Statistical Analysis Plan (SAP)

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Sponsor:	ResMed Corporation
Author:	Leslee Willes, Willes Consulting Group, Inc.
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Approved By:

Name, Title	**Signature**	**Date**
Adam Benjafield, VP Medical Affairs		
Maureen Crocker, Sr CRA, Medical Affairs		
Leslee Willes, President, Willes Consulting Group		

Table of Contents

1. Study Synopsis

Version 3.0 of the protocol excluded subjects who are dependent on ventilator support. During the active stage of this trial, the iVAPS (with manual EPAP) algorithm on the study device (Astral) was cleared by the FDA. The IFU can be applied to both ventilator dependent and non-dependent patients. An increase in enrollment to 40 subjects will ensure that there is a mixture of both non-dependent ventilator support patients (v3.0 of protocol) and ventilator dependent (v4.0 of protocol) patients enrolled. [Note: The assumption is that primary endpoint of upper airway stability will not differ between ventilator dependent and non-dependent groups. A subgroup analysis of the primary endpoint comparing dependent and non-dependent patients will be generated. The expectation is that approximately 10% of the total enrollment goal of 40 will be ventilator dependent].

2. Analysis Populations

The populations are defined as follows.

- The Enrollment population is defined as all patients who are randomized for the study and begin the first study PSG night.
- The Intent-To-Treat (ITT) is defined as all patients in the Enrollment population who meet the inclusion/exclusion criteria.
- The Completed Cases (CC) population is defined as all patients in the ITT population who complete all study visits.

The primary endpoint analysis will be based on the CC subject population. A sensitivity analysis of the primary endpoint will be generated for the Enrollment population for patients who complete all study visits. An additional sensitivity analysis for the primary endpoint will be generated for the ITT population. The ITT population may contain some subjects who complete that first study PSG visit but not the second study PSG visit. This will require the use of imputation methods for missing values which are documented in Section 9.

All safety analyses will be generated for subjects in the Enrollment population. All secondary endpoints will be generated using the CC population.

3. Poolability analysis

The issue of poolability of the data entails two features: the combining of data across study sites and the method of computation of an overall estimate for study endpoints. The justification for combining of data across sites is based on the clinical assessment provided by Meinert (1): the clinical study will be conducted under a common protocol for each investigational site, the study sites will be monitored for protocol compliance, and the same data gathering instrument and method will be used in every site.

The justification for pooling all the data to estimate a common effect across study sites requires the homogeneity of response across study sites. An analysis of variance (ANOVA) of the differences will be generated to test whether the investigational sites differ with respect to primary study endpoint for the CC population (only the site will be included in this analysis model). The test of in homogeneity of response will be based on a two-sided significance test at the 0.15 level of significance. If the sites differ by this test, then a second analysis will be done including study site and all baseline characteristics that have $P<0.10$ in

the analysis of baseline characteristics by site to understand if the imbalance in the primary endpoint between sites is related to an imbalance in baseline characteristics.

The analysis of study sites may require the formation of pseudo-sites because the small study sites will not provide appropriate information to allow the analysis above. Study sites with fewer than 6 subjects will be combined into pseudo-sites for the poolability analysis using the following method. The smallest study site with less than 6 subjects will be combined with the next smallest study site. These two sites may be combined with a third site if the combined number of patients remains less than 6. The combination of sites will be halted if combining these sites makes the new pseudo-site the largest study site. Assigned pseudo-sites will be used for the analysis of poolability described above.

4. General Statistical Analysis Guidelines

The number of observations, mean, median, standard deviation, standard error, minimum and maximum will be calculated for continuous variables, unless otherwise stated. The number of significant digits reported will be as follows: minimum and maximum will have the same number of significant digits as the raw data; the mean, median, standard deviation, and standard error will be reported with one more significant digit than the raw data. Frequencies and percentages will be calculated for categorical data using one significant digit for percentages.

As a routine function in applying statistical procedures, the assumptions underlying those procedures will be evaluated. Equal variance will be tested by Folded F-test or Levene's test depending on the number of groups being compared. Tests for normality will not be done for continuous variables, but data will be inspected for symmetry through histogram plots and severe outliers will be investigated.

5. Subject Accountability

Subjects who withdraw from the study will be tabulated with the reasons for the withdrawal. Compliance with study visits will also be presented.

6. Primary Objective and Endpoint

The primary outcome is the Oxygen Desaturation Index (ODI4%). The primary aim of this protocol is to compare ODI values following the use of the AutoEPAP algorithm with the use of manual EPAP on the Astral ventilator.

The null and alternative hypothesis is based on a non-inferiority test using a non-inferiority margin (d) of 2 events/hour.

H0: $\mu_{A-B} > d$ (new algorithm is inferior)
H1: $\mu_{A-B} \leq d$ (new algorithm is non-inferior)

Where μ_{A-B} is the mean paired difference in ODI4% comparing AutoEPAP and manual EPAP algorithms, and d equals the non-inferiority margin.

6.1. Statistical Analysis of the Primary Endpoint

The primary hypothesis will be tested using a one-sided paired t-test of the difference in ODI between Auto and Manual EPAP and compared to a non-inferiority margin for ODI4% of 2 events/hour. Additionally, the 95% upper one-sided confidence bound for the mean paired difference in ODI between manual and Auto EPAP will be calculated.

A cross-over analysis will be generated to investigate the influence of a possible period effect on the primary endpoint, paired change in ODI4% between Auto and Manual EPAP. Based on previous studies, ResMed does not expect the randomization order in which the subject used Auto versus Manual EPAP to affect the differences in ODI between the methods. A two-sample t-test comparing the two randomized treatment groups based on an alpha of 0.05 will be utilized for this analysis.

6.2. Subgroup Analyses of the Primary Endpoint

Subgroup analyses of the primary endpoint will be conducted for disease type (COPD, OHS, Neuromuscular disease, Other) and ventilator dependency (Dependent vs Non-Dependent). Descriptive statistics will be presented stratified by disease categories and ventilator dependency, including the sample size, mean, standard deviation, median and range of the paired differences in ODI4% comparing Auto and Manual EPAP.

7. Statistical Analysis of Secondary Objectives

Secondary endpoints include (1) the assessment of AHI as measure by the Astral device and (2) sleep-breathing parameters (e.g., nadir spO2 and PtCO2) and sleep parameters (e.g. sleep efficacy index and arousal index) comparing AutoEPAP algorithm to manual EPAP on an Astral Device. Descriptive statistics will be presented for AHI as measured using manual EPAP on the Astral device. Descriptive statistics will be presented separately for sleep-breathing and sleep parameters for AutoEPAP and manual EPAP, as well as for the paired differences comparing results for manual EPAP and AutoEPAP. Descriptive statistics include mean, standard deviation, median, median, inter-quartiles, minimum and maximum values.

8. Additional Analyses

Descriptive statistics of baseline characteristics for all study subjects will be generated. An analysis of comparability of baseline characteristics by study site will be done. Pseudo-sites as described in Section 3 will be used for this analysis. For continuous variables such as age, an analysis of variance or Kruskal-Wallis test will be done to determine if study site is a significant factor with the characteristic being evaluated as the dependent variable. For categorical variables like gender, a Fisher-Freeman Halton test will be used. If the P-value from an analysis is $\leq$0.10, that variable will be considered unbalanced among the study sites and will be used in multivariable analyses of the poolability analysis if indicated.

Serious adverse events and events related to the Astral device will be tabulated for the Enrollment population, presenting the number of patients having one or more of each event and the associated percentage. A distinction will be made as to whether the subjects having adverse events were part of the ITT or Enrollment populations. In addition, a listing of these events will be presented, including the event description, time of occurrence, severity, outcome, action taken and relationship to the study device.

A separate listing of all other adverse events (non-serious and not related) occurring during the study period will be generated, including the event description, time of occurrence, severity, outcome, action taken and relationship to the study device.

9. Handling of Missing Values

The primary analysis will be based on the CC population. A multiple imputation sensitivity analysis will be done in the following way. Patients who dropout between the first and second PSG visit periods, will

have their second PSG visit data imputed, using the multiple imputation procedure MI in SAS. The imputation model will include randomization group and first period ODI4% as predictor variables. Results will be pooled using the MIANALYZE procedure in SAS.

10. Justification of Sample Size

Using a sample size calculation based on a normal distribution, the sample size required for 80% power to detect a difference in ODI of 1 event/hour, using a one-sided significance level of 0.05, was calculated to be 23 subjects assuming a SD of 1.55 in the Astral VAPS AutoEPAP Clinical Trial Protocol.

[Using the normal approximation formula for sample size as written in the protocol, I calculate a sample size of 15 patients required based on SD=1.55, beta=0.2, one-sided alpha=0.05, and a detection difference between groups of 1. Using a two-sided alpha of 0.05, the sample size is 19. Using PASS software (2) which uses the t distribution to calculate the sample size for paired means rather than the z distribution, the sample size is 17 for a one-sided alpha of 0.05, and 21 for a two-sided alpha of 0.05].

11. Protocol Deviations

Protocol deviations occurring during the study will be tabulated.

11. Statistical Software and Programming

The creation of analysis datasets and all statistical analyses will be generated using SAS version 9.3 or later. Graphics will be either generated using SAS software or R software. Good programming techniques including the use of sufficient program documentation, following naming conventions, good code structure, use of independent validation programs, and avoidance of hard coding will be practiced. All programming code will be independently peer-reviewed.

12. References

(1) Meinert, C. (1986). *Clinical Trials: Design, Conduct, and Analysis*. Oxford University Press, New York.
(2) Hintze, J. (2012). PASS 14. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com
(3) Guidance for Industry: E9 Statistical Principles for Clinical Trials. U. S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research. International Committee on Harmonization, September 1998.