of Anesthesiologists physical status of I - III. Children will be recruited from the preoperative clinic and will be divided into three age groups:

- 4 to 8 years
- 9 to 12 years
- 13 to 18 years

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

6.1. Duration

The planned duration of the study is 8 - 12 months. The consented study subject duration of participation is not to exceed the duration of the surgery and post-surgical discharge.

6.2. Rationale

Pediatric patients present a unique challenge during anesthetic delivery and monitoring of sedation. Although a number of studies have been conducted to assess the reliability of BIS™ technology in pediatrics, validation presents more of a challenge in children as compared to adults. The EEG in young children is more age-dependent, with brain maturation and synapse formation continuing until about the age of four [15]. Further, with young children, assessing sedation or sleep with simple responses to voice commands is unreliable, and many clinical endpoints can be ambiguous in this population. In younger children, it is also challenging to distinguish purposeful movements from nonspecific responses. Also, healthy volunteer studies relating to anesthetic concentration to the clinical endpoints performed in adults cannot be replicated in the pediatric population. This clinical study is designed to capture the performance of BIS with anesthetic agents in the pediatric patient population.

The BIS™ ranges are selected based on the prospective, randomized, observer-blinded study listed in *Section 4.1.3.2*. Sebel and his and colleagues enrolled 240 patients from which 38, control group, subject's data were used to define BIS™ targeted ranges. These control patients were anesthetized according to standard institutional practice; the BIS™ values were concealed for this group. For the BIS™ group,

anesthetic delivery was adjusted to achieve a target BIS™ values of 45 – 60 during maintenance and 60 – 75 during the last 15 minutes of the surgical procedure. The results of this study supported that BIS™ guided anesthetic management was associated with a significant reduction in anesthetic consumption and faster recovery. Based on the published results, and to support this study, the guided anesthetic administration will be achieved using a BIS™ target range of 45 – 60 during maintenance of anesthesia and 60 –75 beginning of skin closure.

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 BISx™ unit. The BISx™ unit filters and digitizes the signal, analyzes it for the artifact, and processes it using digital signal processing techniques to derive processed EEG parameters to a single Bispectral Index (BIS™), and finally sends the processed data to the monitor for display. The purpose of processing the EEG waveform data is to extract characteristic features from the complex signal that the BIS™ algorithm can utilize to derive BIS Index.

Table 3: System product/ component information for the US

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

7.2. Manufacturer

BIS™ Complete Monitoring System, BISx™, Patient Interface Cable, BIS™ Sensor, Detachable Power Cord by (15 Hampshire St, Mansfield MA) Medtronic Inc.

7.3. Packaging

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

7.4. Intended Population

The study will be focusing on the pediatric patient population, ages 4 to 18, refer to *Section 9.4.*

7.4.1. 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 and pediatric patients within a hospital or medical facility, providing patient care to monitor the state of the brain by data acquisition of EEG signals. The BIS™ index, one of the Complete Monitor output parameters, may be used as an aid in monitoring the effects of Desflurane, Isoflurane, Propofol, and Sevoflurane with balanced anesthetic techniques in Adults, and with Sevoflurane in Pediatrics. BIS™ usage with Propofol in adults 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.

7.4.2. Pulse Oximetry System Indications for Use

The Nellcor™ N-600x Pulse Oximetry System and Nellcor™ Sensors with OXIMAX technology are indicated for prescription use only for the continuous non-invasive monitoring of functional oxygen saturation of arterial hemoglobin (SpO_2) and pulse rate. The N-600x Pulse Oximeter is intended for use with neonatal, pediatric, and adult patients during both no motion and motion conditions and for patients who are either well or poorly perfused, in hospitals, hospital-type facilities, intra-hospital transport, and home environments.

7.5. Equipment

7.5.1. 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 5**). BIS™ Complete Monitor

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

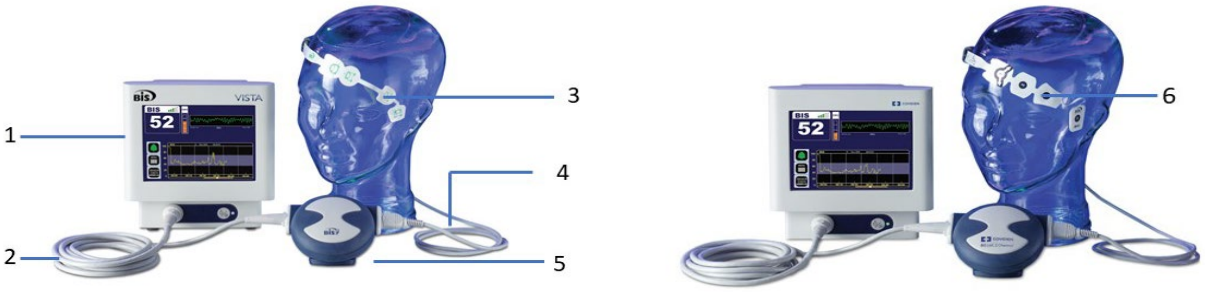


Figure 5: The BIS™ Complete Monitoring System. 1 - BIS™ Monitor 2 - Monitor Interface Cable; 3 - BIS™ Pediatric Sensor; 4 - Patient Interface Cable (PIC); 5 - BISx™ (LoC 2Channel); 6 - BIS™ QUATRO Sensor

7.5.1.1. BIS™ Complete Monitor

BISx™ Modules

The BISx™ 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 BISx™ is shown in **Figure 6**. Its long flexible Monitor Interface Cable connects to the front of the monitor. The Patient Interface Cable (PIC) connects the BIS™ sensor to the BISx™. The attachment clip on the BISx™ is used to secure it in a convenient location near the patient's head. The BISx™ are mutually exclusive parts of the BIS™ Complete Monitoring System. The BISx™ Module processes up to two channels of EEG and computes the BIS™ value and other EEG parameters.

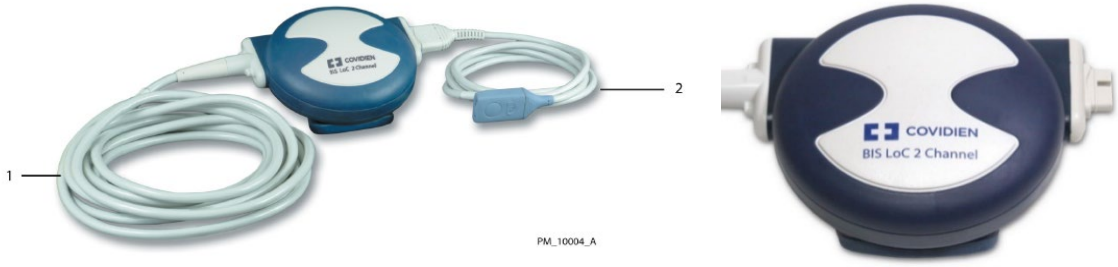


Figure 6: BISx™ Module: 1-Monitor Interface Cable; 2-Patient Interface Cable; and BISx™ (LoC 2Channel)

Patient Interface Cable

Covidien BIS™ Sensor Patient Interface Cable (PIC) connects the BISx4™ to the BIS Sensor, refer to **Figure 6.**

BIS™ Sensor

The sensor is the single-use component of the BIS™ Monitoring System and should be replaced after each use.

BIS™ Sensors

BIS™ Pediatric and QUATRO Sensors, **Figure** 7, are designed with a 4 electrode pre-gelled EEG electrode array that is applied directly to the patient's forehead to transmit EEG signals to the BISx™ Module. The sensor will be applied per IFU.

BIS™ Pediatric Sensor

BIS™ Pediatric Sensor is designed with a 4 electrode pre-gelled EEG electrode array that is applied directly to the patient's forehead to transmit EEG signals to the BISx™ Modules, **Figure** 7. The sensor will be applied per IFU.

BIS™ QUATRO Sensor **BIS™ Pediatric Sensor**

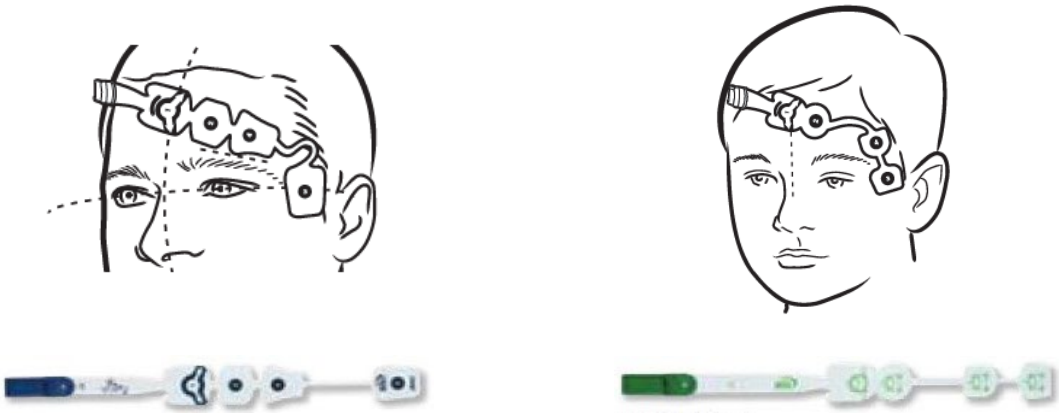


Figure 7: BIS™ Sensors

Nellcor™ N-600x Pulse Oximetry System

The FDA-cleared Nellcor™ N-600x Pulse Oximetry System with N-600X Pulse Oximeter and age-appropriate Nellcor™ Sensors and Cables with OXIMAX technology (**Figure 8**) or another monitor may be provided by the sponsor to the study site. The laptop may be provided to stream SpO_2 data.

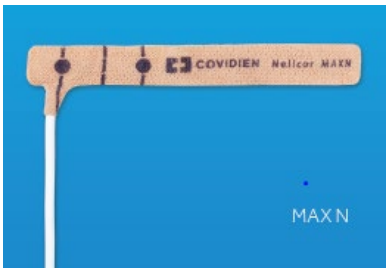
Figure 8: Nellcor™ OxiMax N-600x Pulse Oximeter

Nellcor™ SpO_2 Adhesive Sensor

N-600x pulse oximeter paired with the following type of sensors based on the subject's weight ranges (**Figure 9**):

- For subjects weighing between 3 and 20 kg: MAXI sensor
- For subjects weighing less than 3 kg or weighing more than 40 kg: MAXN sensor (or other production sensors such as Nellcor™ OxySoft sensor)
- For subjects weighing between 10 and 50 kg: MAXP sensor
- For subjects weighing more than 30 kg: MAXA sensor

The Nellcor™ Infant SpO_2 Sensor, model **MAXI**, is indicated for single patient use when continuous noninvasive arterial oxygen saturation and pulse rate monitoring are required for patients weighing between 3 and 20 kg.



The Nellcor™ Neonatal-Adult SpO_2 Sensor, model **MAXN**, is indicated for single patient use when continuous noninvasive arterial oxygen saturation and pulse rate monitoring are required for neonates weighing less than 3 kg or adults weighing more than 40 kg.

The Nellcor™ Pediatric SpO_2 Sensor, model **MAXP**, is indicated for single patient use when continuous non-invasive arterial oxygen saturation and pulse rate monitoring are required for patients weighing between 10 and 50 kg.

The Nellcor™ Adult SpO_2 Sensor, model **MAXA(L)** is indicated for single patient use when continuous non-invasive arterial oxygen saturation and pulse rate monitoring are required for patients weighing more than 30 kg.

Figure 9: SpO_2 Sensors

7.6. Product Use

A member of the Medtronic team may set up the BIS™ system and Pulse Oximeter at each participating research site in person or via remote webcam to ensure all equipment is fully functional as needed. Specific instructions to the Site Investigator and staff on system set up and 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 (PI) 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 PI at each participating site to assure any staff performing tasks related to the clinical trial (e.g., Study Coordinators, Study Nurses, Sub-Investigators, etc.) have been appropriately trained, training documented and included on the Delegated Task List.

7.8. Product Receipt and Tracking

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

7.9. Product Storage

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

7.10. Product Return

All monitors provided by Medtronic free of charge should be returned to Medtronic and documentation of return, e.g., device return forms should be maintained. Devices that are single use provided by Medtronic and used in the study should be discarded and documented as discarded on the device accountability log unless non-functioning. Non-functioning investigational devices must be returned to Medtronic as soon as possible for investigation. Instructions for returning the device will be provided. Un-used devices will be returned to Medtronic at the end of the study.

7.11. Product Accountability

Devices/products will be traced during the clinical study by specific serial numbers (or lot numbers) assigned to each device/product. The Investigator is responsible for the maintenance of a Product Accountability as tracked on source worksheets, device shipment/return forms, and device eCRFs. On this

documentation, the receipt, use, return, and disposal of the investigational devices/products shall be documented. At the end of the clinical study, the Principal Investigator or delegate must sign and date the applicable eCRFs.

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 physicians must be trained in the handling of the 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 the BIS™ Complete Monitoring System
- Disclose potential conflicts of interest, including financial, that interfere with the conduct of the clinical investigation or interpretation of results
- Be able to demonstrate that the proposed investigational study site:
  - Has the required number of eligible subjects needed within the recruitment period
  - Has one or more qualified investigators, a qualified investigational study site team and adequate facilities for the foreseen duration of the clinical investigation

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

8.2 Study Site Activation

During the activation process (prior to subject enrollment), Medtronic will train study site personnel on the clinical investigation plan, on relevant standards and regulations, informed consent, and on data collection and reporting tools. If new members join the study site team, they will receive training on the applicable study requirements relevant to their role before contributing to the study.
Prior to performing study related activities, all regulatory requirements shall be fulfilled, including, but not limited to the following:

- IRB approval (and voting list, as required by local law) of the current version of the CIP and IC.

- RA approval or notification (as required per local law)
- Fully executed CTA
- Financial disclosure
- 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

In addition to performing monitoring and auditing activities, 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 at SIV and training cases under the supervision of a study investigator, but no data entry, shall be performed by Medtronic personnel or their representatives at study sites

9. Selection of Subjects

9.1. Study Population

Male and female pediatric subjects between the ages of 4 to 18 years undergoing routine sevoflurane general anesthesia will be enrolled. The first 2 - 4 subjects per each site will be used for training and to check the data quality. After training subjects have been enrolled, randomization will proceed based on the Sponsor's assessment of data quality. The subjects will be recruited at up to 8 Investigational Sites in the U.S. and divided into three age groups:

- 4 to 8 years
- 9 to 12 years
- 13 to 18 years

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 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 the subject is determined to meet all eligibility criteria.

Study enrollment is accomplished by parent/ guardian signing the informed consent, age-appropriate assent form as required, and successfully passing the study inclusion /exclusion criteria. Subjects who sign informed consent, but are not enrolled, are considered screen failures.

9.3 Inclusion Criteria

1) Pediatric Subjects (ASA PS I or II or III) aged 4 years to 18 years scheduled for procedures with sedation where the process of assessment will not interfere with the procedure, progress, or patient care

9.4 Exclusion Criteria

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
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, hemiplegia, demyelinating disorders, cerebral palsy, congenital anomalies of the brain or spinal cord, or other known neurologic disorders)
3) Severe developmental delay per assessment of investigator or report of parent/guardian
4) Airway abnormalities
5) Pregnancy; subjects of childbearing potential will have a urine screen for pregnancy before surgery
6) If the process of assessment will interfere with the procedure or the progress of the procedure
7) Taking psychoactive medications
8) Taking any medications that may have an impact on the Central Nervous System (CNS)
9) Planned use of any regional anesthesia; a local field block is not included in this exclusion and can be used at the discretion of the anesthesia provider
10) Planned use of dexmedetomidine (Precedex)
11) Refusal to participate in the study

10. Study Procedures

10.1 Schedule of Events

The Flowchart for enrollment and allocation to groups is shown in **Figure 10**. The Schedule of Events, **Table 5,** summarizes the intervals and data collection procedures.

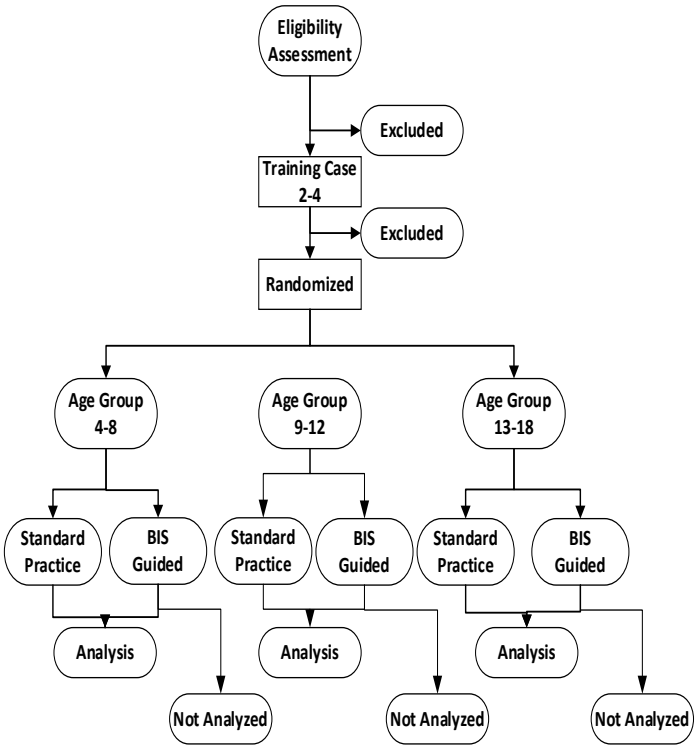


Figure 10: Study Flowchart

10.2 Data Collection

Table 5: Data collection and study procedure requirements at subject visits

Study Tasks	Baseline/ Enrollment	Surgical Procedure			PACU/ Discharge
		Randomization	Induction and maintenance	End of Surgery	
Baseline					

Study Tasks	Baseline/ Enrollment	Surgical Procedure			PACU/ Discharge
		Randomization	Induction and maintenance	End of Surgery	
Informed Consent [1]	x				
Inclusion/exclusion criteria review and confirmation of eligibility status	x	x			
Demographics [2]	x				
Medical History [3]	x				
Pre-operative Vital Signs [3]	x				
Procedure					
Randomization (before the procedure for group assignment) [4]		x			
BIS™ and Nellcor™ sensors placement			x	x	
BIS™, Nellcor™ and other digital data collection			x	x	
Standard surgical procedures			x	x	
ET_{SEVO} concentration and other drug information			x	x	
Cardiovascular Variables [5]	x		x	x	
Event Markers and Assessments collection [6]			x	x	
Anesthesia Airway Management [6]			x	x	
Recovery					
Emergence [7]				x	x
Incidents of postop nausea and vomiting [7]				x	x
Vitals [7]				x	x
Wong-Baker FACES Scale [7]				x	x
Pediatric Anesthesia Emergence Delirium (PAED) [7]				x	x
Modified Aldrete Score				x	x

Study Tasks	Baseline/ Enrollment	Surgical Procedure			PACU/ Discharge
		Randomization	Induction and maintenance	End of Surgery	
Time of Readiness for PACU discharge [6,7]				x	x
Exit					
Reason for Study Exit [8]	x	x	x	x	x
Safety					
Adverse Event Assessment [9]	x		x	x	x
Device Deficiency [9]			x	x	

1) Written informed consent must be obtained before any study-specific evaluations, *Section 10.5*
2) Demographic information, including sex, weight, height, age, ethnicity, race, as well as skin tone, will be recorded refer to *Section 10.6*.
3) Relevant Medical History, including diagnosis and surgery type, will be collected, *Section 10.7*
4) Randomization will be performed before the surgical procedure for group assignment refer to *Section 10.8.*
5) Cardiovascular Variables (heart rate [HR]; systolic and diastolic blood pressure [BP] including hypotension; oxygen saturation; and temperature) refer to *Section 10.9*.
6) For event markers and assessments, refer to *Section 10.9*
7) For recovery data collection, refer to *Sections 10.9*.
8) Details are included in *Section 10.14..1*
9) Details are included in *Section 12*.

10.3 Subject Screening

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.

10.4 Prior and Concomitant Medications/Therapies

There are medication restrictions in this study that include: psychoactive medications and any medication that may have an impact on the CNS. Subjects cannot be on any psychoactive medication and be included in the study.

10.5 Subject Consent

The Investigator or designee must obtain written informed consent before any clinical study related activity takes place. Before entry into the study, the Institutional Review Board (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 the parent or legal guardian of the potential subject.

The Investigator or designee will fully inform the parent or legal guardian of the potential subject of all aspects of the clinical study that are relevant to the decision to participate in the clinical study. These activities may include the rights of the child as a subject in a research project, 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 parent/legal guardian. The parent/legal guardian 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. The parent or legal guardian of a potential subject will be encouraged to discuss participation in the study with their support network (family, friends). All questions about the clinical study should be answered to the satisfaction of the parent/legal guardian.
Neither the Investigator nor the investigation site staff shall coerce or unduly influence a subject and/or the parent/legal guardian 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.

The parent or legal guardian of the potential subject who then wishes to participate, and where the subject meets the inclusion/exclusion criteria, will be asked to sign and personally date the informed consent form on behalf of their child. Children of appropriate age will need to assent to the study and will be provided with an appropriate Institutional Review Board (IRB) approved Research Assent Form (RAF).
The signed original informed consent is maintained in the Investigator's records and a copy given to the parent/legal guardian.

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's parent/legal guardian 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.

10.6 Enrollment

A subject is considered enrolled when the consent process has been finalized. The date the subject (or the subject's authorized/designated representative or guardian) signed the IC and Data Protection Authorization, as required by law, must be documented in the subject's medical records. A log of all

subjects enrolled in the study should be maintained. Enrollment can be a stand-alone visit or can occur on the same day as the baseline visit. Once consent is obtained, report adverse events/deaths, study deviations and subject exits as they occur.

10.7 Baseline

Once ICF is signed, the following will be obtained:

- Demographics (race, ethnicity, sex, height, weight, skin tone,)
- Medical history, including diagnosis for surgery and 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 I, II or III will be enrolled
- Concomitant Medications, including the history of prescription and over the counter medication, will be carefully noted and recorded within 1 month before the surgery. Medication name, indication for use, dose, frequency, route of administration start/stop date
- Cardiovascular Variables - Heart Rate, Systolic, mean, and Diastolic Blood Pressures, Respiratory Rate, Oxygen Saturation (SpO_2)

10.8 Randomization and Treatment Assignment

Prior to Randomization, 2 - 4 subjects from each site will be consented and enrolled. The data will be used to train on the new technology use, and to review the quality of the data collection, refer to *Section 10.2.*

Subjects are eligible for randomization assignment after study enrollment and verification of eligibility criteria. Subjects will be randomized in a 1:1 fashion to the BIS™ group or standard practice group using the RDC electronic system. Randomization schedules will be created by a Medtronic statistician, and randomization assignments will be automatically populated on the Randomization e-CRF after subject consent and eligibility verification have been entered in RDC. The randomization schedule will be stratified by age group and the study site to ensure 1:1 randomization within each study site.

10.9 Surgical Procedure and Data Collection

The surgical procedure will be conducted per Standard of Care (SOC). Subjects are being recruited with a planned maintenance time of 30 minutes or greater. If the subject's maintenance time is less than 25 minutes, the data will continue to be collected, but will not be included in the final data analysis and the subject will be replaced by an additional enrolled subject.

10.9.1 Prior to Induction

Prior to induction, subjects may be pre-medicated with Midazolam (Versed) per institutional guidance. The subject taken into the operating room, and anesthesia delivery system will be applied per institutional guidance.

10.9.1.1 BIS™ Sensor Application

Prior the induction of anesthesia, all subjects will have an age-appropriate BIS™ sensor. The sensor, BIS™ pediatric or BIS™ QUATRO Sensor, will be selected by the clinician based on the size of the forehead and space available on the forehead. The sensor will be placed on the forehead after cleaning the site with an alcohol wipe per the IFU recommendation. The sensor type will be captured on eCRFs.

10.9.1.2 Pulse Oximeter Sensor Application

The age-appropriate pulse oximeter sensor will be applied to the subject per sensor IFU. A left or right index finger is the preferred sensor site. Alternatively, the sensors can be applied to a smaller finger, thumb, or big toe. The sensor type, position and side will be recorded on the eCRF.

If the subject is uncooperative when awake, the BIS™ sensor will be placed after adequate sedation has been achieved with the use of pre-medication drugs.

The choice of pre-medication, dose, and time of administration will be determined by the site anesthesiologist and will not be altered for the study, but the use of these drugs will be recorded on the eCRF.

10.9.2 Induction

Anesthesia will be induced with sevoflurane alone, or a combination of sevoflurane and nitrous oxide (N_2O) in 100% oxygen in both groups. If the nitrous oxide is used, it will be discontinued after the placement of a tracheal tube or laryngeal mask (LMA), or another airway management. If necessary, a neuromuscular blocking agent will be used to facilitate endotracheal intubation. The choice of medication, dose, and time of administration will be determined by the site anesthesiologist and will not be altered for this study, but the use of these drugs will be recorded on the eCRFs. If the subject is in need of a regional block for pain management following the procedure, this block should be placed once skin closure is complete and prior to extubation. This block cannot be placed prior to skin closure. Subjects with the planned use of any regional anesthesia are excluded from this study, however if any regional anesthesia becomes necessary for the subject during the course of the surgical procedure, data will continue to be collected on the subject, however the data will not be included in the data analysis and the subject will be replaced by an additional enrolled subject. The use of dexmedetomidine (Precedex) is prohibited from being used in this study. If it becomes necessary to use this medication during the course of the surgical procedure, data will continue to be collected on the subject, however the data will not be included in the data analysis and the subject will be replaced by an additional enrolled subject.

10.9.3 Maintenance

10.9.3.1 Training Group

A training group, comprising of the first 2 - 4 subjects at each site will be enrolled to train the site team on the new technology and to determine the quality of data collection before randomization.

Sevoflurane administration will be at the discretion of the anesthesiologist using clinical signs and cardiovascular changes to adjust anesthetic concentration. The end-tidal sevoflurane concentrations will be continuously recorded. Fentanyl, propofol, and/or morphine will be administered at the discretion of the anesthesiologist for example, morphine at 1.5 mcg/kg at induction and 0.75 mcg/kg every 30 minutes in accordance with usual clinical indications.

For the SP group, sevoflurane, fentanyl, propofol, and/or morphine will be administered at the discretion of the anesthesiologist for example, fentanyl and morphine at 1.5 mcg/kg at induction and 0.75 mcg/kg every 30 minutes in accordance with usual clinical indications.

The clinician will be blinded to the BIS™ values, and the BIS™ value is not used to guide the conduct of the anesthetic. The SQI number will be visible to the anesthesiologist during the case to capture a good quality signal. The details on SQI monitoring will be provided to the study site.

10.9.3.2 Standard Practice Group

In this group, sevoflurane administration will be at the discretion of the anesthesiologist using clinical signs and cardiovascular changes to adjust anesthetic concentration. The end-tidal sevoflurane concentrations will be continuously recorded. Fentanyl propofol, and/or morphine will be administered at the discretion of the anesthesiologist, for example, morphine at 1.5 mcg/kg at induction and 0.75 mcg/kg every 30 minutes in accordance with usual clinical indications.

The clinician is blinded to the BIS™ values, and the BIS™ value is not used to guide the conduct of the anesthetic. The SQI number will be visible to the anesthesiologist during the case to capture a good quality signal. The details on SQI monitoring will be provided to the study site.

10.9.3.3 BIS™ Guided Group

In the BIS™ group, sevoflurane will be adjusted to achieve a target BIS™ values of 45 – 60 during maintenance of anesthesia and BIS™ values of 60 – 75 beginning of skin closure. Subjects with BIS™ values that are outside of the specified range of 45 – 60 during maintenance of anesthesia for >35% of the maintenance duration will be considered a protocol deviation and the subject will be excluded from the final data analysis and will be replaced by an additional subject. The excluded subject will continue to be monitored for any safety events and the clinical will ensure that medical care is provided should a safety event occur. Data from the excluded subject will be acknowledged in the final study report but will not be

included in the primary statistical analysis. The exception to this exclusion is any data that is outside of the specified range of 45 – 60 as a result of the anesthesiologist titrating medications as a result of clinical signs or cardiovascular changes defined above. Additionally, data points will be excluded if significant artifact is present or if the sevoflurane concentration or BIS™ value is missing.

At the completion of the surgery, and after confirmation of the return of neuromuscular function, sevoflurane will be discontinued, and discontinuation time will be recorded, and as applicable, extubation will be performed when the patients demonstrate the purposeful movement, facial grimace, or eye-opening to jaw thrust.

10.9.4 Monitoring and Cardiovascular Variables

Monitors for the collection of variables such as pulse oximeter, non-invasive blood pressure (NIBP), electrocardiography, and skin temperature will be applied per institutional guidance. The standard monitoring procedures will be conducted per institutional recommendation and are not being mandated by the protocol. The de-identified digital copies of these files will be provided to Medtronic as available.
Pre-surgical Cardiovascular variables (heart rate [HR]; systolic and diastolic blood pressure [BP] including hypotension; oxygen saturation; and temperature), and BIS™ (for the BIS™ group) will be recorded at baseline preferably before administering any pre-medication or sedatives. Cardiovascular variables will be monitored during the surgery, and any abnormal cardiovascular parameters and times will be recorded in the medical record. The de-identified digital copies of these files will be provided to Medtronic as available.

10.9.5 Event Markers and Assessments

During the case, the time of events listed below will be recorded.
The end-tidal anesthetic gas concentration will be time-locked to the BIS™ system recordings. End-tidal sevoflurane, oxygen, and nitrous oxide concentrations will be downloaded from the anesthetic monitoring device, and de-identified digital copies will be provided to Medtronic.

Time and values of BIS™, ET_{SEVO} concentration (%) and other medication, FiO2(%) and EtO2(%), EtCO2(%) will be recorded at the following time intervals:

- Baseline
- Study start
- At IV placement, as applicable
- Start of induction
- Start of N2O, as applicable
- Start of sevoflurane
- At Anesthesia Airway Management (AAM)
- AAM change (including type of AAM)
- At any airway reflex (coughing, choking, laryngospasm)
- Every 15 min after airway management
- At all drug administration (as applicable)
- N_2O off (as applicable)
- Start of the surgery/procedure
- Skin incision, if applicable
- End of surgery/procedure (or skin dressing or cast or splint applied or abdominal block)
- Skin closure, if applicable
- Sevoflurane off
- Termination of all anesthesia
- Extubation
- Physician Awakening subject, if applicable
- Time of emergence (if occurs in OR)
- End of study (removal of device)
- 15 min post dexmedetomidine administration, if applicable
- Time moved to PACU

Any time end-tidal sevoflurane concentration (ET_{SEVO}) is increased or decreased or opioid or other medication is given, the event and time will be marked on the eCRFs. Also, if any changes to the dose or administration regimen are needed, these changes will be noted on the eCRF.

10.9.6 Recovery

Subject recovery will be continuously after the termination of anesthesia for presence of coughing, choking, laryngospasms, and emergence.

Emergence is defined as the time when any of the following first occurred:

- eyes open spontaneously,
- crying or phonating, or
- purposeful movements.

The time of emergence, time subject moved to PACU, and time of readiness for discharge will be recorded. The time of these assessments will be captured in medical records, source, and recorded on the eCRFs.

All subjects will be assessed at 15-minute intervals:

- Pediatric Anesthesia Emergence Delirium (PAED)
- Wong-Baker FACES Pain Scale (when subject is awake)
- PACU discharge readiness - Modified Aldrete Score

PAED, Wong-Baker FACES Pain Scale, and Modified Aldrete Score data will be recorded in source every 15 minutes. Raw data but total scores for the highest amount of delirium from the PAED, the highest amount of pain from the Wong-Baker FACES Pain Scale and the least ready for discharge Modified Aldrete Score raw data will be entered in to the CRF. The final raw data and total scores for the PAED, Wong-Baker FACES Pain Scale and Modified Aldrete Scale will be entered into the eCRF.

10.9.6.1 Presence of laryngospasms, coughing, choking

Presence of laryngospasms, coughing, choking as indicated by the anesthetist, if any present, time, and treatment course will be documented.

10.9.6.2 Pediatric Anesthesia Emergence Delirium (PAED)

Both groups will be assessed using the Pediatric Anesthesia Emergence Delirium (PAED) scale [1]. The PAED is an observational scale that has been validated in children to detect and measure the severity of hyperactive emergence delirium upon awakening from anesthesia. The scale includes 5 items: 1) Child makes eye contact with the caregiver, 2) child's actions are purposeful, 3) child is aware of his/her surroundings, 4) child is restless, 5) child is inconsolable. The scale is included in **Appendix A.** The time and treatments/conmedications given for delirium and will be documented.

10.9.6.3 Wong-Baker FACES Scale

The Wong Baker FACES pain scale is an instrument validated for ages 3+ to measure pain, by selecting a number on an ordinal 0-10 scale ("0" being no pain and "10" being the worst pain ever). Subjects will be instructed to indicate their degree of pain prior to being discharged from the PACU. The Wong-Baker FACES Scale will be administered when the subject is awake and able to perform the assessment. For more information, refer to **Appendix B**.

10.9.6.4 Modified Aldrete Score

End of surgery to post-anesthesia care unit (PACU) discharge readiness will be assessed using the Modified Aldrete Score that examines the following five criteria: motor activity, respiration, blood pressure, consciousness, and color [15, 16]. Before a subject can be safely discharged from the PACU, a score of 12 out of 16 points based on the PACU standard discharge criteria will be achieved. The time and score of PACU discharge reediness will be recorded. The scale is included in **Appendix C.**

10.9.7 Safety Monitoring

The choice of sedative drugs, dose, and route of administration will be based on clinical indications as judged by the Attending Physician and will not be changed for the purposes of the study. The BIS™ monitor will not be used in situations where the placement of the probe will interfere with a procedure, cause scan artifacts, or where the presence of a metal monitor is contraindicated (e.g., MRI scans). Therefore, we believe there is only a minimal increase in risks from participating in the study. This risk relates to the possibility of developing irritation to the skin at the site of sensor placement.

Subjects will be monitored for Adverse Events, Unanticipated Adverse Device Effects, Serious Adverse Events, and Device-Related Adverse Events from BIS™ sensor applications through the BIS™ sensor removal.

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

10.10 Assessment of Efficacy

Refer to Section 14.

10.11 Assessment of Safety

For safety analyses, adverse events will be summarized using frequency counts and percentages, refer to *Section14.*. Descriptive statistics will be provided by event type, severity, and relationship to study procedures and devices. Individual listings of adverse events, including event type, start date, duration, severity, and device-relatedness, will be provided as appropriate. Adverse events occurring during the procedure or 48 hours after the procedure will be recorded. For AEs and AE reporting requirements, refer to *Section 12.*

10.12 Recording Data

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

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

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

10.13 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;
- Late reporting of Serious Adverse Event /Serious Adverse Device Effect /Unanticipated Adverse Device Effect (for reporting refer to Section12).

Deviations will be recorded at the site and reported to Medtronic on the eCRF and via email to the study manager. The Protocol Deviation eCRF document shall be signed and dated by the Investigator or his authorized designee. At a minimum, the following information will be recorded:

- identification of the Investigator and site
- description of deviation
- date of occurrence
- reason for the deviation

- patient identifier, if associated with the event

Deviations will be entered into a database to allow a comprehensive review on a regular basis for identifying trends that warrant additional preventive or corrective actions to mitigate further occurrence. Clinical study management at Medtronic shall conduct this review. Repetitive or serious investigator compliance issues may result in the need to initiate a corrective action plan, and in some cases, freeze enrollment or ultimately terminate the Investigator's participation in the clinical study.
Study deviations must be reported to Medtronic, regardless of whether medically justifiable, pre-approved by the study leader (see contact details section) or taken to protect the subject in an emergency.

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

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

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

10.14 Subject Exit, Withdrawal or Discontinuation

The subject's parent and/or legal guardian or the subject has the 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.

If the subject discontinues participating in the study before 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.

- When and how to withdraw subjects from the study product treatment
- The type and timing of the data to be collected for withdrawn subjects
- Whether and how subjects are to be replaced
- The follow-up for withdrawn subjects.

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

- Screen Failure: Subject did not meet the study inclusion/exclusion criteria;
- Study Withdrawal: Removal from the study after enrollment by either subject /legal guardian, PI, or Sponsor, or technical problems;
- Study Complete: Completion of all study related activity by the subject;
- Other: protocol deviation leads to replacement of subject

10.14.1 Study Exit

A study exit eCRF is required for all subjects. Prior to exiting a subject from the study, it is recommended to follow the subject until all ongoing system and/or procedure related AEs are resolved or unresolved with no further actions planned. Following exit, subjects will continue to receive standard medical care. Upon exiting from the study, no further study data will be collected, or study visits will occur for the subject. All data available through the time of the subject's exit will be used for analysis.

Subjects are urged to remain in the study as long as possible but may be exited from the study for any of the following situations:

- Study completed
- Subject did not meet inclusion/exclusion criteria
- Subject did not provide consent or data use protection authorization
- Subject chooses to withdraw (e.g., consent withdrawal, relocation to another geographic location)
- Investigator deems withdrawal necessary (e.g., medically justified, inclusion/exclusion criteria not met, failure of subject to maintain adequate study compliance)

The following information is required to be collected at study exit:

- Reason for exit

If discontinuation is because of safety, the subject shall be asked to be followed for collecting safety data outside the clinical investigation.

10.14.2 Subject Chooses to Exit (i.e. Revokes Consent)

A subject can withdraw from the study at any time. If the subject wishes to exit from the study (i.e. the subject revokes consent), the study site is required to document the reason for exit on the Exit CRF. In addition, study sites shall follow the regulations set forth by the governing IRB. If possible, the following data should be collected prior to subject withdrawal:

- Reason for exit

10.14.3 Investigator Withdraws Subject

No subjects should be withdrawn by investigators unless compelling medical justification is present. It is recommended investigators discuss any withdrawals with the study team prior to withdrawing subjects. If the subject was randomized, it is preferred to keep the subject in the study and perform study procedures/collect data to the extent possible. If an Investigator Withdrawal is necessary, the following data should be collected prior to subject withdrawal if possible:

- Reason for subject withdrawal

11. Risks and Benefits

11.1. Potential Risks

Risks to participation are primarily physical. There are no social, economic, legal, long-term psychological, or other risks that have been identified. Risks under this protocol relate to both study devices and study procedures. We believe that the risks from the device(s) are in keeping with the definition of non-significant risk devices (NSR). Further, the devices in this study are non-invasive, and the clinical protocol design is minimal risk to the subject. No treatment or treatment decisions will be made during the course of this study. Following is a list detailing potential risks from study devices and the clinical protocol.

11.1.1 BIS™ Sensor Risks

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

- Minor discomfort, allergic reaction, or skin irritation (such as redness, itching) at the sensor application site is probable but is usually self-limited within hours.
- Pressure points/ injury in application areas are possible but anticipated to be rare due to the short duration of the study. Care in the application and removal of the sensors is advised. Skin reactions will be observed during and after the study procedures.
- Electric shock is very rare, and the product design and testing ensure insulation and ground fault detection.
- 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.

For more information on Sensor warnings and cautions, refer to Sensor IFU.

11.1.2 BIS™ Monitoring System Risks

BIS™ Monitoring System will be used per IFU. For more information on warnings and cautions, refer to IFU.

11.1.3 Pulse and Tissue Oximetry Sensor

Pulse and Tissue Oximetry Sensor placement involves positioning pulse and tissue oximetry sensors on the subject per the IFUs.

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 minimal.

A heating pad or hot water bottles may be used on the hands to improve circulation. The subject may experience some mild discomfort if the water is too warm. To minimize the discomfort, the subject will be asked if the heating is too warm, it will be turned on the lowest level possible for comfort, removed or additional separation will be used between the heater and the site for comfort.

11.1.4 General Anesthetics

There are some risks associated with taking general anesthetics, but they are relatively safe when administered correctly. General anesthesia will be administered per institutional guidance. All Subjects will be monitored by health care professionals closely for the effects. The most common side effects of general anesthesia include sore throat due to the breathing tube, nausea, vomiting, dizziness, bruising, or soreness from the IV drip, shivering and feeling cold, difficulty passing urine. These may occur despite the best efforts to avoid them.

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.

11.2. Potential Benefits

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

11.3. Risk-Benefit Rationale

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

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

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.

11.4. Risk Determination

Medtronic has determined that this is a study of "non-significant risk".

[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

12. Adverse Events and Device Deficiencies

12.1 Adverse Events

AE definitions are provided in Table 6.

AE information will be collected throughout the study from the enrollment through study exit.
A list of anticipated adverse events and risks that are expected in nature is included in Section 10.

Reporting of these events to Medtronic will occur via prompt email and the AE eCRF. 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 7), initial reporting must be done by email, phone, , and then on the eCRF completing as much information as possible. The completed AE eCRF must be submitted to Medtronic as soon as possible.

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

All AEs considered at least possibly related to the study will be followed until resolved, stabilized, and/or returned to baseline.

Medtronic will immediately conduct an evaluation of reported events. Table 5 shows event reporting requirements. At a minimum, the following information will be recorded:

- A description of the event
- The date of event onset
- The relatedness of the event to the device
- Actions are taken as a result of the event
- The outcome of the event

Table 5: Definition of Adverse Events and Device Deficiencies

General	
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. *NOTE 1:* This definition includes events related to the investigational medical device or the comparator. *NOTE 2*: This definition includes events related to the procedures involved.

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

Complication	An adverse event that includes the following is considered a complication: • Results in death, • Involves any termination of significant device function, or • Requires an invasive intervention Non-invasive (21 CFR 812.3 (k)): when applied to a diagnostic device or procedure, means one that does not by design or intention: • Penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra, or • Enter the ear beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or the vagina beyond the cervical os Where "penetrate" means: to pass, extend, pierce, or diffuse into or through something; to enter by overcoming resistance; to gain entrance to, and "pierce" means to force a way into or through something NOTE (FDA): Blood sampling that involves simple venipuncture is considered noninvasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for non-investigational purposes is also considered noninvasive.
Observation	Any AE that is not a complication. NOTE 1: Only system or procedure related AEs will be classified as "Complication" or "Observation"

12.2 Reporting of Adverse Events

Principal Investigator must report applicable events and product deficiencies to Medtronic and where appropriate an IRB or regulatory authority. At a minimum, the following information will be recorded:

- A description of the event
- The date of event onset
- The relatedness of the event to the device
- Actions are taken as a result of the event
- The outcome of the event

Study Contact Information:

Clinical Affairs	Medical Affairs

Ami Stuart, PhD, MSCI Clinical Study Manager Medtronic 6135 Gunbarrel Avenue Boulder, CO 80301 Phone: (80i) 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

12.2.1 Adverse Event and Device Deficiency Classification

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

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

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

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

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

Table 6: Adverse Event Classification Responsibilities

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

12.2.2 Adverse Event and Device Deficiency Reporting Requirements

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

Table 7: Reporting Requirements for Events

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

Medtronic	No later than 48 hours after the investigator first learns of the event.
Regulatory Authorities	As per local reporting requirements.
IRB	As per local reporting requirement.
Sponsor submits to:	
Regulatory Authorities	As per local reporting requirements.
IRB	As per local reporting requirement.

12.3 Foreseeable AE or SAE

The information provided in this section pertains to foreseeable adverse events that may be observed in this study and may collectively assist in identifying those events for a given device or therapy that are unexpected in nature. The foreseeable adverse events information consists of two parts: 1) adverse events reported in published literature, and 2) additional foreseeable adverse events. Evaluation of potentially anticipated events, adverse device effects observed in previous clinical studies, and reported events in literature may be used in combination with device labeling, current event reporting information, and other published data to assess for an unexpected occurrence.

12.3.1 Surgical Procedure

The study will be collecting data during the SOC surgical procedure; therefore, standard adverse events associated with a surgical procedure may be experienced (e.g., anesthesia complications, injury, infections, bleeding, exacerbation of pre-existing conditions, healing complications, etc.). Data from peer-reviews literature indicates that approximately 10% of the surgical patients had at least one AE related to the surgical procedures or the hospital environment [18] [19]. These events are not necessarily related to the study devices. In this study, the surgical procedure will be performed per SOC, and events related to the surgical procedure will not be captured.

All device and anesthesia management related to adverse events will be captured.

12.3.2 Anesthesia Management Adverse Events

During anesthesia, the events listed below will be captured:

- Hypotension and hypertension >20% from baseline, cardiac arrest or clinically significant changes in Heart Rate or Blood Pressure >20% from baseline
- The respiratory complications involving:
  - laryngospasm
  - bronchospasm
  - desaturation (SpO2<90%, of any duration)
  - hypercarbia (PCO_2=55mmHg)
- Events related to movement, grimacing, eye opening, tearing, sweating, mydriasis

12.3.3 BIS™ Sensor

Potential risks associated with the BIS™ sensor, as well as risk minimization, are discussed within *Section 11.*. The use of the BIS™ sensors may cause minor discomfort, an allergic reaction or skin irritation such as redness, itching, swollenness and redness, water-filled blister, and reddened scar tissue. These events will be collected during the study.

12.3.4 Adverse Events Reported in Literature

Potential adverse events and patient complications associated with BIS™ sensor reported in the literature, including skin integrity/pressure sores, rash, ecchymosis/heat wounds.

Skin integrity and reactions will be assessed just after sensor removal. All mild events that resolve within 48 hours after sensor removal are anticipated and will not be considered as reportable AE. If pronounced erythema and papules, or vesicular eruption are visible, on the subject's skin after sensor removal or if the subject requires any medical intervention related to the skin event then this event will be considered as AE. For more events and risk assessments, refer to *Section 10.*

In addition, the skin assessment will be reviewed by the Clinical Study Manager (CSM) and Medical Advisor in accordance with Clinical Safety Management and Potential complaint Plan. If the sponsor assessment of event classification differs from those opinions of the reporting investigator, the CSM communicates both opinions to the Site and Medtronic Complaint Handling Unit as needed.

12.4 Product Complaint Reporting

The reporting of product complaints (device deficiencies-DD) is part of the BTIGER Study and should be done in addition to the AE/DD reporting requirements. It is the responsibility of the investigator to report all product complaints associated with a medical device distributed by Medtronic, regardless of 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 (Medical Device Reporting [21 CFR 803] in the US).

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.

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 regulatory authorities 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

12.5 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.

13. Data Review Committees

13.1 Clinical Events Committee Review

This study will have the Steering Committee. The Steering Committee is composed of physicians with expertise in the area of Anesthesiology monitoring in pediatric patients, who will assume a leadership role in the overall study. The Steering Committee's roles are to:

- Develop the protocol along with Medtronic, to ensure its scientific and statistical soundness;
- Review the conduct of the study;
- Help identify and resolve problems with recruitment or performance

This study is considered a non-significant risk for study participants. Thus, the need for additional safety oversight beyond Medtronic's already rigorous safety monitoring processes is not required. A Medtronic Medical Advisor, as needed, will provide an independent medical review according to the study Safety and Complaint Management Plan. The Medical Advisor will not be affiliated with an investigative center.

14. Statistical Design and Methods

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

14.1 General Aspects of Analysis

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

The primary endpoint will be collected as a continuous variable every minute along with the BIS values. The primary analysis will be based on all evaluable data (excluding training subjects). Normality of data will be tested using the Kolmogorov-Smirnov test. Depending on whether normality assumption holds, a two-group t-test or Wilcoxon rank-sum test will be used to compare between the two treatment groups. A *P*-value of less than 0.05 is considered statistically significant unless otherwise specified.
The training subjects will not be included in the analysis set for the primary and secondary endpoints. The training subjects will be summarized descriptively and separately. Any specific findings from these subjects will be noted and discussed in the study report.

The following secondary endpoints will be evaluated:

- Time to first response (emergence)
- Time to PACU discharge readiness using Modified Aldrete Score
- Time to extubation

Upon meeting the primary endpoint, the secondary endpoints will be evaluated using the Holm-Bonferroni method. The method is a sequentially rejective multiple test procedure used to adjust multiplicity and to ensure the overall type I error rate is controlled at the 0.05 level. For statistical inferences, categorical variables will be evaluated using the Chi-square test or Fisher's exact test, and continuous variables will be evaluated using the t-test or Wilcoxon rank-sum test as appropriate. The analysis details will be clearly specified in the Statistical Analysis Plan.

Data Poolability

The clinical study will be conducted under a common protocol for each investigational site with the intention of pooling the data for analysis. Every effort will be made to promote consistency in study execution at each study site.

An assessment of data poolability of the sites will be performed using a mixed-effect model for the primary endpoint. A significance level of 0.15 will be considered. Sites with fewer than five subjects will be combined into large sites to ensure statistical robustness.

If the sites are found to be significantly heterogeneous with respect to the primary endpoint, additional analyses will be conducted to further assess differences between sites in baseline and procedural variables that might contribute the differences.

Missing Data

The primary analysis will include all evaluable data and missing values will not be imputed. BIS™ values that are outside of the specified range of 45 – 60 during maintenance of anesthesia for >35% of the maintenance duration will be considered a protocol deviation and will result in an exclusion of the subject from the primary analysis. The excluded subject will be replaced, and data from all excluded subjects will be noted and discussed in the final study report. Additionally, sensitivity analysis (e.g., multiple imputation) may be performed as appropriate to assess the robustness of study results.

Additional Summaries and Considerations

Cardiovascular variables will be summarized for both treatment groups. The incidence of hypotension will be summarized and compared to anesthesia sedation levels.

The anesthetic requirements with the BIS™ value, the percentage of time during maintenance with BIS™ value within the specified ranges, and number of episodes and duration of burst suppression will be assessed for the BIS and SP groups.

Additional endpoints, including the PAED scale, PACU discharge readiness and a subgroup analysis for subjects requiring neuromuscular blockade, will be evaluated by using descriptive statistics and compared between both groups.

14.2 Sample Size Determination

The first 2 - 4 subjects at each site will be enrolled to train the site team on the new technology and to determine the quality of data collection prior to randomization (n = 16-32). They will not be randomized and will not be included in the final analysis. For the analysis, a minimum of 36 subjects are required in each age group (18 per treatment group) for a minimum of 108 qualifying data sets. Subjects with non-qualifying data sets will be rejected and replaced with a newly randomized subject. This sample size was independently powered for each of the 3 age groups based on data from a previously published study conducted by Emory University.[13] The sample size will provide more than 80% power to detect a difference of 0.5% in end-tidal sevoflurane concentration between the BIS™ and SP groups with a common standard deviation of 0.5% and two-sided significance level of 0.05.

15. Ethics

15.1. Statement(s) of Compliance

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

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

16. Study Administration

16.1. Monitoring

16.1.1 Monitoring Visits

Site monitoring visits will be performed by the study monitor or other qualified sponsor staff per the monitoring plan 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.
- PI eligibility determination of each subject clearly documented.
- Adverse events and protocol deviations are documented and reported. PI AE severity and relationship determination clearly documented.
- Investigational and non-investigational device accountability and disposition are accurately documented.

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

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

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

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

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

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

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

Direct access to patient medical files for source data verification will need to be granted and prepared prior to any monitoring visits.

Raw device data will not be monitored.

16.2. Data Management

The Investigator must ensure accuracy, completeness, and timeliness (goal of 7-10 days) of the data reported in the eCRFs and all other required reports. Data reported on the eCRFs which are derived from source documents must be consistent with the source documents, and discrepancies need to be justified in a documented rationale, signed and dated by the (principal) Investigator, and filed in the patient medical file.

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

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

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

16.3. 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 access to subject medical files for source data verification (if applicable) will need to be granted and prepared prior to any monitoring visits.
Medtronic may conduct audits at participating study sites. The purpose of an audit is to verify the performance of the monitoring process and the study conduct, independently of the personnel directly involved in the study. RAs, such as the FDA, may also perform inspections at participating study sites. The investigator and/or institution shall permit Medtronic, IRBs and RAs direct access to source data and documents during monitoring, audits and regulatory inspections.
Data entered must be traceable to source documents and cannot be directly recorded on the eCRF. Source documentation is defined as the first-time data appearance and may include original documents, data, and records (e.g., hospital records, clinical and office charts, procedure reports, laboratory records, or evaluation checklists, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, subject files.)

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

16.4. 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. 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

Study-related documents including all study-related Source Documents, CRFs, ICFs, Investigator Site File (ISF), Final study reports, etc. should be maintained for a minimum of 2 years after the completion or

termination of the study or until the records are no longer required to support a marketing application (or longer in compliance to local requirements). The retention period may be longer if required by Medtronic or local or global regulatory requirements. Before the destruction of the study related data, the Investigator must notify the sponsor. The Principal Investigator will ensure that essential study documents are not destroyed until written permission has been obtained from Medtronic.

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

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, FDA, RA and the investigator that pertains to the investigation, including required reports.
- Subject's case history records, including:
  - Signed and dated IC.
  - 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
- FD
- Subject screening log & ID log
- Device Disposition Logs containing Model and serial numbers of devices delivered to the study site, received dates of devices, 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, IC,
- 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.
- 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 (if applicable) and current signed CV of principal investigator and key members of the investigation study site team (as required by local law), delegated task list
- All signed and dated case report forms submitted by investigator, including reports of AEs, ADEs and DDs (for non-OC studies)
- All approved IC templates, and other information provided to the subjects and advertisements, including translations
- 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 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

16.8.1. Investigator Reports

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all case report forms, adverse events and adverse device effects (reported per the country-specific collection requirements), device deficiencies, deaths, and any deviations from the clinical investigation plan. If any action is taken by an IRB with respect to this study, copies of all pertinent documentation must be forwarded to Medtronic in a timely manner. Reports are subject to inspection and to the retention requirements as described above for investigator records.
Safety data investigator reporting requirements are listed in Section 12. 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
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 3 months of study completion or termination.

16.8.2. Sponsor Reports

Medtronic shall prepare and submit the following complete, accurate, and timely reports listed in the tables below (by geography). In addition to the reports listed below, 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 prior to the first enrollment.

16.9.1. Publication Committee

Medtronic may form the Publication Committee from study investigators. Medtronic personnel may serve as members of the committee. This committee will manage study publications with the goal of publishing findings from the data. The Publication Committee will develop the final Publication Plan as a separate document.

The Publication Committee's role is to: 1) manage elements addressed in the publication plan as outlined in this appendix, 2) develop the final Publication Plan under separate cover, 3) execute the Publication Plan, 4) oversee the publication of primary and ancillary study results, 5) review and prioritize publication proposals, 6) provide input on publication content, and 7) determine authorship. In addition, the committee will apply and reinforce the authorship guidelines set forth in the Publication Plan.

Membership in the Publication Committee does not guarantee authorship. The committee will meet at regular intervals, as needed.

16.9.2. Management of Primary, Secondary and Ancillary Publications

The data may be published or used by study investigators provided that such publication or use is in accordance with this protocol, the Medtronic Publication and Authorship Policy, and the Clinical Investigation Agreement. The Publication Committee reviews, prioritizes, and manages all publications, including primary, secondary and ancillary publications. Primary and secondary publications are those that address analyses of any or all primary objectives or secondary objectives, respectively, as specified in the Clinical Investigation Plan.

An ancillary publication is any publication that does not address the study objectives identified in the Clinical Investigation Plan. They include publications proposed and developed by other Medtronic departments or entities, clinicians participating in this clinical study, and clinicians not participating in this clinical study.

The committee will work with Medtronic to ensure that requests do not present conflicts with other proposals, are not duplicative, and to determine which ancillary publication proposals, if any, will be supported.

The committee may decide that no publications, including abstracts, will be published prior to the end of the study or with individual site data. Requests for publications on study objectives utilizing subset data (e.g., regional) will be evaluated for scientific validity and the ability of Medtronic to provide resources.

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.

16.9.3. Criteria for Determining Authorship

Publications will adhere to authorship criteria defined by the International Committee of Medical Journal Editors (ICMJE, Uniform requirements for manuscripts submitted to biomedical journals, www.icmje.org). Individual authorship criteria defined by the target journal or conference will be followed when it differs from ICMJE criteria.
Authors, including Medtronic personnel, must at a minimum meet all of the conditions below:

- Substantial contributions to conception and design of the work, or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Decisions regarding authorship and contributor-ship will be made by the committee. The selected authors will be responsible for drafting the publication. All selected authors must fulfill the authorship conditions stated above to be listed as authors, and all contributors who fulfill the conditions must be listed as authors.

All investigators not listed as co-authors will be acknowledged as the “Medtronic <insert study name> Study Investigators” and will be individually listed according to the guidelines of the applicable scientific journal when possible and affiliation. Any other contributors will be acknowledged by name with their specific contribution indicated.

16.9.4. Transparency

Transparency of clinical study results will be maintained by the following means:

- A final report, describing the results of all objectives and analysis, will be distributed to all investigators, ECs and CAs of participating countries when required by local law

- Registering and posting the study results on a <publicly accessible database, e.g., ClinicalTrials.gov> based on the posting rules stipulated
- Submitting for publication the primary study results after the study ends
- Disclosing conflicts of interest (e.g., financial) of the co-authors of publications according to the policies set forth by the corresponding journals and conferences
- Making an individual study sites study data accessible to the corresponding investigator after the completion of the study, if requested

16.10.Suspension or Early Termination

The Sponsor reserves the right to discontinue the study at any stage, with written notice to all investigators and reviewing IRB. Similarly, investigators may withdraw from the study at any time, subject to providing written notification to the Sponsor 30 days prior to the date they intend to withdraw.

The Sponsor and investigators will be bound by their obligation to complete the follow-up of subjects already participating in the study. If the study is terminated or suspended, no additional enrollment will be allowed unless otherwise informed by the sponsor. The current subjects will be followed according to the protocol, and information obtained during subject follow-up shall be reported to the Sponsor on the appropriate eCRF.

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

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

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

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

- Failure to obtain initial IRB approval or annual renewal of the study;
- Consistent non-compliance to the CIP (e.g., failure to adhere to inclusion/exclusion criteria, failure to follow subjects per scheduled follow-ups, failure to implement required corrective and preventive actions, etc.);
- Lack of enrollment;
- Non-compliance 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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14. Akeju, O., et al., *Age-dependency of sevoflurane-induced electroencephalogram dynamics in children.* Br J Anaesth, 2015. **115 Suppl 1**: p. i66-i76.
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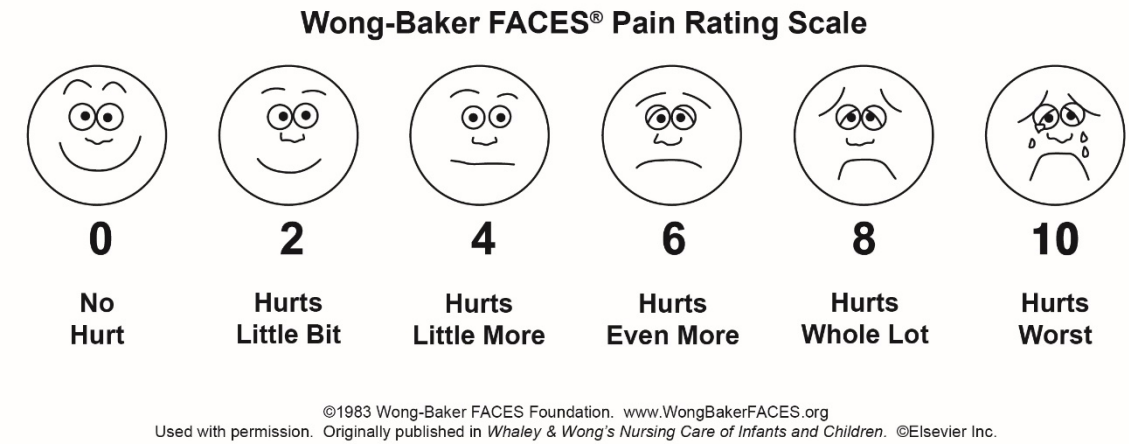
18. Appendices

Appendix A – Pediatric Anesthesia Emergence Delirium (PAED) [1]

The PAED Scale	
Item scores are added together for a total score, with higher scores indicating more severe delirium	
Items 1,2,3 are scored as follow: 4 = not at all 3 = just a little 2 = quite a bit 1 = very much 0 = extremely	Items 4 and 5 are scored as followed 0 = not at all 1 = just a little 2= quite a bit 3 = very much 4 = extremely
Items	**Sore**
1. Child makes eye contact with caregiver	
2. Child's actions are purposeful	
3. Child is aware of his/her surroundings	
4. Child is restless	
5. Child is inconsolable	
Total Score	

Appendix B – Wong-Baker FACES Scale [2, 3]



Date of Assessment: _____ Time of Assessment: _____

Appendix C – Modified Aldrete Scoring System [15, 16]

ACTIVITY	Able to move all extremities voluntarily on command	2
	Able to move 2 extremities voluntarily on command, some weakness	1
	Unable to move extremities	0
RESPIRATION	Able to deep breathe and cough without assistance	2
	Requires airway assistance	1
	Apnea	0
CIRCULATION	Blood pressure and heart rate are within 20% of presedation level	2
	Blood pressure and heart rate are within 20-50% of presedation level	1
	Blood pressure and heart rate are less than 50% of presedation level	0
CONSCIOUSNESS	Fully awake, able to answer questions as appropriate	2
	Arousable with verbal stimulation	1
	Unresponsive	0
OXYGENATION	Able to maintain oxygen saturation >92 percent on room air	2
	Requires supplemental oxygen to maintain oxygen saturation >92 percent	1
	Oxygen saturation <92 percent even with supplemental oxygen	0

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/Sr. Clinical Research Specialist
2.0	• Revision to new Operating Unit • Correction to Wong-Baker Collection criteria	Stephanie Monza, Sr. Clinical Research Specialist
3.0	1. Changes to title page to remove unused rows 2. Addition of signal quality index (SQI) to glossary 3. Change definition of time of surgical procedure to maintenance duration to align with statistical analysis plan 4. Increase number of sites up to eight 5. Addition of pre-operative vitals obtained in pre-operative holding to baseline/enrollment visit procedures and assessments 6. Change of surgeries approved for study to allow for approval of additional surgery types by study team 7. Change in allowed % of time outside of BIS range for BIS-guided subjects from 25% of 35% to improve number of qualifying cases (business decision) 8. Change in Wong-Baker FACES Pain Rating Scale to be performed only when subject is awake to avoid unnecessary protocol deviations 9. Completion of recovery assessments changes from every 5 minutes to every 15 minutes 10. Addition of required variables to list of timepoints for BIS, ETSevo, FiO2, and EtO2 data collection needed for outcome analysis 11. Clarification of procedure and recovery variables	Ami Stuart, Ph.D., Sr. Clinical Research Specialist

	12. Update of missing references throughout document 13. Update to data collection table 5 to include emergence and adverse event assessment in PACU if applicable 14. Removal of confusing language in 10.7 Baseline around what is recorded where. All data should be recorded in source and CRF per section 16.2 and Case Report Form Completion Guidelines. 15. Clarity around Adverse Event language 16. Update to Clinical Affairs Clinical Study Manager (CSM) contact from Stephanie Monza to Ami Stuart as Stephanie Monza is no longer the CSM or Safety Manager 17. Minor grammar/spelling revisions 18. Update to 056-F275, v D Clinical Investigational Plan Template	
4.0	1. Sample size section in summary and 14.2 updated to reflect the required number of cases to be analyzed. 2. Minor grammar/spelling revisions	Ami Stuart, Ph.D., Sr. Clinical Research Specialist
4.1	1. Update to current template	Ami Stuart, Ph.D., Sr. Clinical Research Specialist