Title: SAP0002 Clinical Statistical Analysis Plan

NCT: NCT05445492

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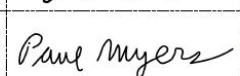
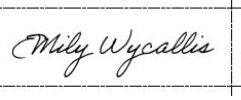
Reviewed By	Paul Myers	Algorithm Engineer		May 11, 2022
	Emily Wycallis	Biomedical Engineer, Clinical Trial		May 12, 2022

Introduction:

This document describes the statistical analysis planned for the clinical evaluation data. The study is described in the clinical evaluation protocol (CEPR0002).

Analysis Plan:

Analysis 1: Respiration rate accuracy

The primary objective of this analysis is to demonstrate whether 85% of the errors are bounded within ±2 bpm. It is noted that we will be using 85% instead of 95% because the CPM system is intended to give a trend, represented by multiple data points over time. This means the errors in the individual data points are averaged out in the trend interpretation, therefore justifying the change from 95% to 85%.

Respiration rate under natural breathing condition, if available, and controlled breathing condition (6, 10, 15, 20, 25, 30, 35, 40 brpm) will be summarized for CPM system and clinician annotated capnography. Although multiple breathing rates conditions are achieved within a subject, each data point is considered independent from each other. Prior look-ahead testing showed that there's no difference in mean errors and median errors across different breathing rate conditions, thereby justifying analyses after pooling all rate conditions together.

The error will be calculated by the difference between the CPM system's estimate and clinician annotated reference for each body posture. The error will be summarized using descriptive statistics and its limits of agreement. If the initial clinician's annotation is strongly suggested to be inaccurate by the compelling evidence (e.g., significant deviation from the simulated breathing or equivalently strong observations), the second annotator may be introduced to read the capnography waveform independently. The final respiration rate is determined based on two annotator readings.

Analysis 1-1: Respiration rate error descriptive statistics

The descriptive statistics includes but not limited to:

- Percentage of the CPM system's RR estimate not reported due to bad signal quality.
- Mean, median, variance, standard deviation, skewness, kurtosis, root mean squared error, and root median squared error.

Analysis 1-2: Percentage of respiration rate error within ± 2brpm

Using the data that are classified by the CPM system as good quality, the percentage of the respiration rate whose error is within ±2 brpm is derived. The confidence interval for the proportion of the errors within ± 2 brpm will also be characterized assuming that the number of data points whose errors are within ± 2 brpm follows binominal distribution.

Analysis 1-3: Respiration rate error limits of agreement

The limits of agreement will be derived using a conventional Bland-Altman analysis as well as non-parametric approach in case the distribution of the error has a long-tail, significant deviation of Normality assumption of the conventional Bland-Altman analysis.

The 85% limits of agreement (bias ± 1.44 standard deviation) will be tabulated. The 95% confidence interval for the limits of agreement will also be derived. In case the kurtosis, calculated in the Analysis 1-1, is high indicating that the distribution of errors has a long tail, non-parametric limits of agreement will also be presented to correctly characterize the range which 85% of the errors are expected to be bounded by. The non-parametric 85% limits of agreement will also be derived based on 7.5% and 92.5% percentile of the errors. The 95% confidence interval for non-parametric limits of agreement will be derived using a bootstrap resampling method.

Analysis 1-4: Other respiration rate accuracy analyses

A 95% confidence interval (CI) for mean error (i.e., bias) will be tabulated. While the primary objective is to show that the CPM estimate is accurate within ±2 brpm, the CI for mean error will additionally show if there is any systemic bias in the CPM estimate. The standard deviation of the paired differences will also be tabulated.

If the lower bound of the 95% confidence interval for the percentage of the errors within ± 2bpm from **Analysis 1-2** exceeds 85%, it is demonstrated with statistical significance that the CPM system's respiration rate accuracy is sufficient in comparison to the reference to support its intended use. Also, the other analyses should provide different lenses to characterize the respiration rate accuracy.

Analysis 2: Accuracy of relative changes of relative tidal volume

The primary objective of this analysis is to demonstrate the CPM system's relative tidal volume (rTV) is accurately tracking true changes in tidal volume (TV).

For each subject, relative tidal volume from the CPM system and the tidal volume from the reference device under the breathing-depth controlled condition (natural ~500 mL, shallow ~ 250 mL, deep ~ 750 mL, very deep >1L) and the breathing-rate controlled condition (e.g., 10, 15, 25, 30 bpm) will be compared for each body posture. A scatter plot of relative tidal volume produced by the CPM system and the tidal volume measured by the reference device will be produced. Each graph will be summarized by two least-squares linear regression fits. One is produced in a linear scale and the other is produced in a log scale to characterize the relative accuracy.

Analysis 2-1: Respiration rate error descriptive statistics

The descriptive statistics includes but not limited to:

- Percentage of the CPM system's rTV estimate not reported due to bad signal quality.
- Mean, median, variance, standard deviation, skewness, kurtosis, root mean squared error, and root median squared error.

Analysis 2-2: Least-squares linear regression analysis in rTV and TV

The accuracy of relative changes of rTV will be summarized by Pearson correlation coefficients across subjects. Then, mean correlations will be determined using Fisher's z-transformation to combine the subject specific coefficients and then back transformed. A 95% confidence interval on mean correlation coefficient will also be derived.

Analysis 2-3: Least-squares linear regression analysis in natural logs of rTV and TV

The accuracy of relative changes of rTV will be summarized by Pearson correlation coefficients across subjects obtained using natural logs of rTV and TV. Then, mean correlations will be determined using Fisher's z-transformation to combine the subject specific coefficients and then back transformed. A 95% confidence interval on mean correlation will also be derived.

After the linear fit, root mean square of the relative residual errors will also be characterized. A 95% confidence interval on the root mean squared relative errors will also be derived using Chi-squared distribution assuming the relative residual errors follows a zero-mean Gaussian distribution.

If the root mean square of the relative errors from **Analysis 2-3** and its confidence interval does not exceed 35% per end-point in the protocol (CEPR0002), it is demonstrated that the CPM system's relative tidal volume is sufficiently accurate in following relative changes in comparison to the reference. Mean correlation coefficients from Analysis 2-2 and 2-3 will also support that the primary objective of this Analysis 2 is achieved.

Analysis 3: ECG and Skin Temperature Capabilities

The primary objective of this analysis is to evaluate the secondary objectives regarding the ECG and skin temperature capabilities of the CPM system. For skin temperature, the descriptive analyses will be performed in comparison the reference measurement For ECG capabilities, if the data is available, the quality of the CPM ECG can be evaluated.