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

Document: Statistical Analysis Plan

Identifier: NCT04466384

Date: 05MAR2020

Medtronic **Statistical Analysis Plan**	
Clinical Investigation Plan Title	[redacted] (SONORA)
Clinical Investigation Plan Identifier	MDT19049SONORA
Sponsor/Local Sponsor	Medtronic Minimally Invasive Therapies Group (MITG) Respiratory, Gastrointestinal & Informatics (RGI) 6135 Gunbarrel Avenue, Boulder, CO 80301 U.S.A.
Document Version	1.0

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1 Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Initial Release	[redacted]

2 List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
BIS	Bispectral Index (BIS) technology monitoring uses processed EEG signals to measure sedation depth based on the level of consciousness
CRF	Case Report Form. Forms where the clinical data are collected. eCRF is the electronic version of the CRF
EC	Ethics Committee
ED	Effective dose
EDC	Electronic Data Capture. Electronic systems where the data are collected through the eCRF (Oracle Clinical). May also be referred to as RDC (Remote Data Capture).
EEG	Electroencephalogram
$EtCO_2$	End-tidal Carbon Dioxide. The value of exhaled carbon dioxide displayed by the capnograph device
ICF	Informed Consent Form
IRB	Institutional Review Board
LMA	Laryngeal mask
LOC	Level of consciousness
MOAA/S	Modified Observer's Assessment of Alertness/Sedation
NCM	Non-contact monitoring
PI	Principal Investigator. The person is responsible for overseeing the study and assuring study completion in compliance with applicable regulations.
PK/PD	Pharmacokinetics and pharmacodynamics
SAP	Statistical Analysis Plan
SpO_2	A non-invasive spectroscopic estimate of arterial oxygen saturation measured transcutaneously by a pulse oximeter
TCI	Target-controlled infusion
TIVA	Total Intravenous Anesthesia
UADE	Unanticipated Adverse Device Effect

3 Introduction

Electroencephalography is an electrophysiological monitoring method to record electrical activity of the brain. An electroencephalogram (EEG) is a test or record of brain activity produced by electroencephalography. Changes in the EEGs are produced by anesthetic agents administered to patients. Bispectral Index (BIS) technology monitoring uses processed EEG signals to measure sedation depth based on level of consciousness (LOC) signals and allows anesthesia providers to titrate general anesthesia to achieve the desired LOC on the brain. BIS technology consists of a sensor, a digital signal converter, and a monitor. The sensor is placed on the patient's forehead to pick up the electrical signals from the frontal cortex and transfer them to the digital signal converter.

This is a single-center, prospective, non-randomized, cross-over study that aims at collecting data for the evaluation of the relationship between BIS and levels of sedation.

The volunteers will receive two regimens of anesthesia with different drug combinations, with at least a 1-week washout period between regimens. Volunteers will be sequentially assigned to start with either Propofol (P) or Propofol with 4 ng/ml of Remifentanil (R) regimens while BIS bilateral sensor placed on the subject's forehead. The Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale will be used to measure the level of alertness in sedated subjects.

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

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

This document provides a detailed description of the statistical methods and procedures to be implemented during the analysis of the study.

This statistical analysis plan (SAP) is based on the CIP Version 1 dated on 12-DEC-2019.

4 Study Objectives

4.1 Primary Objective:

To determine BIS_{50} (BIS value at which 50% of patients will be unresponsive at given drug concentrations) and other dose-response parameters.

4.2 Secondary Objective:

To determine BIS_{95} (BIS value at which 95% of subjects will be unresponsive at given drug concentrations) and other dose-response parameters.

5 Investigation Plan

This is a single-center, prospective, non-randomized, cross-over study that aims at collecting data for the evaluation of the relationship between BIS and level of consciousness for anesthetic regimens. The volunteers will receive two regimens of anesthesia with different drug combinations, with at least a 1-week washout period between regimens. Volunteers will be sequentially assigned to start with either Propofol (P) or Propofol with 4 ng/ml of Remifentanil (R) regimens while BIS bilateral sensor placed on the subject's forehead. The Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale will be used to measure the level of alertness in sedated subjects.

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

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

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

5.1 Study Schedule

The following table summarizes the intervals and data collection procedures.

Table 1: Schedule of Events

Study Tasks	Pre-screening	Enrollment	Execution		Follow up
	No visit	Visit 1	Prior to Procedure	Procedure Visits 2 & 3	Phone call
Eligibility Assessments					
Online or phone call pre-screening survey	x				
Informed Consent [1]		x			
Demographics		x			
Medical History		x			
Physical Exam		x			
Pulmonary function test		x			
Single 12-lead ECG		x			
Urine sample for the presence of cotinine		x	x		
Urine pregnancy test (Female)		x	x		
Complete blood count			x		
Inclusion/exclusion assessment		x	x		
Vital monitoring		x	x	x	
Concomitant Medication		x	x		
Urine drug screen and alcohol breathalyzer			x		
Safety Monitoring				x	
Sensors application				x	
Propofol or Propofol with Remifentanil administration				x	
MOAA/S assessment				x	
NCM Sub-Study [2]				x	
Safety Assessments and Compensation					
Adverse Event Assessment [3]		x	x	x	x
Device Deficiency [4]				x	
Participant stipend [5]		x		x	

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

[2] For NCM Sub-Study, refer to CIP Appendix B.

[3] All Adverse Events, regardless of relatedness or outcome, will be collected and reported; for more details, refer to *CIP Section 11.*

[4] Device Deficiency will be collected and reported; for more details, refer to CIP *Section 11.*

[5] For more details regarding the subject compensation, refer to CIP *Section 15.6.*

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

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

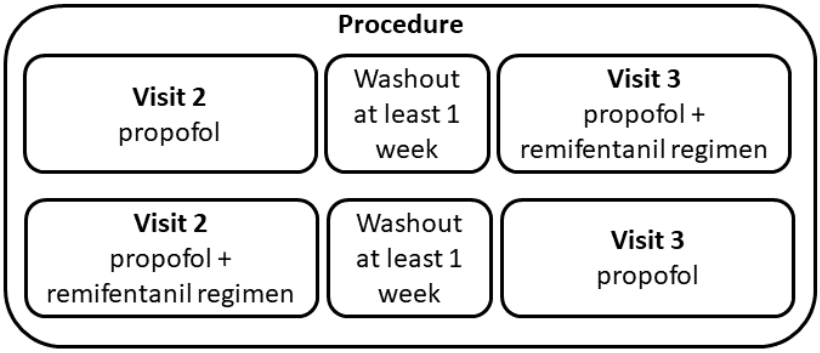


Figure 1: Schematic Representation of Procedure Schedule

Descriptions of the two treatment regimens are as follows:

Propofol (P) Regimen

The initial target effect-site concentrations of propofol will be 0.5 µg/ml followed by incremental increases in the target effect-site concentrations of 1.5, 2, 2.5, 3, 4, 6, or 8 µg/ml until MOAA/S scales at values less than 2 is reached. The propofol concentration will be decreased by the same steps until consciousness re-occurs.

Propofol with Remifentanil (R) regimen

Where remifentanil is administered with propofol, approximately 2 minutes before starting propofol, to attain an effect-site targeted concentration of remifentanil of 4 ng/ml, remifentanil will be given by a continuous infusion. Approximately within 7 minutes, the infusion rate of Remifentanil may be adjusted to maintain the effect-site concentration of remifentanil of 4 ng/ml throughout the study.
The initial target effect-site concentrations of propofol will be 0.5 µg/ml followed by incremental increases in the target effect-site concentrations of 1.5, 2, 2.5, 3, 4, 6, or 8 µg/ml until MOAA/S scales at values less than 2 is reached. The propofol concentration will be decreased by the same steps until consciousness re-occurs.

The equilibration time for each targeted plateau will be at least 12 minutes. The BIS value will be recorded, and MOAA/S score will be assessed when the patient is awake and at the different targeted concentrations.

6 Determination of Sample Size

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

7 Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

Subject disposition will be summarized with frequency tables.

7.1.2 Clinical Investigation Plan (CIP) Deviations

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

Study deviations must be reported, regardless of whether medically justifiable, pre-approved by the study leader, or taken to protect the subject in an emergency. All deviations will be summarized descriptively.

7.1.3 Analysis Sets

All evaluable data analysis: Subjects who signed informed consent, meet all inclusion/exclusion criteria and have valid study data. The primary effectiveness analysis will be based on all evaluable data from this study.

Per-Protocol analysis: A per-protocol analysis will be performed based on all subjects who are compliant with the study protocol, provide valid informed consent, do not experience any major protocol deviations, and complete the study procedure.

Subjects who discontinue participation prematurely will be included in the analysis of results. Subjects who withdraw from the study prior to completing both regimens will be replaced by a new volunteer.

7.2 General Methodology

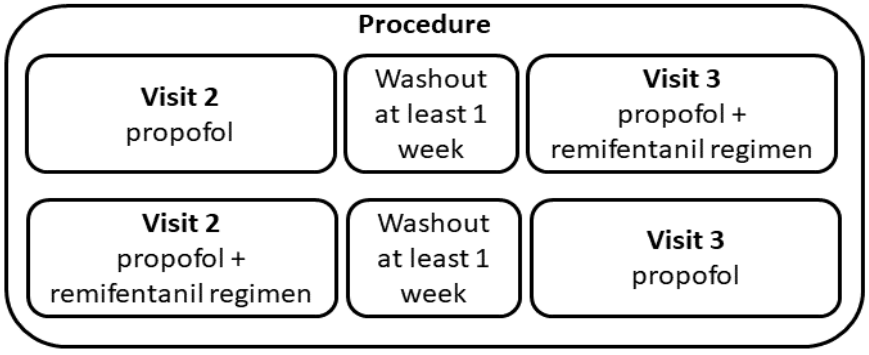
All statistical analyses will be performed using Statistical Analysis System (SAS) for Windows (version 9.2 or higher, SAS Institute Inc. Cary, NC) or other widely accepted statistical or graphical software. In general, data for all study subjects will be presented. Individual data will be presented in subject listings.

Descriptive statistics will be used to present the data and to summarize study outcomes. Discrete variables will be presented using frequency distributions and cross tabulations. Continuous variables will be summarized by presenting the number of observations (N), mean, standard deviation, median, minimum, and maximum values.

For safety assessments, adverse events will be summarized using frequency counts and percentages. Any unexpected adverse events will be reported and discussed.

7.2.1 BIS Value Analysis

The volunteers will receive two regimens of anesthesia with different drug combinations, with at least a 1-week washout period between regimens. Once the pre-procedure part completed, the subject will be sequentially assigned to start with either Propofol (P) or Propofol with 4 ng/ml of Remifentanil (R) regimens, as shown in Figure 1. The volunteers will have BIS Monitoring System, the 4 Channel BISx, and BIS bilateral sensor placed on their forehead during these regimens to study the effects of these drugs on the brain. Each volunteer will be given a dose range of sequences of the target drug to achieve targeted drug concentration



The modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale will be used to perform sedation/ loss of consciousness assessment. Any subject who responds to any verbal command with MOAA/S assessment score of 3, 4, and 5 will be considered as responsive. Subjects with MOAA/S assessment score of 0, 1, and 2 will be considered unresponsive.

The BIS is a variable derived from the electroencephalograph (EEG) that has been reported to have the ability to measure the hypnotic component of the anesthetic state. It is a dimensionless number from 0 to 100, and decreasing values indicate more sedation and hypnosis.

The MOAA/S scales and BIS value will be assessed and recorded when the subject is awake and at different drug concentrations. The relationship between anesthetic agent concentrations and BIS responses will be modeled using the Sigmoid E_{max} model (Hill equation). The model is shown as follows:

$$E = E_0 + \frac{E_{max} \times C^{\gamma}}{(C_{50})^{\gamma} + C^{\gamma}}$$

In this model, the treatment effect (E) is related to the measured concentration (C) of an anesthetic agent according to a nonlinear function with γ defining the steepness of the concentration effect relationship. E_0 is the baseline measurement of the responsive endpoint when no drug is present and E_{max} is the maximum drug effect. The target parameter C_{50} is the concentration at which 50% subjects are unresponsive.

With zero effect when no drug is applied, the above model can be expressed as a fraction of maximum drug effect, that is,

$$P = \frac{1}{1 + (C_{50}/C)^{\gamma}}$$

where P is the fraction E/E_{max}. This is an extended logistic model with P as the probability of "unresponsive". The model will be fit to the data of BIS values along with drug concentrations. The BIS values will be assessed at the different targeted-controlled drug concentrations, or infusion rates, or ET concentration at which 50% (BIS_{50}) and 95% (BIS_{95}) of subjects are unresponsive. The systematic variance between groups will be evaluated. The Prediction Probability score (P_k) for correctly predicting if the subject was responsive or unresponsive will be assessed using the Smith Method.

7.3 Test of Cross Over Effect

This is a cross-over study and potential carry-over effect will be assessed. Logistic regression will be used to test carry-over effect by using the regiment sequence as an indicator variable. A P-value of 0.1 or larger will be deemed as supporting the assumption of no carry-over effect. If the carry-over effect is present, further analysis will be performed by adopting appropriate statistical methods (e.g., *Laird, et al. 1992).*

7.4 Center Pooling

This is a single center study and no pooling analysis is needed.

7.5 Handling of Missing, Unused, and Spurious Data and Dropouts

The primary analysis will be based on all evaluable data. Handling of dropouts and missing data will depend on their frequency and the nature of the outcome measure.

Subjects who discontinue participation prematurely will be included in the analysis of results. Subjects who withdraw from the study prior to completing both regimens will be replaced by a new volunteer.

7.6 Adjustments for Multiple Comparisons

No multiplicity adjustments will be considered in this study.

7.7 Demographic and Other Baseline Characteristics

Subject demographics, medical history will be summarized using descriptive statistics for continuous variables (mean, standard deviation, number of observations, minimum and maximum) and frequency tables for discrete variables.

Baseline demographic data will be summarized and reported. This table summarizes the subject population with respect to age at entry into the study, gender. Age will be reported in years. Age will be summarized using descriptive statistics: n, arithmetic mean, standard deviation, median, and range (i.e., minimum and maximum values). Subjects with missing data that cannot be resolved prior to database lock will not be included in the tabulation and excluded from the summary statistics; gender will be summarized using counts and percentages. In addition to the reported values, unknown or unreported values will also be reported. The supportive data for the demographics table will be presented in a listing.

7.8 Interim Analyses

There is no interim analysis.

7.9 Evaluation of Objectives

The objective of this study is to investigate the relationship between BIS and propofol with/ without remifentanil across a wide range of hypnotic states.

Primary Objective:

To determine BIS_{50} (BIS value at which 50% of subjects will be unresponsive at given drug concentrations) and other dose-response parameters.

Secondary Objective:

To determine BIS_{95} (BIS value at which 95% of subjects will be unresponsive at given drug concentrations) and other dose-response parameters.

The relationship between anesthetic agent concentrations and BIS responses will be modeled using the Sigmoid model (extended logistic model) as discussed previously.

The dose-response relationship by drug concentration will be presented. The estimated BIS values along with 95% confidence intervals will be provided for propofol with or without remifentanil regimens.

7.10 Safety Evaluation

Safety evaluation will be based on all enrolled subjects in this study. Adverse events will be summarized using frequency counts and percentages. Descriptive statistics will be provided by event type, severity, and relationship to study procedures and devices.

Unanticipated device effect (UADE), Serious Adverse Device Effect (SADE) and Unanticipated Serious Adverse Device Effect (USADE) will also be summarized by frequency table. Individual listings of adverse events, including event type, start date, duration, severity, and device-relatedness, will be provided as appropriate.

7.11 Health Outcomes Analyses

This section is not applicable to this study.

7.12 Changes to Planned Analysis

This section is not applicable to this study.

8 Validation Requirements

Output will be validated by level I or II validation.

Level I: The peer reviewer independently programs output and then compares the output with that generated by the original Statistical Programmer.

Level II: The peer reviewer reviews the code; where appropriate, performs manual calculations or simple programming checks to verify the output.

9 References

Smith WD, Dutton RC, Smith NT. Measuring the performance of anesthetic depth indicators. *Anesthesiology* 1996; 84: 38–51.

Laird NM, Skinner J, Kenward M. An analysis of two-period crossover designs with carry-over effects. *Stat Med* 1992;11(14-15):1967-79.

10 Statistical Appendices

Modified Observer's Assessment of Alertness/Sedation scale

Table 2: 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