Medtronic **Statistical Analysis Plan**	
Clinical Investigation Plan Title	Bispectral Index and End-Tidal Anesthetic Gas Concentration in Pediatric Patients undergoing Sevoflurane Anesthesia (BTIGER)
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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Initial Release	Alex Shih, PhD, Principal Biostatistician
2.0	• Update to template • Revised to match CIP V4.1	Ami Stuart, PhD, Sr. Clinical Research Specialist Alex Shih, PhD, Principal Biostatistician

2. List of Abbreviations and Definitions of Terms

Term	*Definition/Acronyms*
AAM	Anesthesia airway management
AE	Adverse event
ASA	American society of anesthesiology
BIS™	Bispectral Index (BIS) technology monitoring uses processed EEG signals to measure sedation depth based on the level of consciousness
CSR	Clinical study report
EEG	Electroencephalogram
GA	General anesthesia
LOC	Level of consciousness
PACU	Post-anesthesia care unit
PEAD	Pediatric anesthesia emergence delirium
SAP	Statistical analysis plan
SAS	Statistical analysis system
SP	Standard practice

3. Introduction

This statistical analysis plan (SAP) specifies the statistical methods to be implemented for the analysis of data used in the Medtronic clinical study titled as “Bispectral Index and End-Tidal Anesthetic Gas Concentration in Pediatric Patients undergoing Sevoflurane Anesthesia (BTIGER)”. It elaborates the statistical analyses specified in the BIS BTIGER CIP 2.0, dated 22-FEB-2021.

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.

General anesthesia (GA) is a reversible state of controlled unconsciousness that is achieved with drugs that prevent awareness, pain, recall, distress, and movement in patients during surgery. Maintaining an adequate level of anesthesia depth is essential to the attenuation of these responses. During the surgery operation, monitoring the depth of anesthesia could help the anesthesia professional avoid intraoperative awareness and help to ensure that an appropriate dose of anesthetic drugs is given for each patient.

Bispectral Index (BIS™) technology monitoring uses the processed electroencephalogram (EEG) signalsto measure sedation depth based on level of consciousness (LOC) signals. Its values quantify changes in the electrophysiologic state of the brain during anesthesia. It has been known that the use of BIS™ during general anesthesia improves the titration of anesthetics in adults.

4. Study Objectives

1.1 Primary Objective

To characterize BIS™ performance with the anesthetic agent in pediatric patients 4 to 18 years of age.

1.2 Endpoints

The primary endpoints are End-Tidal Sevoflurane concentration in both patient groups acquired during maintenance of anesthesia.

The secondary and exploratory endpoints include:

- Recovery assessments in patients receiving BIS™ monitoring compared to standard anesthetic practice:
    - Emergence,
    - PACU discharge readiness using Modified Aldrete Score
    - Anesthesia Airway Management (AAM)
- Clinical Anesthesia Assessment, recorded as the incidence of movements, grimacing, eye opening, tearing, sweating, mydriasis and cardiovascular changes while undergoing anesthesia
- Pediatric Anesthesia Emergence Delirium (PAED),
- Wong-Baker FACES Pain Rating Score

5. Investigation Plan

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

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

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

For the BIS group, sevoflurane will be adjusted to achieve a target BIS™ values of 45–60 during maintenance of anesthesia and BIS™ values of 60–75 beginning of skin closure. For the SP group, sevoflurane administration will be at the discretion of the anesthesiologist using clinical signs and hemodynamic changes to adjust anesthetic concentration.

6. Determination of Sample Size

The first 2 - 4 subjects at each site will be enrolled to train the site team on the new technology and to determine the quality of data collection prior to randomization (n = 16-32). They will not be randomized and will not be included in the final analysis. For the analysis, a minimum of 36 subjects are required in each age group (18 per treatment group) for a minimum of 108 qualifying data sets. Subjects with non-qualifying data sets will be rejected and replaced with a newly randomized subject. This sample size was independently powered for each of the 3 age groups based on data from a previously published study conducted by Emory University.

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

Discuss potential CIP deviations or violations and how they will be reported.

7.1.3 Analysis Sets

All study subjects (excluding training) that satisfied the inclusion and exclusion criteria will be included in the analysis.

7.2 General Methodology

All statistical analyses will be performed using Statistical Analysis System (SAS) for Windows (version 9.4 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.

7.3 Center Pooling

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

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

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

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

The primary analysis will include all evaluable data and missing values will not be imputed. BIS™ values that are outside of the specified range of 45 – 60 during maintenance of anesthesia for >25% of the maintenance period will be considered a protocol deviation and will result in an exclusion of the subject from the primary analysis. The excluded subject will be replaced, and data from all excluded subjects will be noted and discussed in the final study report. Additionally, sensitivity analysis (e.g., multiple imputation) may be performed as appropriate to assess the robustness of study results.

7.5 Adjustments for Multiple Comparisons

No multiplicity adjustments will be considered in this study.

7.6 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 in a table entitled “Summary of Subject Demographics”. This table summarizes the subject population with respect to age (in years) at entry into the study, gender. Age will be summarized using descriptive statistics: n, arithmetic mean, standard deviation, median, and range. 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.

7.7 Treatment Characteristics

Surgical procedure characteristics and exposure to study product will be summarized using descriptive statistics. Describe how concomitant therapies and medications will be summarized using descriptive statistics.

7.8 Interim Analyses

No interim analyses are planned for this study.

7.9 Evaluation of Objectives

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

The primary endpoint will be collected as a continuous variable every minute along with the BIS™ values. The primary analysis will be based on all evaluable data (excluding training subjects). Normality of data will be tested using the Kolmogorov-Smirnov test. Depending on whether normality assumption holds, a two-group t-test or Wilcoxon rank-sum test will be used to compare between the two

treatment groups. A P-value of less than 0.05 is considered statistically significant unless otherwise specified.

The mean BIS™ and standard deviation will be determined at each concentration of sevoflurane. A semi- logarithmic plot of sevoflurane concentration versus BIS™ will be provided, and the correlation will be quantified by using an inhibitory sigmoid E_{max} model (Denman et al., 2000) on steady state points. The model is formulated as:

$$E = E_0 - \frac{(E_{max})(C^{\gamma})}{EC^{\gamma}_{50} + C^{\gamma}}$$

As noted by Denman, the E_0 is specified to be 100, γ (gamma) is the scale factor, and E_{max} is the maximal effect constrained to 100. The EC_{50} is the sevoflurane concentration corresponding to the half-maximal effect (e.g., BIS™ of 50), and this value will be estimated, along with 95% confidence intervals, for each age group.

The training subjects will not be included in the analysis set for the primary and secondary endpoints. The training subjects will be summarized descriptively and separately. Any specific findings from these subjects will be noted and discussed in the study report.

The following secondary endpoints will be evaluated:

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

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

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

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

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

7.10 Safety Evaluation

Subjects will be monitored for Adverse Events, Serious Adverse Events, and Device-Related Adverse Events from BIS™ sensor applications throughout the BIS™ sensor removal. Adverse events will be summarized descriptively using frequency counts and percentages. A summary of events by severity and relationship will also be provided for each study group.

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.

Summary of Changes

Version	Effective Date	Summary of Changes	Change Author
2.0	24-Nov-2015	Initial Release	Lisa Tonder
3.0	01-Jun-2017	• Made Version History title black text as table was already black and should be required • Added additional regulatory requirements for Australia, India, and Taiwan in blue text • Minor administrative changes • Moved template-specific information to the footer • Migrated document to the new branded Corporate QMS document template.	Lisa Tonder
A	15-May-2018	• Added blue text language on front page for visibility to ClinicalTrials.gov posting requirements. • Added blue text in sections 7.6 and 7.9 to provide direction for compliance with FDAs age, race, and ethnicity guidance. • Minor administrative changes as migrated to new template.	Lisa Tonder
B	15-May-2020	• Title page: removed document version and document reference number • Section 3 Introduction: added recommendation on copying text from CIP to SAP • Added requirements based on ISO 14155:2020 • Section 7.10 Safety Evaluation: added Serious Adverse Events and Unanticipated Serious Adverse Device Effects	Jiaowang Dong
C	10-Dec-2021	• Added blue text language on front page for awareness of journal requirements • Added Statistical Analysis Plan Version Date to cover page due to ClinicalTrials.gov requirements	Baerbel Maus