A Comparison of Capnography Sampling Lines Trial

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- Statistical Analysis Plan, version 1 dated 28 August 2018

Medtronic

Statistical Analysis Plan

Clinical Investigation Plan Title	A Comparison of Capnography Sampling Lines
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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• New Document	Yun Bai, PhD, Biostatistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
ADE	Adverse Device Effect
CO_2	Carbon Dioxide
CO_2 monitoring	Capnography
CS35	Capnostream®35
CCSF	CO_2 cannula sampling filterline
$EtCO_2$	End Tidal CO_2
$FiCO_2$	Fractional inspired carbon dioxide
NC	Nasal Cannula
NIV	Non-invasive ventilation
O_2	Oxygen
SpO_2	Pulse Oximetry
RR	Respiration Rate
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event

3. Introduction

This is a Prospective, Interventional, Single Center, comparative product study to collect CO_2 measurements on human subjects as a function of the carbon dioxide (CO_2) cannula sampling filterline (CCSF) during simulated patient activity to provide guidance on filterline selection in the clinical setting for Microstream™ enabled monitors.

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 2.0 dated on 30MAY2018.

4. Study Objectives

4.1. Primary Objective(s)

The primary objective of this clinical study is to compare the performance of the Medtronic Microstream™ FilterLine™ compared to the non-Medtronic CCSF products during predefined expected patient activities to provide a quality sample of breath gas to the Microstream™ enabled capnography monitor.

The primary endpoints will be the frequency and duration of false physiological alarms, device notifications regarding a reduction in CO_2 Waveform device messages/notifications such as filterline blockage, performing auto zero, clearing the filterline and CO_2 error.

4.2. Secondary Objective(s)

The secondary objective is to score the performance of the non-Microstream™ CCSFs compared to the Medtronic (MDT) Microstream™ FilterLine™. The endpoints will be the foundation to score sampling performance per activity by subject and in aggregate.

The need to score performance by the scripted simulated patient activities will provide information on optimal filterline selection based upon end use clinical setting and expected patient activity.

5. Investigation Plan

Prospective, interventional, single center, comparative product study design on a convenience sample of out-of-hospital volunteers.

There is no blinding or randomization to subject procedure. Intervention assignments (CCSF sequence) for each subject will be based upon a randomized sequence by subject ID. Subjects will serve as their own control within each of the repeated scripted activity periods (such as variations on mouth positions,

partial and full unilateral nasal obstruction, nasal/oral respiration shifting pattern, variations in respiratory effort and rate, variations of head position, variations of body position) in the study design.

6. Determination of Sample Size

Up to 50 consented subjects at one clinical site in USA to secure a minimum of 30 evaluable subject data sets. Based upon a previous study on cannula design investigating both CO_2 sampling and O_2 delivery (Ebert & Novalija, 2015), a sample size of 30 will provide more than 90% power to test a normalized effect size of 5 or more using the Tukey-Kramer multiple comparison test at the 0.05 significance level.

7. Statistical Methods

7.1. Study Subjects

7.1.1. Disposition of Subjects

Subject disposition (e.g., number completing the study) will be summarized with frequency tables.

7.1.2. Clinical Investigation Plan (CIP) Deviations

Deviations are instance(s) of failure to follow, intentionally or unintentionally, the requirements of the CIP. All deviations must be documented and explained, regardless of the reason for the deviation.

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

In general, descriptive statistics will be used to summarize baseline and study outcomes. For continuous variables, number of available observations, mean, standard deviation, median, minimum and maximum values will be provided. For categorical variables, frequency and percentage will be used. Unless otherwise specified, statistical assessments will be based on 2-sided tests at an alpha level of 0.05.

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.

The study objectives will be based on all evaluable data from this study. The primary objective will be evaluated using the Tukey- Kramer honest significant difference test for multiple mean comparisons. All corresponding P values and confidence intervals for pairwise mean differences will be Tukey corrected as appropriate. Descriptive statistics and exploratory data analysis will be used to generate measures of central tendency and to perform data distribution diagnostics.

Analysis of variance (ANOVA) will be used to compare across multiple groups. Moreover, multivariate regression models will be used to explore the relationship between $EtCO_2$ and supplemental O_2 flow rate after adjusting for factors including cannula type, subject activity and O_2 flow rate.

7.3. Center Pooling

N/A

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

Electronic device data will be compared to subject CRF to verify the match in CCSF code name and time for activity effect on the device measured data. A subject will be withdrawn from the final data pool if there is missing electronic device data for that subject.

7.5. Adjustments for Multiple Comparisons

For Tukey- Kramer honest significant difference test, all corresponding P values and confidence intervals for pairwise mean differences will be Tukey corrected as appropriate. Multivariate regression models will be used to explore the relationship between EtCO2 and supplemental O2 flow rate after adjusting for factors including cannula type, subject activity and O2 flow rate.

7.6. Demographic and Other Baseline Characteristics

Demographic information and baseline characteristics data will be summarized using descriptive statistics.

7.7. Treatment Characteristics

N/A.

7.8. Interim Analyses

An early evaluation of the device data will be conducted after the first 5-10 subjects enrolled. This evaluation may result in a reduction in the CRF scripted activities for the remaining subjects in order to remove those activities that would need more than a total of 30 subjects to detect a statistically significant difference in $EtCO_2$ means as a function of the CCSF for each activity period. This adaptive filtering of the CRF activities purpose is to reduce enrollment time down to activities that may be identified as a potentially statistically significant difference in the sample size and not include those activities that would require an unnecessarily large sample size for significance.

7.9. Evaluation of Objectives

The study hypothesis is that the Medtronic (MDT) solution of pairing the Microstream™ FilterLine to the Microstream™ enabled device provides a more reliable gas sample for measurement across many of the

patient simulated scripted activities. Performance reliability of each CCSF for sampling breath gas will be measured using the mean and standard deviation for $EtCO_2$, the frequency of false physiological alarms, the frequency of CS35 device notifications, and the frequency of missing CO_2 data (drop-outs) as a function of both the CCSF variable and activity variable by subject and in aggregate.

This hypothesis is based upon the CS35 IFU that recommends that Microstream® $EtCO_2$ consumables (FilterLine) should be used to ensure the monitor functions properly.

The statistical design is a randomized CCSF sequence assignment with each subject serving as their own control within each scripted activity period with the up to study design of 8 CO2 sampling cannula filterline designs worn in each separate activity period. The randomized sequence by subject is by CCSF code name letters from A – F with the CCSF product assignment to the code name letters done by Clinimark and blinded to MDT until after the device data has been evaluated.

7.10.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.

7.11.Health Outcomes Analyses

N/A

7.12.Changes to Planned Analysis

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

8. Validation Requirements

Primary and secondary objectives will be validated by level I validation and the rest of the tables, listings and figures will be validated by level 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

1. Ebert, T. J., & Novaliia, J. M. (2015, February). The Effectivieness of Oxygen Delivery and Reliability of Carbon Dioxide Waveforms: A Crossover Comparison of 4 Nasal Cannula. *Anesthesia & Analgesia, 120*(2), 342-248.

2. Marshall, S. G., Henry, N. R., & Russian, C. (2016, April). Right Versus Left Prong Nasl Annula FLow Delivery and the Effects of Nasal Cycling on INspired FiO2 in an Adult Anatomical Model. *Respiratory Care, 61*(4), 397-404.