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Medtronic

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	The influence of age on EEG signals and consciousness during anesthesia (TIARA)
Clinical Investigation Plan Identifier	MDT18067TIARA
Study Product Name	Bispectral (BIS™) index complete monitoring system
Sponsor/Local Sponsor	Sponsor Medtronic Medical Surgical Portfolio Patient Monitoring Operating Unit 6135 Gunbarrel Avenue, Boulder, Colorado, 80301 USA Local Sponsor EU Legal Representative Medtronic Bakken Research Center Endepolsdomein 5 6229 GW Maastricht The Netherlands
Document Version	5.1
Version Date	12DEC2022

1. Investigator Statement

Study product Name	Bispectral (BIS™) index complete monitoring system (BIS™Monitoring System; The 4 Channel BISx™; BIS™ bilateral sensor)
Sponsor	Sponsor Medtronic Medical Surgical Portfolio Patient Monitoring Operating Unit 6135 Gunbarrel Avenue, Boulder, Colorado, 80301 USA Local Sponsor EU Legal Representative Medtronic Bakken Research Center Endepolsdomein 5 6229 GW Maastricht The Netherlands
Clinical Investigation Plan Identifier	MDT18067TIARA
Version Number/Date	Version 5.1, 12DEC2022
I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated. *I agree to comply with Good Clinical Practice principles outlined in ISO 14155, and other applicable regulatory guidelines under which the study is being conducted. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of Medtronic.* *I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Medtronic. I will discuss this material with them to ensure that they are fully informed about the products and the study.*	
Investigator's Signature:	
Investigator's Name:	
Institution:	
Date:	

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2. Glossary

Acronym	Definition
ADE	Adverse Device Effect Adverse event related to the use of an investigational medical device. (ISO 14155)
AE	Adverse Event Untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated. (ISO 14155)
A-Line	Arterial catheterization A catheter inserted into the artery that allows measurement of Mean Arterial Pressure (MAP) and sampling of arterial blood gas samples.
ASA	American Society of Anesthesiology
BIS	Bispectral Index™ This monitoring technology uses processed EEG signals to measure sedation depth based on the level of consciousness.
Ce	Effective Site Concentration
CE	"Conformité Européenne" (French for European Conformity) CE marking is a certification indication in the European Economic Area that the device or product being sold meets the expected health, safety and environmental standards.
CIP	Clinical Investigation Plan ("Protocol") Official document that states the rationale, objectives, design, conduct, monitoring, etc. of the clinical investigation.
CO_2	Carbon Dioxide Levels can be monitored with a capnograph, a device that measures the concentration of carbon dioxide from each inspired and expired breath. Gases are collected with a non-invasive side stream from the inhaled and exhaled gases of the subject. Capnograph outputs numeric values and waveforms of the fractioned concentration of CO_2 of each breath.
CRF	Case Report Form Forms where the clinical data are collected. eCRF is the electronic version.
CTA	Clinical Trial Agreement A formal legal contract executed by both the sponsor (Medtronic) and participating Institution which outlines study expectations, including compensation.
CV	Curriculum Vitae Written record of an individual's education, qualifications and work history.
DD	Device Deficiency Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. (ISO 14155)
EC	Ethics Committee Responsible for ensuring that research is carried out in a safe and ethical manner in accordance with all local and international law.
ECG	Electrocardiogram A diagnostic tool that measures and records the electrical activity of the heart.
eCRF	Electronic Case Report Form

Acronym	Definition
ED	Effective dose The minimum dose or concentration of a drug that produces the intended biological response.
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 A record of the brain activity.
EFS	Edmonton Frail Scale Assessment measuring domains of frailty.
ET	End-tidal concentration This is a clinical indicator for predicting the emergence from inhalation anesthetics.
EMG	Electromyogram
EMR	Electronic Medical Record Digital version of a patient's medical record within a single facility.
$EtCO_2$	End-tidal Carbon Dioxide The value of exhaled carbon dioxide displayed by the capnograph device.
EtO_2	Fraction of inspired oxygen
FiO_2	End expiratory oxygen
GCP	Good Clinical Practice An international quality standard for conducting clinical trials.
GDP	Good Documentation Practice Guidelines or standards by which documents are created and maintained.
HC	Helsinki Committee Responsible for ensuring that research is carried out in a safe and ethical manner in accordance with all local and international law.
ICF	Informed Consent Form An informational document that serves as a voluntary agreement to participate in research.
IFU	Instructions for Use
IRB	Institutional Review Board An administrative body created to protect the rights and welfare of human research subjects.
ISF	Investigator Site File Structured regulatory binder(s) supplied by the sponsor for study record maintenance.
LMA	Laryngeal mask airway Medical device that keeps a patient's airway open during anesthesia.
LOC	Level of consciousness This is a measurement of a person's responsiveness to stimuli or arousability.
MAC	Minimum alveolar concentration The concentration of the vapor in the alveoli of the lungs that is needed to prevent movement or motor response of patients in response to surgical stimulus, including pain.
MMSE	Mini Mental State Examination This is a standardized assessment for measuring cognitive function.

Acronym	Definition
MNA®-SF	Mini Nutritional Assessment This is a standardized assessment for identifying malnutrition in elderly persons.
MOAA/S	Modified Observer's Assessment of Alertness/Sedation Scale A six-point sedation scale to assess sedation levels.
NMBA	neuro-muscular blocking agents
PI	Principal Investigator The person responsible for overseeing the study and assuring study completion in compliance with applicable regulations.
PIC	Patient Interface Cable This sensor cable connects the BISx4 to the BIS Sensor.
RDC	Remote Data Capture The collection of scientific data for clinical trials, often referred to as electronic data capture (EDC).
SAE	Serious Adverse Event Adverse event that led to death, serious deterioration in the health of the subject…fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment. (ISO 14155)
SpO_2	Peripheral capillary oxygen saturation A non-invasive spectroscopic estimate of arterial oxygen saturation measured transcutaneously by a pulse oximeter
SOP	Standard Operating Procedures Instructions compiled by an organization to assist in carrying out complex routine operations, aiming to achieve efficiency and quality output.
TCI	Target-controlled infusion This technique of infusing IV drugs to achieve a user-defined predicted drug concentration.
TMF	Trial Master File The collection of all essential documents which allows the conduct of a trial to be traced and evaluated.
TIVA	Total Intravenous Anesthesia A technique of general anesthesia in which agents are given exclusively intravenously without the use of inhalation agents.

3. Synopsis

Title	The influence of age on EEG signals and consciousness during anesthesia (TIARA)
Product Name	Bispectral (BIS™) index complete monitoring system
Sponsor	Medtronic Medical Surgical Portfolio Patient Monitoring Operating Unit 6135 Gunbarrel Avenue, Boulder, Colorado, 80301 USA
Local Sponsor	EU Legal Representative Medtronic Bakken Research Center Endepolsdomein 5 6229 GW Maastricht The Netherlands
Indication under investigation	The BIS™ system will be used on-label as approved in the respective study site country to monitor and non-invasively measure and interpret brain wave activity directly related to the effects of anesthetic agents.
Investigation Purpose	To evaluate the relationships between BIS parameters, age, and depth of anesthesia in patients undergoing surgery under general anesthesia. In particular, to improve the BIS™ Index performance in the elderly population.
Product Status	All Medtronic products used in this study are commercially available in the study site's country and will be used within the specifications of the product labeling.
Primary Objective	To evaluate the relationships between BIS™ parameters, age, and depth of anesthesia in patients undergoing surgery under general anesthesia.
Secondary Objective	To investigate BIS™ parameters, depth of anesthesia and physical and cognitive states in these patient populations.
Study Design	Multicenter, non-invasive, interventional, data collection study to improve the current BIS™ algorithm. Eligible consented subjects 18 years or older will be given pre-surgical assessments. Subjects will have the BIS™ sensors applied to their forehead during the duration of the surgery.
Sample Size	It is planned to enroll up to 100 subjects from 2 centers. It is anticipated that approximately 35% of enrolled patients will be between ages 18-64 years old, and approximately 65% of patients will be above the age of 65 years.

Inclusion/Exclusion Criteria	Inclusion Criteria A potential subject may be included for participation in the study if the subject has/is: 1. ≥ 18 years of age 2. ASA physical status I-III 3. Able and willing to participate in the study and sign the informed consent form 4. Will undergo non-ambulatory elective surgery under general anesthesia 5. Has an expected surgery time > 1 hours Exclusion Criteria A potential subject will be excluded from participating in the study if the subject has/is: 1. Pregnant 2. Unwilling to undergo EEG measurement 3. Undergone brain surgery procedure or had a cerebrovascular accident or severe head trauma in the last 10 years 4. Alcohol or illicit drug use, which prevents normal functioning in society or has led to organ toxicity. Chronic use of opioids, narcotics, or analgesics, which may limit a subject's responsiveness to analgesic dosages. 5. Known or suspected electroencephalograph abnormality (e.g., epilepsy or scarring) 6. Presence of a major psychiatric condition such as Bipolar disorder/ schizophrenia/ Alzheimer's disease/ dementia/ Parkinson's disease /major depression 7. Severe visual or auditory disorder 8. Cannot understand or is unwilling to perform the study assessments, according to the investigator's judgment
Study Procedures and Assessments	Subjects will be considered enrolled at the time they sign the informed consent. Basic demographic and Medical History data will be collected at the baseline visit, and subjects will be given three assessments: ▪ Mini Mental State Examination (MMSE) ▪ Mini Nutritional Assessment (MNA®-SF) ▪ The Edmonton Frail Scale (EFS) During the surgical procedure, the BIS™ sensors will be placed on the subject's forehead before any anesthetics are given, and data will be collected throughout the duration of the surgery. The subject will also be fitted with Nellcor™ pulse oximetry sensors.

	Prior to induction subjects will be assessed using the Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S). A slower induction of anesthesia will be achieved by setting a lower initial target propofol dose and making an incremental increase in the targeted dose. This is a conservative approach which maintains consistency across all study subjects and will ensure safety of the elderly patients included in the study, which should also closely align with standard institutional practices. The propofol will be administered using target-controlled infusion (TCI) pump, and the initial targeted effective site concentration (Ce) will be half of the effective site propofol concentration based on drug Instructions for Use (IFU) and on the subject's body mass used for induction. The TCI will calculate the initial bolus and infusion rate required to rapidly achieve and maintain this drug level based on propofol's population pharmacokinetics using the Schnider Model. At this step, the depth of anesthesia will be assessed using MOAA/S after an equilibrium time of approximately 5 minutes (from the start of propofol infusion.) After this initial step, the target effect site concentration is subsequently adjusted in an attempt to maintain the desired level of sedation and three-quarters of the Ce will be administered. This second step will also require depth of anesthesia assessment using MOAA/S after an equilibrium time of approximately 5 minutes. Lastly, the final/full Ce of the propofol will be administered, and the MOAA/S will be assessed after another equilibrium time of 5 minutes is reached. The specified induction period will last approximately 15 minutes in order to record and monitor the BIS values, EEG readings, and MOAA/S scores across the anesthetic agent introduction into the subject. After these steps, anesthesia will be delivered and maintained per institutional guidance. During the anesthesia maintenance phase, anesthesia medications will continue according to standard practice without any other intervention. The depth of anesthesia will be assessed at the beginning of the maintenance period to confirm a MOAA/S of 0 has been achieved. The administration of anesthetic drugs, neuro-muscular blocking agents (NMBA), NMBA reversal drugs, anti-nausea drugs, and drugs that reduce pain will be recorded on the electronic Case Report Form (eCRF) (administration time and dosage). BIS values and EEG data will be recorded with a USB storage device connected to the BIS complete monitor. Blood pressure, $EtCO_2$, SpO_2, pulse rate, respiration rate, end-tidal anesthetic gas, FiO_2%, EtO_2%, and temperature will be gathered from the hospital computerized database and the Nellcor system, digital records, labeled with patient ID, will be provided to Medtronic. The BIS data file labeled with patient ID will be provided to Medtronic.

	Only adverse events related to the BIS™ and Nellcor™ systems will be reported.
Statistics	Descriptive statistics will be used to summarize study outcomes. Subjects with valid recorded data from the study device (EEG signals) and a completed eCRF will be included in the data analysis. Up to 100 subjects are planned to enroll, with 65% subjects over the age of 65 years. The sample size is not powered to detect a statistically significant difference as this study is a feasibility study. The relationships between BIS™ parameters, age, physical and cognitive state, and depth of anesthesia in patients undergoing surgery under general anesthesia will be assessed. Pearson's correlation or Spearman's rank correlation will be calculated as appropriate. Continuous variables will be evaluated using analysis of variance or nonlinear E_{max} model, and categorical variables will be evaluated using the chi-square or Fisher's exact test, as well as multivariate logistic regression with age as an explanatory factor. A P-value of less than 0.05 is considered statistically significant unless otherwise specified. An early data review will be performed for the first 40 enrolled subjects to ensure data validity and no safety concern. Sample size re-estimation may be performed to ensure sufficient data to be collected to meet the study objectives.

4. Introduction

4.1 Background

Brain function monitoring with Bispectral Index™ (BIS™) technology during surgical procedures gives anesthesia providers the ability to directly monitor the anesthetic effect on the patient's brain and optimize the anesthetic dosing for the individual.

The BIS™ technology converts raw EEG data acquired from the frontal cortex into a single number between 0 (isoelectric EEG) and 100 (fully awake). Given the numerous changes that occur in brain anatomy and physiology with typical aging, it is reasonable to assume that the EEG patterns of elderly patients and young patients under general anesthesia differ.

In general, elderly patients are more sensitive to anesthetic agents. Less medication is usually required to achieve a desired clinical effect, and drug effect is often prolonged[1]. We might thus hypothesize that the BIS™ technology should be age adjusted under the assumption that the anesthetic state is also dependent on the patient's physical, mental, and cognitive state.

4.2 Purpose

To evaluate the relationships between BIS™ parameters, age, and depth of anesthesia in patients undergoing surgery under general anesthesia. In particular, to improve the BIS™ Index performance in the elderly population.

5. Objectives and/or Endpoints

5.1 Objectives

This study is evaluating the BIS™ system's response under specified and standard clinical practices for patients undergoing elective surgery under general anesthesia.

5.1.1 Primary Objective(s)

To evalute the relationships between BIS™ parameters, age, and depth of anesthesia in patients undergoing surgery under general anesthesia.

5.1.2 Primary Endpoint

All data gathered by the BIS™ system during general anesthesia, including:

- EEG waveforms
- Electromyogram (EMG)
- BIS Number
- Total Power
- Anesthesia records

5.1.3 Secondary Objective(s)

To investigate BIS™ parameters, depth of anesthesia and physical and cognitive states in the study subject population.

5.1.4 Secondary Endpoint

Assessments of the subject's demographics, age and blood panel as well as the physical and cognitive state using:

- Mini Mental State Examination (MMSE)
- Mini Nutritional Assessment (MNA®-SF)

- Edmonton Frail Scale (EFS)

6. Study Design

This is a multicenter, non-invasive, interventional data collection study to improve the current BIS™ algorithm. Subjects undergoing a standard of care, elective non-ambulatory surgery under general anesthesia will be recruited. Eligible patients 18 years and older, will be informed of the study and invited to participate. Each eligible and consented subject will undergo the study assessments and procedures. The BIS™ sensors will be applied to the patient's forehead before anesthesia is administered. The BIS™ data will be collected throughout the surgery. The data recorded during the surgery will be provided to Medtronic.

It is planned to enroll up to 100 subjects from 2 centers. It is anticipated that approximately 35% of enrolled patients will be between ages 18-64 years old, and approximately 65% of patients will be above the age of 65 years. In addition to basic demographic data collection, three assessments, the Mini Mental State Examination (MMSE), the Mini Nutritional Assessment (MNA®-SF), and the Edmonton Frail Scale (EFS) will be administered to each subject prior to surgery.

Study sites that enroll faster than others will be allowed to do so in order to maintain an adequate enrollment rate.

6.1 Duration

Enrollment begins at patient consent and lasts through the duration of the surgery. This may span one day or multiple days depending on site-preference and consent timing. No additional follow-up visits will be required after the surgery is complete.

The trial is expected to last approximately 2 years after subject enrollment begins.

6.2 Rationale

The BIS™ technology converts raw EEG data acquired from the frontal cortex into a single number between 0 (isoelectric EEG) and 100 (fully awake). Given the numerous changes that occur in brain anatomy and physiology with typical aging, it is reasonable to assume that the EEG patterns of elderly patients and young patients under general anesthesia differ. Medtronic is continuously improving its monitoring devices to improve performance and widen the range of capabilities. To assess an algorithm, more robust clinical data is required to ensure the optimal functionality of the system. All data collected will be stored and may be used for future research and 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. The bilateral sensor placed on the patient's head collects EEG signals and transmits them to the BISx4™ unit. The BISx4™ unit filters and digitizes the signal, analyzes it for the artifact, and processes it using digital signal processing techniques to derive processed EEG parameters such as the BIS index, 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 ultimately derive the BIS™ Index.

The Nellcor™ Pulse Oximetry System continuously records SpO_2 measurements through one or more sensors. The Nellcor™ Adult SpO_2 Sensor, is indicated for single patient use when continuous noninvasive arterial oxygen saturation and pulse rate monitoring is needed.

7.2 Manufacturer

BIS™ and Nellcor™ are manufactured by Covidien LP, an indirect wholly owned subsidiary of Medtronic plc. with an address at Mansfield, MA USA.

7.3 Packaging

The BIS™ Complete Monitoring System will be provided by the sponsor at no charge and will be used as a study product. The Nellcor™ Pulse Oximetry System may also be provided to study sites at no charge and used as a study product as needed.

Conformité Européenne, or European Conformity (CE) marked devices will be used within intended use as described in the approved Instructions for Use (IFU) for which CE mark has been obtained.

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

The consumables (BIS™ bilateral sensor and Nellcor™ adult sensor) are for single patient use, and each consumable is packaged individually.

7.4 Intended Population

The BIS™ EEG complete monitor system is intended for use under the direct supervision of a licensed healthcare practitioner or by personnel trained in its proper use. The system, and all its associated parameters, is intended for use on adult and pediatric patients within a hospital or medical facility providing patient care to monitor the state of the brain by data acquisition of EEG signals. The BIS™ index, one of the Complete Monitor output parameters, may be used as an aid in monitoring the effects of certain anesthetic agents; and its usage with certain anesthetic agents may be associated with a reduction in primary anesthetic use and a reduction in emergence 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.

In this study, the intended population is adults undergoing standard of care, elective non-ambulatory surgery with general anesthesia.

7.5 Equipment

The following equipment will be made available at each study site to support study activities.

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 forehead 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 as shown below in **Figure 1**:

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

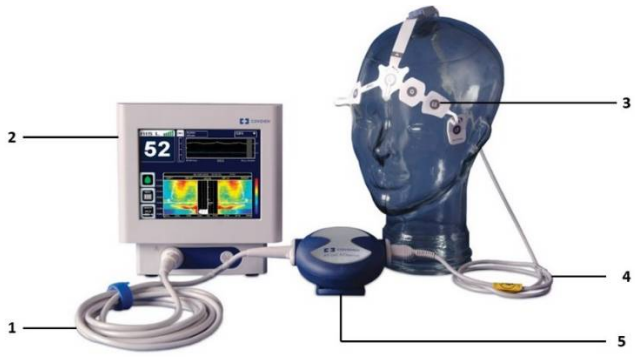


Figure 1: The BIS™ Complete Monitoring System. 1 - Monitor Interface Cable; 2 - BIS™ Monitor; 3- BIS™ bilateral sensor will be used; 4- Patient Interface Cable (PIC); 5- BISx4™ (LoC 4 Channel)

7.5.2 BISx4™

The BISx4™ receives, filters, digitizes and processes patient EEG signals. It is located close to the patient's head, where the EEG signal is less subject to interference from other medical equipment. The BISx4™ is shown in **Figure 2.** Its long flexible Monitor Interface Cable connects to the front of the monitor. The Patient Interface Cable (PIC) connects the BIS sensor to the BISx4™. The attachment clip on the BISx4™ is used to secure it in a convenient location near the patient's head. The BISx4™ Module is a variant of the BISx™ Module, and it processes up to four channels of EEG data. In this study, BISx4™ Module will be used with Bilateral Sensor.

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

7.5.3 Patient Interface Cable

The Patient Interface Cable (PIC) connects the BISx4™ to the BIS™ Sensor, refer to **Figure 2** above.

7.5.4 BIS™ Bilateral Sensor

The sensor is the single-use component of the BIS™ Monitoring System and should be replaced after each use. BIS™ Bilateral Sensors are designed with a 6 electrode pre-gelled EEG electrode array that is applied directly to the patient's forehead to transmit EEG signals to the BISx4™ Module as shown below in **Figure 3**. When the System is connected to a BISx4™ module and a BIS™ Bilateral Sensor, the monitor displays four channels of EEG.

Figure 3: BIS™ Bilateral Sensor

7.5.5 Bispectral Index™ (BIS)

Bispectral Index™ (BIS) monitoring systems allow anesthesia professionals the ability to access processed EEG information as a measure of the effect of certain anesthetics during the care of patients they select to monitor. The clinical impact of BIS™ monitoring has been demonstrated in a variety of randomized controlled trials that reveal the potential for BIS monitoring to facilitate improvements – including patient safety – in anesthesia care[2].

The BIS™ Index is a number between 0 and 100 scaled to correlate important clinical endpoints, such as moderate sedation or deep anesthesia, and EEG states during the administration of anesthetic agents (see **Figure 4**). BIS™ values near 100 represent an "awake" clinical state while 0 denotes the maximal EEG effect possible (i.e., an isoelectric EEG). A BIS™ value of 60 has a high sensitivity for identifying drug-induced unconsciousness. However, in some settings and with some combinations of sedatives and analgesics, unconscious individuals may have BIS™ values >60.

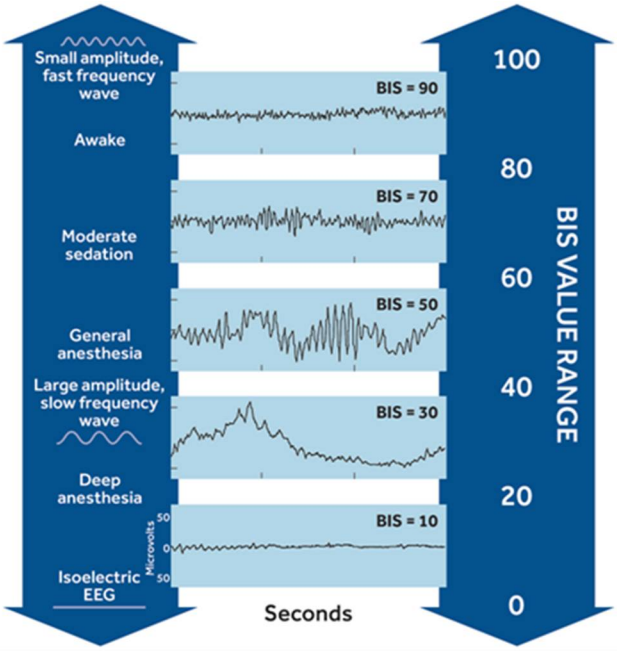


Figure 4: BIS™ Index Scale

Consideration of BIS™ information may be useful in various clinical situations that develop during anesthesia care, such as intra-operative awareness and too deep anesthesia. Ideally, BIS™ information can be integrated with other available monitoring information and patient assessment. As defined in the

A Pocket Guide for Clinicians of the BIS™, several clinical situations can influence the accuracy of the BIS™ value as an indicator of anesthetic hypnotic effect. Four key areas include the influence of muscle tone (EMG) from the forehead muscles; electrical and mechanical artifacts from medical devices; abnormal EEG states; and certain anesthetic agents and adjuvants – which can all lead to elevated BIS™ values. Serious clinical conditions – which may require a prompt response – have been associated with the sudden appearance of low BIS™ values. BIS™ responses are similar when most, but not all, anesthetic agents are administered in increasing amounts. Specifically, BIS™ responses to typical hypnotic agents (midazolam, Propofol, thiopental, isoflurane) were similar[3,4]. However, halothane has been found to have higher BIS™ values at an equipotent minimum alveolar concentration dose[5]. Further, BIS responses to ketamine administration are atypical[6.7]. In addition, BIS™ responses to administration of analgesic agents – including opioid analgesics and nitrous oxide –depend on the level of concomitant stimulation.

A significant correlation between BIS™ Index values and reduction in whole brain metabolic activity due to increasing anesthetic effect was measured using positron emission tomography[8]. Thus, factors other than drug administration that can influence brain metabolism (e.g., alterations in temperature or physiologic homeostasis) may also produce changes in the BIS™ Index.

7.5.6 Nellcor™ Pulse Oximetry System

The Nellcor™ bedside respiratory patient monitoring system provides continuous $Sp0_2$ recording through one or more sensors. The market-approved system, sensors and cables or other monitor may be provided by the sponsor to the study site. A laptop may also be provided to stream and record the $Sp0_2$ data if needed.

The Nellcor™ Adult SpO_2 Sensor, is indicated for single patient use when continuous noninvasive arterial oxygen saturation and pulse rate monitoring are required for patients weighing more than 30 kg. One or more sensors may be used, and can be applied to a small finger, thumb, or big toe.

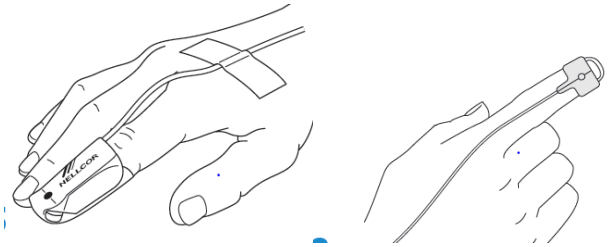


Figure 5: Nellcor Adult $Sp0_2$ Sensor

7.6 Product Use

A member of the Medtronic team will set up the BIS™ system at each participating research site upon site initiation and will ensure all equipment is fully functional. Specific instructions for the Site Investigator(s) and staff on system set up, use sensor application, and data transfer will be provided before subject enrollment.

7.7 Product Training Materials

All investigators and study staff members will be trained by the sponsor. The training will be performed prior to site activation and the recruitment of the first subject. Investigators or staff members are not permitted to perform any activity in the study before training is completed and correctly documented. Training will include at least the following topics:

- Study procedures
- Informed consent procedures and documentation
- Adverse Events (AEs), Safety Events, Device Deficiencies (DDs) and the reporting procedures of these events
- Good Clinical Practice (GCP)
- Study device management
- Case Report Form (CRF) completion
- Overview of the physical and cognitive assessment procedures
- Overview of ISO14155

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

7.8 Product Receipt and Tracking

The investigator or designee will maintain records of all devices or products provided by Medtronic free of charge to the study site.

Due to potential device variations across the regions in which the study will be conducted, all device components for both the BIS™ and Nellcor™ systems, including models and versions will be specified according to product accountability records.

7.9 Product Accountability

Product accountability will be documented by the PI or an authorized designee, using the sponsor shipping records, the Product Accountability Log, and also entry into the Device Accountability eCRF. The PI or an authorized designee shall keep source records documenting the receipt, use, return, and disposal of the study devices, which shall include (but is not limited to):

- Date of receipt, and name of person who received the shipment
- Identification of each study device (e.g. model number/part number, serial number/lot number, firmware/software number, etc.),
- Expiration date, if applicable,
- Subject ID association (applicable for Sensors only)
- Return or disposal date, including reason and name of person who disposed or returned device

The monitor is responsible to verify that the product is stored and maintained as described in Sections 7.9-7.11 and to verify the product accountability using the Device Accountability eCRF.

All products used in this study are market released in the geographies they are used. Additional device traceability may be required per local laws and regulations. If there are additional local requirements beyond what is collected by Medtronic on the eCRF, this is the Investigator's responsibility and should be recorded in the subject's medical records, but will not be collected by Medtronic (e.g., identification code linked to names and contact information, log of all subjects enrolled in the study, batch number, etc.).

7.10 Product Storage

The study equipment will be stored in a locked room, ideally in the Anesthesiology and Recovery Room department, whenever possible. The PI or his or her delegate is responsible for the appropriate storage of the product according to the study protocol and the device operator's manual. The study equipment should be easily identifiable and stored in a dry room at ambient temperature. Only the study staff delegated to use the equipment by the PI and trained by the sponsor should have access to the study equipment.

7.11 Product Return

All the study products will be returned to the sponsor at the end of the study. The product return will be documented in the Trial Master File (TMF) and Investigator Site File (ISF). All used single-patient consumables shall be destroyed, and the sponsor will provide further instructions to do so. All unused consumables will be returned to the sponsor.

8. Study Site Requirements

8.1 Investigator/Investigation Site Selection

All investigators managing the subject's anesthesia during surgery must be qualified and experienced practitioners. The physicians be experienced and/or trained in the handling of the BIS™ and Nellcor™ systems.

The role of the PI 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 PI shall:

- Be qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation
- Be experienced in the field of application and training in the use of BIS
- 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 as well as financing agreements shall be fulfilled, including, but not limited to the following:

- Institutional Review Board/ Ethics or Helsinki Committee (IRB/EC/HC) approval (and voting list, as required by local law) of the current version of the Clinical Investigation Plan (CIP) and Informed Consent Form (ICF).

- Regulatory Authority approval or notification (as required per local law)
- Fully executed Clinical Trial Agreement (CTA)
- Financial disclosure
- Curriculum Vitae (CV) of investigators and key members of the investigation study site team (as required). The signature on the CV must be dated within 3 years prior to the date of activation of the study site.
- Documentation of delegated tasks
- Documentation of study training
- Additional requirements imposed by local regulations, the IRB/EC/HC and Regulatory Authority shall be followed, if appropriate.

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

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

8.3 Role of the Sponsor Representatives

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

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

9. Selection of Subjects

9.1 Study Population

Potential subjects will include patients scheduled for a standard of care, elective non-ambulatory surgery under general anesthesia who meet all the inclusion and none of the exclusion criteria as specified in Sections 9.3 and 9.4.

9.2 Subject Enrollment

Subjects are eligible for enrollment into the study only after all inclusion and exclusion criteria have been reviewed and verified by the PI or a delegated study staff member. Study enrollment is accomplished by signing the Informed Consent Form (ICF) and documenting the entire informed consent process. Subjects who sign informed consent, but later are discovered to not meet and inclusion or exclusion criteria, will be withdrawn from the study.

9.3 Inclusion Criteria

A potential subject may be included for participation in the study if the subject has/is:

1. ≥ 18 years of age
2. ASA physical status I-III
3. Able and willing to participate in the study and sign the informed consent form
4. Will undergo non-ambulatory elective surgery under general anesthesia.
5. Has an expected surgery time > 1 hours

9.4 Exclusion Criteria

A potential subject will be excluded from participating in the study if the subject has/is:

1. Pregnant
2. Unwilling to undergo EEG measurement
3. Undergone brain surgery procedure or had a cerebrovascular accident or severe head trauma in the last 10 years.
4. Alcohol or illicit drug use, which prevents normal functioning in society or has led to organ toxicity. Chronic use of opioids, narcotics, or analgesics, which may limit a subject's responsiveness to analgesic dosages.
5. Known or suspected electroencephalograph abnormality (e.g., epilepsy or scarring).
6. Presence of a major psychiatric condition such as Bipolar disorder/ schizophrenia/ Alzheimer's disease/ dementia / Parkinson's disease /major depression.
7. Severe visual or auditory disorder.
8. Cannot understand or is unwilling to perform the study assessments, according to the investigator's judgment.

10. Study Procedures

Study Procedures will take place during the Baseline and Surgery phase of the study, which may be split into two separate days, or combined into one. A Schedule of Events table is located in Section 10.1 below, with additional details following.

10.1 Schedule of Events & Data Collection

Table 1. Schedule of Events & Data Collection Requirements

Data	Baseline	Surgery
Informed Consent Process and Documentation	X	
Inclusion/Exclusion criteria evaluation	X	
Demographic & Medical history	X	
Mini Mental State Examination (MMSE)	X	
Mini Nutritional Assessment (MNA-SF®)	X	
Edmonton Frail Scale	X	
Blood sample - levels of albumin, total protein, hemoglobin, total cholesterol	X	
Pregnancy screening (See section 10.6.1)		X
BIS™ sensor and Nellcor™ sensor application		X
BIS™ data collection		X
Patient vital signs (blood pressure, $EtCO_2$, SpO_2, pulse rate, FiO_2%, EtO_2%, respiration rate and temperature)		X
DOA according to the Modified OAA/S Responsive Scale		X
Drug administration during the surgery - Anesthetic drugs, drugs that induced or reduced paralysis, anti-nausea drugs, drugs that reduce pain (drug, dosage and time)	X	X
Adverse Events as described in Section 12		X
Protocol Deviations		X
Reason for Premature Study Termination (including patient death)	X	X

10.2 Subject Screening

Patients will be identified as potential study candidates at the pre-surgical evaluation when being considered for surgery.

The investigator will ensure that the patient can be enrolled in the study according to the inclusion/exclusion criteria, including the ability to sign the informed consent form. The delegated study team member performing the consent process will be responsible for all documentation of the informed consent process.

The investigator will register the subject in the enrollment log with their name, ID number, and unique study code. The study code assigned after the enrollment process will be used for all data identification. The identifying details of the subject will be written only in the enrollment log and the ICF and will not be transmitted to the sponsor or any other unauthorized person or entity.

10.3 Subject Consent

Informed consent initiates enrollment, and therefore must be obtained before any study-specific procedures are initiated. Only the PI or authorized designee may conduct the informed consent process, and this should be done only after all inclusion and exclusion criteria have been verified. The ICF used must be the most recent form that was approved by the sponsor and the Institutional Review Board/ Ethics or Helsinki Committee (IRB/EC/HC) and implemented to the site through proper training. The ICF must be current on the date signature. The ICF should be in a language that is clear to the subject. The subject must have ample time and opportunity to read and understand the informed consent form, to inquire about the details of the study, and to decide whether or not to participate in the clinical study. All questions about the study should be answered to the satisfaction of the subject. The original ICF, as well as all corresponding documentation, must be placed in the subject's original source file. A copy of the ICF should be given to the subject.

In the event the subject cannot read and/or write, the informed consent process shall be obtained through a supervised oral process. An independent and impartial witness must be present during this process. All ICF and any other information must be read aloud to the prospective subject, and when possible, the subject shall personally sign and date the ICF. The witness signs and personally dates the ICF attesting that the information was accurately explained and that informed consent was freely given.

Consistent with the DoH, vulnerable adults (i.e. those subjects mentally incapable of giving consent) are excluded from this protocol. Any subjects with mental incompetence (e.g. Alzheimer's, dementia, psychiatric disorders, developmental disorders) should be assessed for vulnerable status. If the ICF is signed by an individual other than the subject, the monitor may discuss whether the Investigator believes the subject meets the definition of a vulnerable adult. This protocol defines vulnerable adult as those

subjects mentally incapable of giving consent, in the Investigator's opinion. The Investigator should consider the definition of vulnerable adult per ISO 14155, which defines vulnerable adults as: "individuals who are unable to fully understand all aspects of the investigation that are relevant to the decision to participate, or who could be manipulated or unduly influenced as a result of a compromised position, expectation of benefits or fear of a retaliatory response. For example, this could include Individuals with loss of autonomy due to immaturity or through mental disability, persons in nursing homes, children, impoverished persons, subjects in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, and those incapable of giving informed consent. Other vulnerable subjects could include, for example, members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the sponsor, members of the armed forces, and persons kept in detention.

Legally authorized/designated representatives or guardians will not be permitted to execute the informed consent for this study.

Participation in this study is voluntary. The subject may elect not to be a part of the study or to leave the study at any time, for any reason. If the subject elects not to be a part of the study or to leave the study, this will not result in any penalty, and the subject will not lose any benefit to which the subject is entitled. This will not affect the routine treatment the subject receives, their relationship with the hospital, the clinic, or their doctors.

10.4 Enrollment

A subject is considered enrolled when the informed consent process has been finalized. The date the subject signed the ICF (and Data Protection Authorization, as required by local law) must be documented in the subject's medical records. A log of all subjects enrolled in the study should be maintained, as this study following ISO 14155 standards. Enrollment can be a stand-alone visit or can occur on the same day as the baseline.

10.5 Baseline

The baseline study procedures can be a stand-alone visit, or can be performed on the same day prior to the start of the surgery.

The following subsections outline the required procedures and data collection.

10.5.1 Demographic and Medical History

Demographic details (i.e., gender, weight, height, age, skin pigmentation), and medical history including primary and secondary diagnosis will be transcribed into the eCRF.

There are no medication/therapy restrictions in the study unless they are investigational and may confound the study results, in which case, prior approval would be needed from Medtronic. All prescription and over-the-counter medications taken within 14 days prior to screening will be collected and transcribed into the eCRF. The name of the medication, dose, and frequency and start and stop dates will be recorded.

If the baseline procedures occur on a separate date from the surgery visit, the subject should identify to the study team, the name and contact information of an individual that can be contacted in case the subject cannot be reached for any reason. This individual may be asked how the study subject may be reached, and about the subject's health status.

Subjects who are completing the baseline and surgery requirements on the same day will not be required to provide a contact person as there is no follow-up period beyond surgery.

10.5.2 Vital Signs

Baseline vital signs will be collected and transcribed into the eCRF. All baseline vitals should be collected prior to any surgery or induction procedures and will include the following:

- Systolic Blood Pressure
- Diastolic Blood Pressure
- Mean Blood Pressure
- SpO_2
- Heart Rate
- Respiratory Rate

10.5.3 Physiological & Cognitive Assessments

Three assessments, the Mini Mental State Examination (MMSE), the and the Mini Nutritional Assessment (MNA®-SF), and the Edmonton Frail Scale (EFS) will be administered to evaluate the subject's cognitive function. The test will be administered at the baseline visit or prior to surgery.

10.5.3.1 Mini Mental State Examination (MMSE)

The MMSE is widely used for a measure of cognitive function[9]. The MMSE consists of a variety of questions, has a maximum score of 30 points, and ordinarily can be administered in 5-10 minutes. The questions are grouped into seven categories, each rationally representing a different cognitive domain or function: Orientation to time (5 points); Orientation to place (5 points); Registration of three words (3 points); Attention and Calculation (5 points); Recall of three words (3 points); Language (8 points) and

Visual Construction (1 point). The total score will be recorded on the eCRFs. A sample copy is located in Appendix B.

10.5.3.2 Mini Nutritional Assessment – Short Form (MNA®-SF)

The MNA®-SF provides a simple and quick method of identifying elderly persons who are at risk for malnutrition, or who are already malnourished.[10] It identifies the risk of malnutrition before severe changes in weight or serum protein levels occur. The MNA®-SF was developed by Nestlé and leading international geriatricians and remains one of the few validated screening tools for the elderly. It has been well validated in international studies in a variety of settings. The scoring provides a maximum subtotal of 14 points, and it takes 5-10 minutes to administer. The score between 12-14 points is considered normal nutritional status; 8-11 points indicate the patient is at risk of malnutrition, and 0-7 points are malnourished. The total score will be recorded on the eCRFs. See Appendix C for a sample copy of the scale.

10.5.3.3 Edmonton Frail Scale (EFS)

Frailty is a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency. The Edmonton Frail Scale assesses nine domains of frailty including a cognition evaluation (i.e. hand-draw a face clock), functional performance (i.e. timed get up & go test), general health status, functional independence, social support, medication usage, nutrition, mood, and continence.[11] It can be administered in 5-10 minutes and is scored from 0 to 17. A higher score indicates a higher degree of frailty, scores 10+ in the severe range. The total test score will be recorded on the eCRFs. A sample copy of the scale can be found in Appendix D.

10.5.4 Blood Samples

Blood sample collection can be completed after informed consent has been obtained. The blood sample can be collected at Baseline, before surgery, or at the start of the surgery visit. If the blood sample is taken after the patient has been sedated and anesthesia induction begins, the blood sample should be taken from the opposite arm from which the intravenous therapy infusion of propofol was administered. The blood sample should be taken as soon as possible, but is required to be taken before intubation or the first surgical incision is made (whichever comes first).

Blood samples to assess the levels of the following will be collected and documented in the eCRF:

- Albumin (gm/dL)
- Hemoglobin (gm/dL)
- Total cholesterol (mg/dL)
- Total protein (gm/dL)

10.6 Surgery

The following sub-sections outline the required procedures and data collection during the surgery.

10.6.1 Pregnancy Screening

Due to the potential risk the surgery and anesthesia administration might pose, pregnant women should not take part in this study. It is expected that female subjects of child-bearing potential (i.e. not post-menopausal or surgically sterile) will be screened for pregnancy according to standard institutional policies before the surgery visit. If standard screening is not in place, then a urine or blood pregnancy test must be administered, and results confirmed as close to the time the surgery begins as possible to confirm they are not pregnant.

If the Baseline and Surgery visits take place on separate days, female subjects must agree to not become pregnancy during the study by using a medically acceptable method of birth control. If a subject does become pregnancy, there may be risks to the subject or to their unborn child that are not yet known. Subjects must notify the study doctor immediately if they think they are pregnant or if they become pregnant during the study. If in the Investigator's opinion enough time has passed between the test and the time of surgery, the subject may be required to undergo another pregnancy test.

Site personnel are responsible for the following:

- Documenting all available information regarding the pregnancy in the source documents and notifying Medtronic study personnel
- Notifying the IRB per the study site's requirements

Exiting the subject from the study and completing the appropriate eCRF(s) according to Section 10.10.1.

10.6.2 Sensor Application

Prior to any anesthesia administration and following preparation of the skin of the subject's forehead, a bilateral BIS™ sensor will be applied. The BIS™ data collection will start with sensor application and continue throughout the entire duration of the surgery.

One or more Nellcor™ sensors may also be applied at this time to collect pulse oximetry data. The sensor(s) should be placed on a finger on the opposite arm in which the intravenous therapy line is located or can also be placed on a big toe. The precise location of each sensor will be captured in the eCRF.

10.6.3 Induction Period

During the induction procedure, subjects will be pre-medicated per institutional guidance. All pre-medications, doses, and times of administration will be recorded in the eCRFs.

Prior to induction, subjects will be assessed using the Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) which can be referenced in Appendix A.

A slower induction of anesthesia will be achieved by setting a lower initial target propofol dose and making an incremental increase in the targeted dose. This is a conservative approach which maintains consistency across all study subjects and will ensure safety of the elderly patients included in the study, which should also closely align with standard institutional practices. The propofol will be administered using target-controlled infusion (TCI) pump, and the initial targeted effective site concentration (Ce) will be half of the effective site propofol concentration dosage based on drug Instructions for Use (IFU) based on the subject's body mass used for induction. The TCI will calculate the initial bolus and infusion rate required to rapidly achieve and maintain this drug level based on propofol's population pharmacokinetics using the Schnider Model. At this step, the depth of anesthesia will be assessed using MOAA/S after an equilibrium time of approximately 5 minutes (from the start of propofol infusion.) After this initial step, the target effect site concentration is subsequently adjusted in an attempt to maintain the desired level of sedation and three-quarters of the Ce will be administered. This second step will also require depth of anesthesia assessment using MOAA/S after an equilibrium time of approximately 5 minutes. Lastly, the final/full Ce dose of the propofol will be administered, and the MOAA/S will be assessed after another equilibrium time of 5 minutes is reached. The specified induction period will last approximately 15 minutes in order to record and monitor the BIS values, EEG readings, and MOAA/S scores across the anesthetic agent introduction into the subject.

10.6.4 Maintenance & Recovery

After the specified induction period, anesthesia will continue according to standard practice/institutional guidance.

At the beginning of induction, the depth of anesthesia will be assessed to ensure a MOAA/S of 0 has been obtained.

In addition, the time of the following assessments will be collected during the surgery:

- Start of induction of anesthesia
- Intubation
- Surgical Incision
- Skin Closure
- End of The Surgery
- Extubation
- Immediately Prior To BIS™ Sensor Removal

10.6.5 Data Collection

The start time of any drug infusion, target effect-site concentrations, infusion rate, the start time of the assessment including BIS value prior to MOAA/S assessment, and MOAA/S assessment will be recorded in the eCRFs. Any adjustments to the infusion rate and time of adjustment will be recorded, and any changes to subject management during the procedure will be noted on the eCRFs.

The MOAA/S score, time of and main procedural event will be recorded on the eCRFs.

The anesthetic drugs, muscular blocking agents (NMBA), NMBA reversal drugs, anti-nausea drugs, and drugs that reduce pain the drug, dosage, and time will be recorded on the eCRF.

Blood pressure, $EtCO_2$, SpO_2, pulse rate, respiration rate, end-tidal anesthetic gas, FiO_2%, EtO_2%, and temperature will be gathered from the hospital computerized database, and digital records will be provided to Medtronic. BIS values and EEG data will be recorded with a USB storage device connected to the BIS™ complete monitor. The BIS data file labeled with patient ID will be provided to Medtronic.

10.7 Assessment of Safety

Subjects will be assessed from enrollment through the end of the study for all safety events related to the BIS™ and Nellcor™ devices as well as any device deficiencies. Events will be reported to Medtronic and the IRB/EC/HC according to Section 11.

10.8 Recording Data

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

pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, device data and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the study).

Electronic data will be downloaded from the BIS™ device and the hospital computerized system. Evaluation of data quality of the recorded data will be performed after the first 3 or 5 valid subjects and for at least every 10 subjects afterward.

This study will be utilizing a Remote Data Capture (RDC) system to collect study required Case Report Form (CRF) information. Electronic CRFs (eCRFs) will be provided by the sponsor and required data will be recorded from source documents and entered into the study database via the eCRFs by the appropriately delegated site personnel, in accordance with applicable regulations.

The PI or appropriately delegated individuals are responsible for entering data for the study on the eCRFs. The PI is required to approve all data on eCRFs via electronic signature.

In general, eCRFs (or paper copies) may not serve as source documents.Source documentation for data elements not routinely captured in medical records may vary from study site to study site; the study site may use source document worksheets if identified as source documents.

The investigator must ensure the availability of source documents from which the information on the eCRFs was derived. The type and location of source documents should be documented. Where printouts of electronic medical records, are provided as source documents, or where copies of source documents are retained as source documents, those should be certified. Certification must contain:

1. The signature of the individual making the copy,
2. the date the copy was made, and
3. a statement attesting to the accuracy and completeness of the copy.

The source documents must be made available for monitoring or auditing by Medtronic's representative or representatives of the competent authorities and other applicable regulatory agencies.

10.9 Deviation Handling

A study deviation is defined as an event within a study that did not occur according to the CIP or the CTA.

Prior approval by Medtronic is expected in situations where the investigator anticipates, contemplates, or makes a conscious decision to deviate. Prior approval is not required when a deviation is necessary to protect the safety, rights or well-being of a subject in an emergency or in unforeseen situations beyond

the investigator's control (e.g. subject failure to attend scheduled follow-up visits, inadvertent loss of data due to computer malfunction, inability to perform required procedures due to subject illness).

All study deviations must be reported on the CRF regardless of whether medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the subject in an emergency. Multiple deviations of the same type at the same visit may be reported on one case report form.

In the event the deviation involves a failure to obtain a subject's 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 EC as well as Medtronic within five (5) working days. Reporting of all other study deviations should comply with EC policies and/or local laws and must be reported to Medtronic as soon as possible upon the study site becoming aware of the deviation. Reporting of deviations must comply with IRB/EC/HC policies, local laws, and/or Regulatory Authority requirements.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the CIP, conduct additional training, terminate the investigation). Repetitive or serious investigator compliance issues may result in initiation of a corrective action plan with the investigator and study site, and in some cases, may necessitate suspending enrollment until the problem is resolved or ultimately terminating the investigator's participation in the study. Medtronic will provide study site-specific reports to investigators summarizing information on deviations that occurred at the investigational study site on a periodic basis.

In case of major deviation from the protocol or missing data, the data manager may consider excluding the subject from the study. If so, the data will not be used, and if needed, a new subject will be recruited into the study.

Examples of study deviations include but are not limited to:

- Failure to obtain proper Informed Consent
- Failure to collect required study data (e.g. MOAA/S Scores, patient assessments, BIS raw signals)
- Inclusion/exclusion criteria not met
- Missing required anesthesia administration documentation

10.10 Subject Exit, Withdrawal or Discontinuation

It is the subject's right to withdraw from the study at any time and for any reason without sanction, penalty or loss of benefits to which the subject is otherwise entitled, and without jeopardizing their future medical care. The investigator may withdraw the subject at any time to protect the health, safety, or welfare of the subject. Every effort should be made to collect the status of any ongoing adverse events,

at a minimum. All subjects will be encouraged to remain in the study through the follow-up phone call. If the subject discontinues participating in the study prior to completing the study requirements, the reason for withdrawal will be recorded in the subject's study records and eCRF. If withdrawal from the study is due to problems related to the investigational device safety or performance, the investigator shall ask for the subject's permission to follow his/her status outside the clinical study.

10.11 Study Exit From Study

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 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 may still 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 death
- Subject did not meet inclusion/exclusion criteria
- Subject did not provide consent
- Subject chooses to withdraw for any reason (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:

- Date of Study Exit
- Subject's status upon Exit
- Any applicable AE or death information

10.11.1 Study Completed

At the completion of the surgery, subjects will be exited from the study. There are no further follow-up visits required for this study.

10.11.2 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 EC.

10.11.3 Investigator Withdraws Subject

No subjects should be withdrawn by investigators unless compelling medical justification is present or surgical procedure is cancelled. It is recommended investigators discuss any withdrawals with the study team prior to withdrawing subjects.

11. Risks and Benefits

11.1 Potential Risks

Both the BIS™ monitor system and Nellcor™ system is cleared in the United States, CE marked, AMAR approved in Israel, and used routinely in clinical care to monitor patients. In the routine clinical procedure, the anesthetist uses unilateral sensor, and in some surgeries the BIS™ is part of the monitoring system. For the study, the BIS™ will be used as a standalone monitor with the bilateral sensor. During the surgery, the BIS™ value will be calculated from the left side, as in the routine clinical procedure. The BIS™ device that will be used as study product will be stored outside the operating room after the study procedure. The monitor is being used in accordance with the intended use that has been cleared by regulatory authorities worldwide.

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. The risks from the device(s) are in keeping with the definition of non-significant risk devices. 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 Instructions for Use (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 a full list of Sensor Warnings and Cautions, refer to the country-specific IFU.

11.1.2 BIS™ Complete Monitoring System Risks

BIS™ Complete Monitoring System will be used per IFU. More information on warnings and cautions should be referenced in the country-specific IFU.

11.1.3 Nellcor™ Oximetry Sensor Risks

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 Surgery

Data from peer-reviews indicates that 14.4% of the surgical patients had at least one AE or SAE[12]. The patient may suffer from AEs or SAEs that are related to the standard clinical procedures or the hospital environment and not to the study. Patients should be given the applicable consent forms to understand the risks of the surgery and environment to which they will be exposed.

11.1.5 General Anesthetics

Along with the protocol-specified propofol induction period, general anesthesia maintenance will resume per institutional practice as is needed for the surgical procedure.

There are some risks associated with general anesthetics, which should be explained to the patient and covered in the standard surgery clinical consent form. 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 intravenous therapy drip, shivering and feeling cold, and 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 delegated anesthesiologist will be present during the procedure to minimize all risks related to anesthesia.

11.2 Potential Benefits

There are no expected direct 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 investigational device is not intended as an implant and does not present a potential for serious risk to the health, safety, or welfare of a subject;
- The investigational device is not purported or represented to be for use supporting or sustaining human life and does not present a potential for serious risk to the health, safety, or welfare of a subject;
- The investigational device is not for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health, and does not present a potential for serious risk to the health, safety, or welfare of a subject; and
- The investigational device does not otherwise present a potential for serious risk to the health, safety, or welfare of a subject.

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

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

12. Adverse Events and Device Deficiencies

For the purposes of the clinical study, adverse events will be categorized according to the latest version of ISO 14155. Where the definition indicates "device", it refers to BIS™ and Nellcor™ devices used in the study. See **Table 3** below for Adverse Event (AE) and Device Deficiency (DD) Definitions.

[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

12.1 Adverse Events

AE definitions are provided in Table 3. Events related to the surgical procedure including anesthesia administration will not be collected as they related to standard of care practices. AEs will only be collected as they are related to the BIS™ and Nellcor™ devices as well as any device deficiencies as these are commercially released products. All reportable AE information will therefore only be collected beginning at the time of the BIS™ and Nellcor™ sensor placement at the start of surgery and ending when the BIS™ and Nellcor™ sensors are removed.

12.1.1 Foreseeable AE or SAE

Any foreseeable events are discussed in Section 11.1 Potential Risks.

12.2 Device Deficiency

The DD definition is provided in Table 3 below. 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.

12.3 Definitions/Classifications

Where the definition indicates “device”, it refers to BIS™ and/or Nellcor™ devices used in the study.

Table 3: Adverse Event and Device Deficiency Definitions (ISO 14155)	
Adverse Event (AE)	Untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated NOTE 1: This definition includes events related to the investigational medical device or the comparator. NOTE 2: This definition includes events related to the procedures involved. NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.
Adverse Device Effect (ADE)	AE related to the use of an investigational medical device NOTE 1: This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from an error use or from intentional misuse of the investigational medical device. NOTE 3: this includes 'comparator' if the comparator is a medical device.
Device Deficiency (DD)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance. NOTE 1: DD include malfunctions, use errors and inadequacy in the information supplied by the manufacturer including labeling. NOTE2: This definition includes device deficiencies related to the investigational medical device or the comparator.

Seriousness	
Serious Adverse Event (SAE)	AE that led to any of the following a) death, b) serious deterioration in the health of the subject, users or other persons as defined by one or more of the following: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, including chronic disease, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered an SAE.
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Serious Adverse Device Effect (USADE)	A SADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. Note: Anticipated Serious Adverse Device Effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.
Serious Health Threat	A signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons. Note: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

12.3.1 Adverse Event and Device Deficiency Reporting Requirements

AE and DD information will be collected throughout the study from the BIS sensor application until end of the surgery. A list of anticipated adverse events and risks that are expected in nature is included in Section 11.

Adverse Event assessment for the purposes of this study will cease after the procedure. All AEs considered at least possibly related to the study devices will be followed until resolved, stabilized, and/or returned to baseline.

Medtronic will immediately conduct an evaluation of reported events. Table 4 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 4: 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.

12.4 Reporting of Adverse Events

Principal Investigators must report applicable events and product deficiencies to Medtronic and where appropriate an EC or Regulatory Authority.

Study Contact Information:

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

12.5 Product Complaint Reporting

It is the responsibility of the investigator to report all product complaint(s) associated with a medical device distributed by Medtronic, regardless whether they are related to intended use, misuse or abuse of the product. Reporting must be done immediately and via the regular channels for market-released products. The reporting of product complaints by the clinical team must be done according to the local Standard Operating Procedures. Medtronic will notify the 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

13. Data Review Committees

No Data Monitoring Committee, Clinical Events Committee or other external committee will be nominated for this study as the study includes no significant interventions (i.e. blood draw only) intended to sustain life or reduce risk of a major adverse health outcome.

14. Statistical Design and Methods

This is a preliminary study aimed at collecting data from enrolled subjects for algorithm development and improvement. Subjects with valid recorded data from the study device (EEG signals) and a completed eCRF will be considered as valid subjects and will be included in the primary analysis.

A statistical analysis plan with detailed statistical procedures and methods will be finalized prior to data analysis. Any changes in statistical methods will be detailed in the Clinical Study Report.

14.1 Sample Size Justification

Up to 100 subjects will be enrolled in the study, with 65% subjects over the age of 65 years. The sample size estimate was not based on hypothesis testing. The primary objective is to evaluate the age impact on the relationship between the BIS score and the depth of anesthesia. The sample size is not powered to detect a statistically significant difference as this study is a feasibility study.Statistical Methods

Descriptive statistics will be used to summarize study outcomes. Subjects with valid recorded data from the study device (EEG signals) and a completed eCRF will be included in the primary analysis.

The relationships between BIS parameters, age, physical and cognitive state, and depth of anesthesia in patients undergoing surgery under general anesthesia will be assessed. Pearson's correlation or Spearman's rank correlation will be calculated as appropriate. Continuous variables will be evaluated using analysis of variance (ANOVA) or nonlinear E_{max} model, and categorical variables will be evaluated using the chi-square or Fisher's exact test, as well as multivariate logistic regression with age as an explanatory factor. A P-value of less than 0.05 is considered statistically significant unless otherwise specified.

An early data review will be performed for the first 40 enrolled subjects to ensure data validity and no safety concern. Sample size re-estimation may be performed to ensure sufficient data to be collected to meet the study objectives.

For safety assessments, AEs will be summarized using frequency counts and percentages. Descriptive summary will be provided by severity and relationship as needed.

15. Ethics

15.1 Statement(s) of Compliance

The MDT18067TIARA study will be conducted in full conformity with this study protocol, with its ethical principles having origin in the Declaration of Helsinki. TIARA was designed to reflect the GCP principles outlined in the latest version of ISO 14155 and other international clinical requirements outlined below. These include the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the clinical investigation and the definition of responsibilities of the sponsor and investigators. In accordance with ISO 14155, the sponsor shall avoid improper influence on, or inducement of, the subject, monitor, any investigator(s) or other parties participating in, or contributing to, the clinical investigation. All investigators shall avoid improper influence on or inducement of the subject, sponsor, monitor, other investigator(s) or other parties participating in or contributing to the clinical investigation. AE and DD handling in the TIARA study is ISO 14155 compliant for all participating geographies. As the ISO 14155 AE collection requirements are focused on pre-market release studies, AEs will only be collected as they are related to the BIS™ and Nellcor™ devices as well as any device deficiencies as these are post-market or commercially released products. USADE assessment is not applicable for this reason. Events related to the surgical procedure including anesthesia administration will not be collected as they related to standard of care practices.

Ultimately, all study sites in all geographies will follow and comply with:

- The CTA
- The procedures described within this CIP
- Local IRB/EC/HC Requirements

No study procedures at the site will be performed until the governing IRB/EC/HC provides approval. Any action that is taken by the local IRB/EC/HC with respect to this study will be forwarded to the sponsor as soon as possible.

In addition to the regulatory requirements outlined above, the study will be conducted according to federal, national and local laws, regulations, standards, and requirements of the countries/geographies where the study is being conducted. These include but are not limited to:

- In Europe the study will be conducted in compliance with the DoH version 2013.

The study will be publicly registered in the US prior to any enrolments in accordance with ISO 14155 on http://clinicaltrials.gov. In addition, the study may be registered in local regulatory databases where required by local law including the Israel Ministry of Health website for clinical trials at https://my.health.gov.il/MyPortal/CliniTrials/Pages/Editor.aspx. For the Netherlands, it is expected that the study may be listed at www.rijksoverheid.nl/mensenonderzoek. Requirements for each region will be confirmed once sites are selected.

Approval of the CIP and CIP amendments is required from the following groups prior to any study procedures at a study site:

- Medtronic
- Principal Investigators (where required by local law/regulations)
- Geography-specific regulatory authorities (if regulatory approval is required)
- An independent medical IRB/EC/HC

16. Study Administration

16.1 Monitoring

It is the responsibility of Medtronic to ensure proper monitoring of this study. Trained Medtronic personnel or delegates appointed by Medtronic may perform study monitoring at the study site or remotely in order to ensure that the study is conducted in accordance with the CIP, the CTA, and the applicable regulatory and local requirements. Medtronic, or delegates, must therefore be allowed access to the subjects' case histories (i.e. clinic and hospital records, and other source data/documentation) upon request as per the ICF, Research Authorization (where applicable) and CTA. The PI should also be available during monitoring visits, as detailed in the monitoring plan, to review together with the monitor the visit outcomes and general study progress.

16.1.1 Monitoring Visits

Frequency of monitoring visits may be based upon subject enrollment, study compliance, number of adverse events, number of deviations, observations from previous monitoring visits and any suspected

inconsistency in data that requires investigation. Regulatory documents will be reviewed at each study site. Monitoring for the study, site initiation visits, interim monitoring visits, and closeout visits, will be done in accordance to the study-specific monitoring plan.

Monitoring visits may be conducted periodically to assess study site progress, the investigator's adherence to the CIP, regulatory compliance including but not limited to IRB/EC/HC approval and review of the study, maintenance of records and reports, and review of source documents against subject CRFs in accordance to the study-specific monitoring plan. Monitors review study site regulatory and study compliance by identifying observations of non-compliance and communicating those observations along with recommendations for preventative/corrective actions to study site personnel. Monitors may work with study personnel to determine appropriate corrective action recommendations and to identify trends within the study or at a particular study site.

16.2 Data Management

Data will be collected using an electronic data management system for studies. CRF data will be stored in a secure, password-protected database which will be backed up nightly. Data will be reviewed using programmed and manual data checks. Data queries will be made available to study sites for resolution. Study management reports may be generated to monitor data quality and study progress. At the end of the study, the data will be frozen and will be retained indefinitely by Medtronic.

All records and other information about subjects participating in this study will be treated as confidential. Data will be transferred and processed by Medtronic or a third party designated by

Procedures in the CIP require source documentation. Source documentation will be maintained at the study site. Source documents, which may include worksheets, forms, subject medical records, programmer printouts, and interrogation files, must be created and maintained by the investigational study site team.

The investigator will clearly mark clinical records to indicate that the subject is enrolled in this clinical investigation.

The data reported on the CRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing.

Device data s will be uploaded to secure servers. Save-to-disk data collected at the site will be sent to Medtronic. Upon receipt, device data will be maintained and retrieved for analysis and reporting.

16.3 Direct Access to Source Data/Documents

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. Regulatory Authorities may also perform inspections at participating study sites. The investigator and/or institution shall permit Medtronic, governing IRB/EC/HCs and Regulatory Authorities direct access to source data and documents during monitoring, audits and regulatory inspections.

16.4 Confidentiality

All information and data sent to parties involved in study conduct concerning subjects or their participation in this study will be considered confidential. Study sites will assign a unique subject ID to each subject. Records of the subject and subject ID relationship will be maintained by the study site. The subject ID number is to be recorded on all study documents to link them to the subject's medical records at the study site. Confidentiality of data will be observed by all parties involved at all times throughout the clinical investigation. All data shall be secured against unauthorized access. The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data to maintain confidentiality, the subject's name or any other protected health information should not be recorded on any study document other than the ICF. This scenario will be covered in the ICF. In the event a subject's name is included for any reason, it will be blinded as applicable. In the event of inability to blind the identification (e.g., digital media), it will be handled in a confidential manner by the authorized personnel. Data relating to the study might be made available to third parties (for example in case of an audit performed by the Regulatory Authority), provided the data are treated as confidential and that the subject's privacy is guaranteed. No identifiable subject information will be published.

16.5 Liability/Warranty/Insurance Information

Medtronic maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable law and custom concerning specific insurance coverage. A Clinical Trial Insurance statement/certificate will be provided to the IRB/EC/HC in the submission.

16.5.1 Insurance

Medtronic Bakken Research Site B.V. is a wholly owned subsidiary of Medtronic, which as the parent company of such entity 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 Trial insurance statement/certificate will be provided to the IRB/EC/HC.

16.6 CIP Amendments

Any revisions or amendments to the CIP or ICF document, along with a statement of justification for the changes, will be submitted to all affected Regulatory Authorities and governing IRB/EC/HCs, according to applicable regulations. All amendments to the CIP shall be agreed upon between Medtronic and the principal investigator(s), or the coordinating investigator. Approval by regulatory agencies and IRB/EC/HCs (where applicable) must be obtained prior to implementing a CIP revision at the study site.

16.7 Record Retention

Study-related documents including all study-related Source Documents, CRFs, ICFs, ISFs, 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. Prior to the destruction of the study related data, the investigator must notify the sponsor. The PI 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.

16.8 Publication and Use of Information

Publications from the MDT18067TIARA study will be handled according to Standard Operating Procedures and as indicated in the CTA. The investigator will not publish any data from the study without the sponsor's permission.

The sponsor may publish the results from the influence of age on EEG signals and consciousness during anesthesia (TIARA) study in a timely manner as data becomes available. These publication activities may include abstracts, presentations/posters to scientific meetings, and manuscripts. Investigators who gathered data for this study (i.e., enrolled subjects and complied with the protocol) may be asked to write or contribute to the writing of abstracts and manuscripts based on the results of this study. Investigators who meet the study-specific criteria above will be considered for abstract/manuscript authorship if they meet the International Committee of Medical Journal Editors, Ethical Considerations in the Conduct and Reporting of Research criteria.

The sponsor will register the study at the U.S. National Institutes of Health clinical trials website (https://clinicaltrials.gov/), and may register as required, according to local regulations in Israel's Ministry of Health website for clinical trials (https://my.health.gov.il/MyPortal/CliniTrials/Pages/Editor.aspx) as well as the Netherlands' webpage (www.rijksoverheid.nl/mensenonderzoe).

16.9 Suspension or Early Termination

The Sponsor reserves the right to discontinue the study at any stage, with written notice to all investigators, all reviewing IRB/EC/HCs. 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/EC/HC 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/EC/HC) 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/EC/HC and provide a detailed written explanation of the termination or suspension. The sponsor will inform the regulatory authorities (if required.)

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

- Failure to obtain initial IRB/EC/HC approval or annual renewal of the study
- Consistent non-compliance to the CIP (e.g., failure to adhere to inclusion/exclusion criteria, failure to follow subjects per scheduled follow-ups, failure to implement required corrective and preventive actions, etc.)
- Lack of enrollment

- Noncompliance to regulations and the terms of the CTA (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/EC/HC 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)

17. References

1. Kanonidou, Z. and G. Karystianou, *Anesthesia for the elderly*. Hippokratia, 2007. **11**(4): p. 175-7.

2. Punjasawadwong, Y., A. Phongchiewboon, and N. Bunchungmongkol, *Bispectral index for improving anaesthetic delivery and postoperative recovery*. Cochrane Database Syst Rev, 2014(6): p. CD003843.

3. Glass, P.S., et al., *Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers*. Anesthesiology, 1997. **86**(4): p. 836-47.

4. Flaishon, R., et al., *Recovery of consciousness after thiopental or propofol. Bispectral index and isolated forearm technique*. Anesthesiology, 1997. **86**(3): p. 613-9.

5. Schwab HS, S.M., Eger EI, Kindler CH, Filipovic M. , *Sevoflurane decreases bispectral index values more than does halothane at equal MAC multiples*. . Anesth Analg., 2004. **99**: p. 1723-1727.

6. Hans P, D.P., Brichant JF, Bonhomme V, *Comparative effects of ketamine on Bispectral Index and spectral entropy of the electroencephalogram under sevoflurane anaesthesia*. Br J Anaesth, 2005. **94**: p. 336-340.

7. Sengupta, S., et al., *Effect of ketamine on bispectral index during propofol--fentanyl anesthesia: a randomized controlled study*. Middle East J Anaesthesiol, 2011. **21**(3): p. 391-5.

8. Alkire, M.T., *Quantitative EEG correlations with brain glucose metabolic rate during anesthesia in volunteers*. Anesthesiology, 1998. **89**(2): p. 323-33.

9. Werner, P., et al., *Examining the reliability and validity of the Hebrew version of the Mini Mental State Examination*. Aging (Milano), 1999. **11**(5): p. 329-34.

10. Vellas, B., et al., *Overview of the MNA--Its history and challenges*. J Nutr Health Aging, 2006. **10**(6): p. 456-63; discussion 463-5.

11. Perna, S. et al., *Performance of Edmonton Frail Scale on frailty assessment: its association with multi-dimensional geriatric conditions assessed with specific screening tools*. BMC Geriatrics, 2017. doi: 10.1186/s12877-016-0382-3. url: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5209899/

12. Anderson, O., et al., *Surgical adverse events: a systematic review*. Am J Surg, 2013. **206**(2): p. 253-62.

18. Appendices

18.1 Appendix A - Modified Observer's Assessment of Alertness/Sedation scale (MOAA/S)

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

18.2 Appendix B – Mini Mental State Examination (MMSE)

Mini-Mental State Examination (MMSE)

Subject's ID: _____ Date: _____

Instructions: Ask the questions in the order listed. Score one point for each correct response within each question or activity.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day of the week? Month?"
5		"Where are we now: State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible. Number of trials: _____
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, …) Stop after five answers. Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

(Adapted from Rovner & Folstein, 1987)

18.3 Appendix C – Mini Nutritional Assessment (MNA®-SF)

Mini Nutritional Assessment

MNA®

Nestlé Nutrition Institute

Last name: First name:

Sex: Age: Weight, kg: Height, cm: Date:

Complete the screen by filling in the boxes with the appropriate numbers. Total the numbers for the final screening score.

Screening

A Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?
0 = severe decrease in food intake
1 = moderate decrease in food intake
2 = no decrease in food intake ☐

B Weight loss during the last 3 months
0 = weight loss greater than 3 kg (6.6 lbs)
1 = does not know
2 = weight loss between 1 and 3 kg (2.2 and 6.6 lbs)
3 = no weight loss ☐

C Mobility
0 = bed or chair bound
1 = able to get out of bed / chair but does not go out
2 = goes out ☐

D Has suffered psychological stress or acute disease in the past 3 months?
0 = yes 2 = no ☐

E Neuropsychological problems
0 = severe dementia or depression
1 = mild dementia
2 = no psychological problems ☐

F1 Body Mass Index (BMI) (weight in kg) / (height in m)^2 ☐
0 = BMI less than 19
1 = BMI 19 to less than 21
2 = BMI 21 to less than 23
3 = BMI 23 or greater ☐

IF BMI IS NOT AVAILABLE, REPLACE QUESTION F1 WITH QUESTION F2.
DO NOT ANSWER QUESTION F2 IF QUESTION F1 IS ALREADY COMPLETED.

F2 Calf circumference (CC) in cm
0 = CC less than 31
3 = CC 31 or greater ☐

Screening score ☐☐
(max. 14 points)

12-14 points: ☐ Normal nutritional status
8-11 points: ☐ At risk of malnutrition
0-7 points: ☐ Malnourished

Save Print Reset

Ref. Vellas B, Villars H, Abellan G, et al. *Overview of the MNA® - Its History and Challenges.* J Nutr Health Aging 2006;10:456-465.
Rubenstein LZ, Harker JO, Salva A, Guigoz Y, Vellas B. *Screening for Undernutrition in Geriatric Practice: Developing the Short-Form Mini Nutritional Assessment (MNA-SF).* J. Geront 2001;56A: M366-377.
Guigoz Y. *The Mini-Nutritional Assessment (MNA®) Review of the Literature - What does it tell us?* J Nutr Health Aging 2006; 10:466-487.
Kaiser MJ, Bauer JM, Ramsch C, et al. *Validation of the Mini Nutritional Assessment Short-Form (MNA®-SF): A practical tool for identification of nutritional status.* J Nutr Health Aging 2009; 13:782-788.

For more information: www.mna-elderly.com

18.4 Appendix D – Edmonton Frail Scale (EFS)

The Edmonton Frail Scale

1/2

Bedside Version

Date ×1 = B

Examiner ×2 = C

(name, relationship to patient)

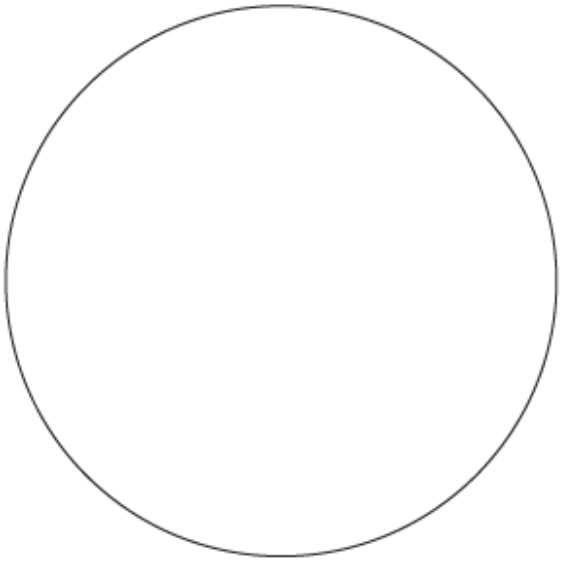
Additional Source Total Score

PATIENT IDENTIFICATION

Scoring the EFS	FIT			VULNERABLE		MILD		MODERATE		SEVERE
	1	2	3	4	5	6	7	8	9	10+
						FRAILTY				

Questions	A	B	C
For each item choose only one option in column A, B or C. Points are assigned based on the column. Please see the EFS Tool Kit for more detailed instructions.	A = 0	B = 1	C = 2
1. Cognition			
Clock Drawing Test "Please imagine that this circle is a clock. I would like you to place the numbers in the correct positions, then place the hands to indicate a time of *ten after eleven.*"	PASS	FAIL WITH MINOR ERRORS	FAIL WITH MAJOR ERRORS

Fold at the dotted line before asking the patient to start in order to conceal distracters.



The Edmonton Frail Scale

Bedside Version

Questions	A	B	C
If the clock drawing test (item 1) scores in column B or C, then subsequent items marked with an asterix may be scored based on the best information available.*	A = 0	B = 1	C = 2
2. General Health Status			
* a) In the past year, how many times have you been admitted to a hospital?	0	1–2	>2
b) In general, how would you describe your health? *(Select one)*	EXCELLENT VERY GOOD GOOD	FAIR	POOR
3. Functional Independence			
* With how many of the following activities do you **require** help? ☐ Meal Preparation ☐ Shopping ☐ Telephone ☐ Housekeeping ☐ Taking Medications ☐ Transportation ☐ Laundry ☐ Managing Money	0–1	2–4	5–8
4. Social Support			
When you need help is there someone who you can count on who is willing and able to meet your needs?	ALWAYS	SOMETIMES	NEVER
5. Medication Use			
* a) Do you use 5 or more prescription medications on a regular basis?	NO	YES	
* b) At times have your forgotten to take your prescription medications?	NO	YES	
6. Nutrition			
* Have you recently lost weight such that your clothing has become loose?	NO	YES	
7. Mood			
Do you often feel sad or depressed?	NO	YES	
8. Continence			
* Do you have a problem with losing control of urine when you don't want to?	NO	YES	
9. Functional Performance			
Timed Get Up & Go Test - 3 meters "I would like you to sit in this chair with your back and arms resting. Then, when I say *GO*, please stand up and walk at a safe and comfortable pace to the place I show you, return to the chair and sit down." **Total time recorded** _____ seconds *Score this test item as >20 seconds if:* a) The individual is reluctant or unable to complete the test. b) Safe performance of the test requires a safety belt, walking aid or assistance from another person.	0–10 SECONDS	11–20 SECONDS	>20 SECONDS

Based on the original version © 2000 presented at the Canadian Geriatric Society Annual Scientific Meeting, later published in abbreviated format in Rolfson DB, et al,Validity and reliability of the Edmonton Frail Scale, Age and Ageing 2006; 35(5): 526–529 doi: 10.1093/ageing/afl041.

19. Version History

Version	Summary of changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/Title
1.0	▪ Not Applicable, New Document	N/A	N/A	N/A	Maegan J. Johnson, Clinical Research Specialist
2.0	Administrative Updates: ▪ Correcting/adding expected baseline vitals collection ▪ Formatting and text consistency updates	▪ Baseline vitals was a planned collection point and was inadvertently left off ▪ Improve visual structure of document	N/A	N/A – The planned baseline vitals collection was already reflected in the eCRFs	Maegan J. Johnson, Clinical Research Specialist
3.0	Administrative Update: ▪ Removed Nellcor system and sensor model specification	▪ To ensure models used are licensed and consistent across all study site countries	N/A	N/A – This change does not affect the CIP synopsis or other documents	Maegan J. Johnson, Clinical Research Specialist

4.0	▪ Added additional product information regarding Nellcor, as well as possibility of using more than one sensor ▪ Removed Nellcor measurements as primary endpoint ▪ Provided more detail regarding product accountability per ISO 14155 standards ▪ Added additional ISO 14155 language for subject consenting ▪ Added collection of contact person information if baseline and surgery procedures occur separately ▪ Added pregnancy screening details for surgery procedure ▪ Clarified AE collection details per ISO 14155	▪ More product details provided for usage specifications ▪ Nellcor may not be able to be used at all sites, therefore was removed as endpoint to not affect other data analysis ▪ As product models and shipping methods may vary across the various regions, additional details were provided on how to maintain oversight ▪ Additional information for ISO compliance ▪ Additional information for ISO compliance ▪ Defined process on how this exclusion criteria can be verified if the process is not part of the institution's standard of care	N/A	▪ Study ICF(s)	Maegan J. Johnson, Clinical Research Specialist

	▪ Updated various regional registration websites ▪ Updated Edmonton Frail Scale assessment template in appendix ▪ Formatting and text consistency updates	▪ Additional information for ISO compliance ▪ Including more specifics on regional registration ▪ Updated to version obtained by assessment license holder ▪ Improve visual structure of document			
5.0	▪ Subject Number updated to 100 from 200 ▪ Site number reduced from approximately 5 to 2 ▪ Safety Contact information changed to Stephanie Monza from Julia Katilius ▪ MOAA/S assessment changed from every 20 minutes to once at the beginning of maintenance and at the end of emergence ▪ Inclusion criteria decrease from 2 to 1.5 hours for surgery length	▪ Business request ▪ Business request ▪ Julia Katilius no longer with OU ▪ MOAA/S assessment is not appropriate while subject is in maintenance ▪ 1.5 hours is adequate for collection of subject data and will improve study recruitment	N/A	N/A	Stephanie Monza, Senior Clinical Research Specialist

5.1	▪ Safety Contact information changed to Ami Stuart from Stephanie Monza ▪ Primary objective updated ▪ Sample size determination sections updated	▪ Stephanie Monza no longer with OU ▪ The primary objective was updated from "to determine" to "to evaluate" as this is a feasibility study. ▪ The sample size was based on the idea that this protocol was written as a validation study when the study was planned by the business to be a feasibility study.			Ami Stuart, Senior Clinical Research Specialist