Medtronic **Statistical Analysis Plan**	
Clinical Investigation Plan Title	Validation of Next Generation INVOS NIRS Cerebral and Tissue Oximeter to Measure Cerebral and Somatic Tissue Oxygen Saturation in Healthy Volunteers
Clinical Investigation Plan Identifier	MDT16010MAVJB3
Sponsor/Local Sponsor	Medtronic MITG, Patient Monitoring & Recovery (PMR) 6135 Gunbarrel Avenue, Boulder, CO 80301 U.S.A.
Document Version	B

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1. Version History

Version	Revision Date	Summary of Changes	Author(s)/Title
A	24MAY2017	New Document	[redacted]
B	18JUL2017	• Added Matlab software to list of software than can be used for analysis • Bootstrap of Arms, Mean Bias and Standard Deviation removed as not intended for study endpoint acceptance criterion • Revise requirements for Bland-Altman and Linear Regression graphs • Updates to subgroup analysis requirements • Lin's CCC does not have regression coefficients as this is not regression model but only correlation statistic • Sample Size justification statement justification	[redacted]

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
A_{RMS}	Arithmetic Root Mean Square
CIP	Clinical Investigation Plan
$etCO_2$	End Tidal Carbon Dioxide
fSO_2	Global Field Saturation
NIRS	Near Infrared Spectroscopy
OPC	Objective Criterion
rSO_2	Regional Saturation Measured by NIRS System
SAP	Statistical Analysis Plan
SaO_2	Saturation of Arterial Blood
$SjvO_2$	Jugular Bulb Venous Saturation
SpO_2	Arterial Blood Oxygen Saturation
$St0_2$	Absolute Levels of Blood Oxygenation Saturation in the Tissue
UCB	Upper Confidence Bound

3. Introduction

This document describes the statistical analyses and data presentations to be performed for Medtronic Study Protocol, MDT16010MAVJB3, "Validation of Next Generation INVOS NIRS Cerebral and Tissue Oximeter to Measure Cerebral and Somatic Tissue Oxygen Saturation in Healthy Volunteers" This statistical analysis plan (SAP) provides a comprehensive and detailed description of the strategy, rationale, and statistical techniques to be used to validate the [redacted] System (investigational preamplifiers, monitor, and associated cables) in conjunction with Adult sensor [redacted].

All statistical analyses detailed in this SAP will be conducted using SAS® Version 9.3 or higher, JMP Version 11.2.0, Minitab Version 17.1.0, Matlab Version 2015a or higher, or other validated software.

4. Study Objectives

The primary objective of the study is to validate that the [redacted] System in conjunction with Adult Sensors [redacted] meet product requirements for cerebral accuracy, cerebral trending accuracy, and somatic trending.

5. Investigation Plan

This is a prospective data collection, non-randomized, single center study to validate an investigational Next Generation INVOS system. An investigational next generation INVOS Near Infrared Spectroscopy (NIRS) system includes production equivalent [redacted] System (investigational preamplifiers, monitor, and associated cables) in conjunction with Adult sensor [redacted] (INVOS system).

This study will be conducted in three phases: Enrollment Phase, Desaturation Phase, and Follow-up Phase. During enrollment phase, subjects will be screened and qualified subjects will be enrolled. After enrollment, during desaturation phase, two investigational INVOS sensors are placed on the patient's forehead and other sensors may be placed on somatic sites. The Next Generation INVOS system will be evaluated for a targeted range of 70-100% arterial blood oxygen saturation (SpO_2) levels that are measured by a pulse oximeter. Hypoxic mixtures of gas are delivered and INVOS and SpO_2 data are collected at approximately 5-minute intervals during periods of ascending and descending concentration of control of blood carbon dioxide and oxygen levels. At each plateau, blood samples are drawn simultaneously from both jugular bulb and the radial arterial catheters and analyzed for hemoglobin oxygen saturation levels using a co-oximeter.

[redacted]

- 2 sensors on cerebral site (left, right side of forehead)
- 2 blood draws and monitor measurements at each oxygenation plateau
- 1st data point at beginning of each sequence for trending accuracy used for baseline reference
- Somatic Trending Accuracy data is collected for all Sequences #1-3. [redacted] does not have an effect on somatic blood oxygenation levels.

[redacted]

During the invasive breathe-down protocol, a subject breathes varying levels of oxygen (desaturation sequence) while paired venous and arterial blood draws are collected. [redacted] Based on the measured oxygenation content of each blood sample, a calculated estimate of SO_2 (fSO_2) is created for each paired blood draw. The calculated fSO_2 (blood reference) is compared to the average rSO2 from each INVOS sensor during the time span of collection for the paired blood draw [redacted].

[redacted]

6. Determination of Sample Size

[redacted]

Cerebral Overall Accuracy:

Based on data from similar studies, a mean value of [redacted] is assumed for A_{RMS} with a standard deviation of [redacted] assumed. A total of 25 subjects will provide sufficient data information [Table 2] to assess the statistical hypothesis. [redacted] power and an alpha of [redacted] are assumed in the estimation.

[redacted]

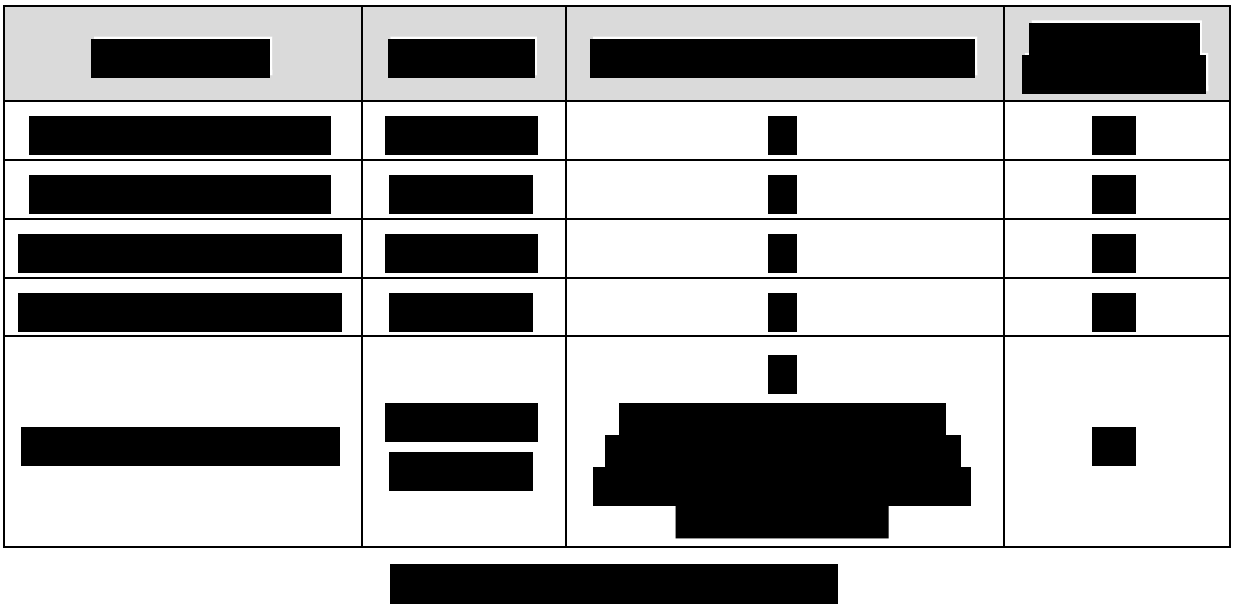
Cerebral Trending:

Based on data from similar studies, a mean value of [redacted] is assumed for A_{RMS} with a standard deviation of [redacted] assumed. A total of 25 subjects will provide sufficient data information [Table 2] to assess the statistical hypothesis. [redacted] power and an alpha of [redacted] are assumed in the estimation.

Somatic Trending:

Based on data from similar studies, a mean value of [redacted] is assumed for A_{RMS} with a standard deviation of [redacted] assumed. A total of 25 subjects will provide sufficient data information [Table 2] to assess the statistical hypothesis. [redacted] power and an alpha of [redacted] are assumed in the estimation.

Based on the study desaturation sequence profile it is required secondary to the minimum number of subjects, that a minimum number of paired measurements for each study endpoint and capnic state will be collected as defined in Table 2.



7. Statistical Methods

7.1. Study Subjects

7.1.1. Disposition of Subjects

Subject disposition (e.g., number completed the study, discontinued along with primary reason for discontinuation, lost-to-follow-up) will be summarized with frequency counts and the corresponding percentages.

7.1.2. Clinical Investigation Plan (CIP) Deviations

The number of subjects with major protocol deviations (e.g. informed consent process or procedures are not followed, violation to inclusion or exclusion criteria, or issues with study data collection) will be summarized with frequencies and percentages.

7.1.3. Analysis Sets

Subjects will be considered enrolled in the study once it has been confirmed that they meet all the inclusion and none of exclusion criteria. Unless otherwise specified, analysis of reported outcomes will include all available data for all subjects enrolled.

7.2. General Methodology

All statistical analyses will be performed using SAS® Version 9.3 or higher, JMP Version 11.2.0, Minitab Version 17.1.0, Matlab Version 2015a or higher, or other validated software. In general, descriptive statistics will be used to summarize the baseline and study outcomes. The statistics for continuous variables may include the number of observations (N), mean, standard deviation, median, minimum, and maximum. Categorical variables are presented using frequencies and percentages.

7.3. Center Pooling

Center Pooling not applicable as this is a single center study.

7.4. Handling of Missing Data and Dropouts

No imputation or other adjustment techniques are planned for the missing data to be included in the analyses.

7.5. Adjustments for Multiple Comparisons

No adjustments for multiple comparisons will be made.

7.6. Demographic and Other Baseline Characteristics

The baseline characteristics, including age, gender, race, ethnicity, skin tone and BMI will be summarized by using descriptive statistics.

7.7. Interim Analyses

There are no requirements for an interim analysis.

7.8. Evaluation of Objectives

The next generation [redacted] system measures hemoglobin under the Sensor, allowing determining absolute levels of blood oxygenation saturation in the tissue ($St0_2$). The INVOS algorithm determines the $St0_2$ values for the tissue under the sensor. The next generation INVOS system will be validated over a clinical range of arterial oxygen saturations (e.g. pulse oximeter) of 70 - 100% in healthy volunteers. Next generation INVOS regional saturation (rSO_2) performance will be compared to the calculated global field saturation (fSO_2) value obtained from simultaneous arterial and jugular venous blood samples for the cerebral site and it will be compared to legacy INVOS rSO_2 on the somatic site. Human volunteers will undergo oxygen desaturation in order to test the system over a clinical range of arterial oxygen saturation levels of 70 - 100%.

The cerebral tissue saturation can be estimated using the saturation of arterial blood (SaO_2) and jugular bulb venous saturation ($SjvO_2$).

Co-oximetry is used to determine the $SjvO_2$ and SaO_2 values (SaO_2 value is taken as the average of the 2 arterial blood samples). The arteriovenous (fsO_2) saturation is calculated as a 75:25 ratio of venous to arterial blood.

$fs0_2 = (0.75 \times SjvO_2) + (0.25 \times SaO_2)$.

Global field saturation, fsO_2 is calculated as approximation of the cerebral oxygen saturation and is used as the reference value for assessing accuracy for cerebral.

Overall accuracy will be evaluated:

At the cerebral site, by comparing next generation INVOS rSO_2 with blood fSO_2 values.

[redacted]

Trending accuracy will be evaluated:

At the cerebral site, by comparing the next generation INVOS rSO_2 with blood fSO_2 values.

[redacted]

At the somatic site, by comparing next generation INVOS rSO_2 with legacy INVOS rSO_2 values.

[redacted]

[redacted]

Arithmetic Root Mean Square (A_{RMS}), standard deviation of the error and mean bias will be calculated as defined in the equations below. The primary endpoint will be evaluated to calculated pooled subject A_{RMS}. The equations below represent calculataions for overall accuracy with the error component of each equation being replaced with the error as defined in Figure 2 for trending accuracy.

$$Arms = \sqrt{\sum_{i=1}^{n} \frac{((rSO_2)_i - (fSO_2)_i)^2}{n}}$$

$$Std\ Dev = \sqrt{\sum_{i=1}^{n} \frac{((rSO_2)_i - (fSO_2)_i - Bias)^2}{n-1}}$$

$$Bias = \sum_{i=1}^{n} \frac{((rSO_2)_i - (fSO_2)_i)}{n}$$

Cerebral Accuracy Overall and Trending:

1 Regression of the [redacted] rSO_2 data vs. the reference fsO_2 data with the calculation of r^2 assessing the strength of the linear relationship between the two continuous variables. Calculations and fitted line plots will be performed for pooled population data. Regression coefficients, slope and intercept will be reported with bootstrap 95% Confidence Limits.

2 Bland Altman plot (Bland and Altman, 1986)[1], (Bland and Altman, 2007)[2] defined limits of agreement provide the approach to agreement between different methods for measuring the same quantity. Individual subject and pooled population data will be graphed.

3 Random Coefficients Model; subject dependent variable added to model as random effect. Regression coefficients, slope and intercept will be reported with bootstrap 95% Confidence Limits.

4 Concordance correlation coefficient (CCC) analysis (Lin, 1989)[3]. This index is the correlation between the two paired measurements that fall on the 45° line through the origin.

Somatic Accuracy Trending:

1 Regression of the [redacted] rSO_2 data vs. the predicate system 5100C rsO_2 data with the calculation of r^2 assessing the linear relationship between the two continuous variables. Calculations and fitted line plots will be performed for pooled population data. Regression coefficients, slope and intercept will be reported with bootstrap 95% Confidence Limits.

5 Bland Altman plot (Bland and Altman, 1986)[1], (Bland and Altman, 2007)[2] defined limits of agreement provide the approach to agreement between different methods for measuring the same quantity. Individual subject and pooled population data will be graphed.

2 Random Coefficients Model; subject dependent variable added to model as random effect. This is performed on pooled data across subject study population and addresses the dependence of subject based repeated measurements. Regression coefficients, slope and intercept will be reported with bootstrap 95% Confidence Limits.

3 Concordance correlation coefficient (CCC) analysis (Lin, 1)[3]. This index is the correlation between the two paired measurements that fall on the 45° line through the origin.

Subgroup Analysis:

1 Left and right cerebral sensor placement groups for absolute and trending accuracy will be evaluated by calculation of A_{RMS}, mean bias, and standard deviation of errors.

2 A_{RMS}, mean bias and standard deviation of errors for skin tone groups will be calculated for cerebral and somatic endpoints. Skin pigmentation is classified by 3 levels: light, medium, dark

Capnic State Analysis:

The pCO2 will be averged for the two arterial blood draws taken at each oxydenation plateau and multiple COOX measurements evaluating the samples.

pCO_2 measured by blood draw co-ocimeter analysis will be analyzed per subject for normocapnic [redacted] states independently by mean, median, standard deviation, min, max.

Additonal statistical analyses may be performed for supporting evidence in meeting study endpoints.

7.9. Safety Evaluation

Adverse events for all enrolled subjects will be collected and reported. Summary of overall event, events relatedness, seriousness and severity will be provided. To assess safety, the number and percentage of subjects with adverse events will be summarized by severity. And the total number of events will be provided as well.

7.10. Health Outcomes Analyses

N/A

7.11. Changes to Planned Analysis

Any deviations from the original statistical plan will be justified and documented appropriately.

8. Validation Requirements

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

9. References

[1] Bland J. Martin, Altman, Douglas G. Agreement between Methods of Measurement with Multiple Observations Per Individual. Journal of Biopharmaceutical Statistics. 2007; 17: 571-582.

[2] Bland JM, Altman DG. Statistical Methods for Assessing Agreement between Two Methods of Clinical Measurement. Lancet 1986; 1(8476):307–10.

[3] Lin, Lawrence I-K A concordance correlation coefficient to evaluate reproducibility. Biometrics, 45: 255-268 (1989).