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APPROVALS

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Medtronic **Statistical Analysis Plan**	
Clinical Investigation Plan Title	The influence of age on EEG signals and consciousness during anesthesia (TIARA)
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1 Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Initial Release	Alex Shih, PhD, Principal Biostatistician

2 List of Abbreviations and Definitions of Terms

Term	*Definition/Acronyms*
ADE	Adverse Device Effect
ANOVA	Analysis of Variance
BIS	Bispectral Index
CSR	Clinical Study Report
DD	Device Deficiency
EEG	Electroencephalogram
EFS	Edmonton Frail Scale
EMG	Electromyogram
MMSE	Mini Mental State Examination
MNA®-SF	Mini Nutritional Assessment
MOAA/S	Modified Observer's Assessment of Alertness/Sedation Scale
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System

3 Introduction

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.

The purpose of the TIARA clinical study is 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.

This statistical analysis plan (SAP) specifies the statistical methods to be implemented for the analysis of data used in the TIARA clinical study. It elaborates the statistical analyses specified in the CIP version 4, Dated November 9, 2020.

This document is created for internal use as a guideline for study Biostatistician and Statistical Programmer(s). Analysis results obtained from the analyses outlined in this document will be the basis of the Clinical Study Report (CSR) for this study.

As with any statistical analysis plan, the proposed methods and approaches to the data analysis should be considered as flexible to accommodate necessary changes. Changes to the plan may arise if the emerging picture suggests that deviations from the original plan would provide a more reliable and valid analysis of the data. The purpose of this plan is to provide general, and in some instances, specific guidelines from which the analysis will proceed. Nonetheless, sound statistical reasoning must substantiate deviations from these guidelines.

The planned analyses identified in this statistical analysis plan (SAP) may be included in regulatory submissions and/or future manuscripts. Additional exploratory analyses, not identified in this SAP, may be performed to support the clinical development program. Any post-hoc, or unplanned, analyses that are performed but not identified in this SAP will be clearly identified in the CSR.

4 Study Objectives

4.1 Primary Objective

The Primary objective of this clinical study is to determine the relationships between BIS parameters, age, and depth of anesthesia in patients undergoing surgery under general anesthesia. It is also to improve the BIS™ Index performance in the elderly population.

For the primary objective, the following data gathered by the BIS™ system during general anesthesia, will be collected:

- EEG waveforms
- EMG
- BIS Number
- Total Power
- Anesthesia records

4.2 Secondary Objective

The secondary objective is to investigate BIS parameters, depth of anesthesia and physical and cognitive states in the study populations using the following tools:

- Mini Mental State Examination (MMSE)
- Mini Nutritional Assessment (MNA®-SF)
- Edmonton Frail Scale (EFS)

5 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 200 subjects from approximately 5 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. To retain a good balance however, no more than 50% of total subjects expected to enroll at an individual study site.

6 Determination of Sample Size

Up to 200 subjects will be enrolled in the study, with 65% subjects over the age of 65 years. The sample size will provide adequate data information to assess the age impact for elder subjects with greater than 90% power to detect a distributional shift of BIS and MOAA/S scores between ages 18-64 and ⩾65 years old (BIS 5-point, MOAA/S 0.5-point). Sample size calculations are based on the PASS software with a standard deviation of 10-point for BIS and 1.2 for MOAA/S. The sample size will also ensure high confidence to detect any rare safety events with an incidence as low as 2% (>98% confidence) or 1% (>86% confidence).

7 Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

Subject disposition will be summarized with frequency tables.

7.1.2 Analysis Sets

All subject data that satisfied the inclusion and exclusion criteria will be included in this analysis.

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.

7.2.1 Statistical Method

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. Also, the relationship between BIS and MOAA/S will be examined by subjects under 65 and by subjects over 65 years old. 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.

Specifically, for the primary objective, a polytomous logistic regression model will be employed to assess the relationship between the MOAA/S scale and the BIS score/age groups (18-64 vs. 65+). The interaction between age and BIS score will be included. Another dichotomous logistic regression model will be utilized as well, when the MOAA/S scale is classified as responsive (scale of 2, 3, 4, and 5) and non-responsive (scale of 0 and 1).

The BIS scores at various time stamps (e.g., first response, extubation, etc) will be compared between the two age groups.

A simplified Sigmoid E_{max} model will also be used to analyze the relationship between the BIS™ index and loss of responsiveness through the probability of response curves. The values of BIS™ at which 50% (BIS_{50}) and 95% (BIS_{95}) of subjects are unresponsive, and their 95% confidential intervals will be derived. The systematic variance between groups will be evaluated.

The model is as follows:

$$P = \frac{e^{a+bX}}{1 + e^{a+bX}}$$

where *P* is the probability of "unresponsive", *X* is the explanatory variable (BIS™ value or anesthetic agent concentration on the log scale), and *a* & *b* are model parameters.

For each age subgroup, one can estimate the BIS™ value and the effect-site concentration at which 50% subjects are unresponsive, i.e., BIS_{50} and EC_{50} respectively. The corresponding 95% confidence intervals and standard errors for the estimates will be derived. The same evaluation will be performed for BIS_{95}, at which 95% subjects are unresponsive. The systematic variance between groups will be evaluated accordingly.

Multivariant logistic regression model will be used to study the effects of other baseline covariates (gender, blood panel, physical and cognitive states).

7.3 Center Pooling

There are five participating centers in this study. Clinical procedure and data collection were executed under the same protocol. Every effort will be made to promote consistency in study execution at each study site.

Data poolability across sites will be assessed descriptively. Summary statistics of the primary outcomes (BIS, MOAA/S) will be presented by site, and statistical inferences may be provided for reference purposes. If the sites are found to be significantly heterogeneous, additional analyses will be conducted to further assess the differences between sites in baseline and procedural variables that might contribute to the differences.

7.4 Adjustments for Multiple Comparisons

No multiplicity adjustments will be considered in this study.

7.5 Demographic and Other Baseline Characteristics

Subject demographics, medical history, blood panel and cognitive state (including MMSE, MNA-SF and EFS) 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 in a table entitled “Summary of Subject Demographics”. This table summarizes the subject population with respect to age at entry into the study, gender. Age will be reported in years. Subjects with missing data that cannot be resolved prior to database lock will not be included in the tabulation and will be 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 (if any). The supportive data for the demographics table will be presented in a listing entitled “Subject Demographics”.

7.6 Interim Analyses

An early data review will be performed for the first 40 enrolled subjects to ensure data validity and no safety concern. This analysis will not affect the evaluation of the primary endpoints. The enrollment and study procedure will not be affected and will be proceed as planned.

7.7 Safety Evaluation

For safety assessments, Adverse events (AE) and adverse device effect (ADE) will be summarized using frequency counts and percentages. Descriptive summary will be provided by severity and relationship as needed. In addition, device deficiency (DD), which may or may not pose a safety concern to participants will be summarize as well.

7.8 Health Outcomes Analyses

This section is not applicable to this study.

7.9 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.