Statistical Analysis Plan

Hill-Rom/ Protocol CR-RR2015- 001

Evaluation of a practice change to include The MetaNeb® System to reduce postoperative pulmonary complications

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Signatures/Approvals

Prepared by: PI [redacted]

PI [redacted] 16 Aug 2016
Date

Reviewed and approved by: PI [redacted] 16 AUG 2016
Date

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List of Abbreviations

CPAP	Continuous Positive Airway Pressure
ICU	Intensive Care Unit
LOS	Length of Stay
MV	Mechanical Ventilation
NIV	Noninvasive Ventilation
OSA	Obstructive Sleep Apnea
PPC	Postoperative Pulmonary Complication
PSHA	Post-Surgical Hospital Admission

1 Introduction

The study will be conducted in two stages.

Stage I of the study, STANDARD THERAPY, is a retrospective review of medical records for 200 randomly selected post-surgical patients, who received standard of care therapy as defined by current hospital and respiratory care department policies and procedures. Data collected in Stage I will include data from the medical records of eligible patients treated during the year prior to the start of Stage II. This allows for inclusion of patients from the seasonally consistent time period as well as those from most recent time period, during which care practices are most similar between the 2 stages.

Stage II of the study, a CHANGE IN PRACTICE will be made and patients will receive standard care with the addition of therapy with The MetaNeb® System. Other standard airway clearance and lung expansion therapies typically delivered by Respiratory Therapy will not be delivered during Stage II. Data from approximately 200 patients will be collected from the medical records at 3 sites. However, an adjustment in sample size may be made based on the incidence rate for post-operative pulmonary complications in Stage I, to allow for a robust estimate and assessment of the effect of therapy with The MetaNeb® System. Stage II will start after gathering and analysis of data from Stage I

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objective and Endpoint

The primary objective of Stage I of this study is to estimate the incidence of postoperative pulmonary complications (PPC) in post-surgical patients receiving standard of care per hospital and respiratory care department procedures and policies.

The primary objective of Stage II of this study is to estimate the incidence of PPC in post-surgical patients receiving change in practice therapy regimen, which includes the addition of the MetaNeb® System to the standard of care per hospital and respiratory care department procedures and policies.

The primary endpoint at each stage is to evaluate the proportion of subjects who experience a significant PPC within seven (7) days of: post-surgical hospital admission (Stage I) or post-surgical hospital admission and MetaNeb® System administration (Stage II). A PPC is defined as having one or more of the following:

1. **Patient requires prolonged mechanical ventilation for > 24 hours**
   Invasive mechanical ventilation (MV) for > 24 hours from post-surgical hospital admission (PSHA)

2. **Patient requires prolonged respiratory support for > 24 hours from PSHA**

- Requirement for non-invasive ventilation (NIV) or continuous positive airway pressure (CPAP) above patient's baseline requirement, not related to obstructive sleep apnea (OSA), for > 24 hours from PSHA
- Requirement for O_2 therapy > 40 % FiO_2 or > 5 LPM via NC (and above patient's baseline), for > 24 hours from PSHA

3. **Diagnosis of Pneumonia within 7 days from PSHA**
- Physician documented pneumonia, and
- Radiologists report indicating pneumonia / new or expanded infiltrate, and
- Elevated or low Temperature (> 38° C or < 36° C, or as defined by the site) and/or elevated white count above the upper level of normal as defined by the site

4. **Readmission to ICU (or transfer to an elevated level of care) for pulmonary complications**
Defined as readmission to the ICU or readmission to an elevated care unit within 7 days from PSHA

2.2 Secondary Endpoints

Secondary endpoints include the following:

1. **Requirement for invasive mechanical ventilation for > 48 hours**
Invasive mechanical ventilation (MV) for > 48 hours within 7 days from PSHA

2. **Requirement for respiratory support for > 48 hours**
- Requirement for non-invasive ventilation (NIV) above patient's baseline requirement after hour 48 from PSHA, or continuous positive airway pressure (CPAP) above patient's baseline requirement, not related to obstructive sleep apnea (OSA), for > 48 hours within 7 days from PSHA
- Requirement for O_2 therapy > 40 % FiO_2 or > 5 LPM via nasal cannula (and above patient's baseline), for > 48 hours within 7 days from PSHA

3. **ICU Length of Stay**
ICU length of stay, during initial PSHA, will be determined by calculating the number of days/hours spent in ICU. The following will be documented:
   - Time of initial admission to the ICU to actual time of initial discharge from the ICU
   - Total ICU days/hours (includes readmissions), during the initial hospital stay

4. **Hospital Length of Stay (LOS)**
Hospital length of stay will be determined by calculating the number of days/hours spent in hospital. LOS will be calculated for initial and total hospital stays. The following will be documented:

- Time of admission to time of discharge from the hospital (total days/hours), for each hospital admission.

5. **Time on Mechanical Ventilation**
   Time on mechanical ventilation, during the initial hospital stay, will be documented as follows:
   - Time to initial extubation
   - Total time on invasive mechanical ventilation - will be determined for each patient by calculating the total number of days/hours intubated and mechanically ventilated from the time of PSHA until the time of initial hospital discharge.
   - Total time on non-invasive ventilation - will be determined for each patient by calculating the total number of days/hours ordered for non-invasive ventilation from the time of PSHA until the time of initial hospital discharge.

6. **Readmission to ICU and transfers to elevated level of care for pulmonary complications**
   Readmissions to ICU and transfers to an elevated level of care, during the initial hospital stay, will be documented for each event. The following will be documented:
   - Number of readmissions to ICU or elevated level of care events
   - Number of patients requiring readmission to the ICU or to an elevated level of care

7. **Readmission to Hospital**
   Hospital records will be reviewed at each site, 30 days after the last patient has been discharged from the hospital. Readmissions, for any cause, within 30 day of hospital discharge for any study patient will be documented.

3 STUDY DESIGN

This is a non-randomized facility level pre-post intervention study conducted in two stages for the primary purpose of evaluating the effect of The MetaNeb® System on postoperative pulmonary complications in high risk patients undergoing thoracic and abdominal surgeries. The study will be conducted in two to four (2-4) tertiary academic medical facilities in the US that have not previously used The MetaNeb® System in post-thoracic, post-aortic, or post-upper abdominal surgery patients. After assessing outcomes during a baseline period, therapy with The MetaNeb® System will be introduced and incorporated into the respiratory care treatment regimens and outcomes will be assessed after the change in practice.

Stage I

In Stage I of the study, a retrospective review of medical records for post-surgical patients, who received STANDARD THERAPY as defined by current hospital and Respiratory Care department policies and procedures. This will be a retrospective data collection only. Respiratory Care therapies (e.g. nebulizer treatments, chest physiotherapy, etc.) that were

delivered during the first seven (7) days following surgery, including delivered frequency, will be collected.

The purpose of study Stage I is to estimate the incidence of postoperative pulmonary complications in post-surgical patients receiving standard of care per hospital and Respiratory Care department procedures and policies. Data collected in Stage I will include data from the medical records of 200 randomly selected, eligible patients treated during the year prior to the CHANGE IN PRACTICE.

Stage II

In Stage II, a CHANGE IN PRACTICE will be made and patients will receive the routine standard care prescribed by the patient's health care team with the addition of therapy with The MetaNeb® System. With the exception of standard airway clearance and lung expansion procedures, other components of the patients respiratory care regimen will remain the same as during the standard therapy period, however the CHANGE IN PRACTICE will incorporate the use/treatment with The MetaNeb® System as an alternative to usual airway clearance and lung expansion procedures. Use of The MetaNeb® System will follow the labeling of the device. During Stage II, data from approximately 200 patients will be collected from the medical records across the sites. Respiratory Care therapies, including therapy with The MetaNeb® System, that are delivered during the first seven (7) days post-surgery hospital admission in Stage II, including delivered frequency, will be collected.

Exceptions to the above treatment protocols required for patient care as determined by the treating physician will be collected

4 Study Activities

Table 1. Study Observation Table:

Day	Pre-Surgery	Day of Surgery	Post Surgery Day 1 - Day 7	Hospital Discharge	Early Term	Day 30 Post Discharge
Selection Criteria / Enrollment	X					
Informed Consent *	X					
Demographic Data	X					
Medical History	X					
Pre-Surgery Respiratory Status (Patient's Baseline)	X					
Post-Surgical Data (day 0) at day of surgery.		X				
Location (7A & 7P)		X	X			
Respiratory Status (Each Shift)		X	X			
Respiratory Milestones		X	X			
Respiratory Treatments		X	X			
Hospital Discharge Summary				X		
ICU Admission/Discharge Summary (Day 8 - Discharge)				X		
Discharge Respiratory Summary (Day 8 - Discharge)				X		
30-day Readmission						X
Study Exit Form					X	X

5 SAMPLE SIZE JUSTIFICATION

No formal sample size determination was performed for this study.

6 STATISTICAL ANALYSIS METHODS

The statistical software, SAS®, will be used for all summaries and statistical analyses.

Summary statistics will be used throughout. For continuous endpoints, the summary statistics will generally include: number of subjects with data (n), mean, standard deviation (SD), median, and range (Min, Max). For categorical endpoints, the summary statistics will generally include: number of subjects randomized and dosed, number with data, and the percentage of those with data in each category.

All statistical tests will be 2-sided with a type I error rate of 5%, unless otherwise specified.

6.1 Description of Analytical Methods

6.1.1 Derived Variables

Primary Endpoint: occurrence of a postoperative pulmonary complication (PPC).

Stage I: during the 7 days post-surgery hospital admission (PSHA)

Stage II: during the 7 days PSHA. Event must occur after MetaNeb® administration.

For each subject, occurrence of a PPC will be set to yes if one or more of the four conditions below occur.

i. PPCflg$_1$: Patient Requires Prolonged Mechanical Ventilation beyond Hour 24 from PSHA.

Duration of invasive mechanical ventilation (IMV) is defined as IMV stop time minus IMV start time where:

IMV Start Time=date & time of the later of start of IMV or PSHA

IMV Stop Time=date & time of the earlier of stop of IMV or PSHA+7

If IMV is required on more than one occasion during the 7 days following PSHA, then the cumulative sum will be calculated.

$$PPCflg_1 = \begin{cases} 1 & \text{if the latest IMV stop time is more than 24 hours after PSHA} \\ 0 & \text{otherwise} \end{cases}$$

If IMV start date is available, but the start time is missing, then a clock time consistent with the earliest possible time of the day will be imputed, ex. Hour 00.00 or PSHA clock time.

If the IMV stop date is available, but the stop time is missing, then the IMV stop time will be taken as the assessment time.

ii. PPCflg$_2$: Patient Requires Prolonged Respiratory Support beyond Hour 24 from PSHA

a) Duration of non-invasive MV (NIMV) is defined as NIMV Stop time minus NIMV start time. NIMV start and stop times are defined similarly to those of IMV. Imputations for missing NIMV start or stop times will be used similarly to those of IMV.

b) Duration of CPAP is defined as CPAP Stop time minus CPAP Start time.

c) Duration of O_2 therapy [if >40% FiO2 or >5 LPM via Nasal Cannula] will be calculated similarly.

Duration of respiratory support is defined as the sum of durations of NIMV, CPAP, and O_2 therapy during the 7 days following hospital admission.

$$PPCflg_2 = \begin{cases} 1 & \text{if the latest NIMV, CPAP, or O2 therapy stop time} \\ & \text{is more than 24 hours after PSHA} \\ 0 & \text{otherwise} \end{cases}$$

iii. PPCflg$_3$: Diagnosis of pneumonia

iv. PPCflg$_4$: Readmission to ICU (or transfer to an elevated care) for PPC with 7 days of PSHA

Secondary Endpoints derivations will follow similar logic as that of the primary endpoint, when calculating incidence of PPC > 48 hours. For time to initial extubation, if extubation occurred prior to hospital admission, then time to initial extubation will be set to zero.

6.1.2 Accounting of Subjects

Numbers (and percentage) of subjects enrolled in Stage I and Stage II, will be presented by site and overall.

6.1.3 Demographic and Baseline Characteristics

Demographic and baseline data will be summarized separately for Stage I and II. Demographic data including age (years), age category (<35, 35-54, 55-64, ≥65), gender, race, ASA score, height, weight, BMI, and documented obesity (BMI≥30kg/m^2) will be summarized.

6.1.4 Time on Study

The total number of days the subject is followed up will be summarized as continuous variable and categorized into 1-week intervals.

6.1.5 Medical History

The pulmonary status will be tabulated, including the presence/absence of asthma, cystic fibrosis, bronchiectasis, COPD, neuromuscular disease, obstructive sleep apnea, other pulmonary conditions.

6.1.6 Pre-Surgery Respiratory Status

Pre-surgery status of invasive mechanical ventilation, non-invasive mechanical ventilation, CPAP, and supplemental oxygen will be tabulated.

6.1.7 Post-Surgery Location

The post-surgery location upon return to the hospital unit or floor (ICU, general care, etc.) will be tabulated.

6.2 Analysis Population

Two analysis populations will be defined:

- FAS: The full analysis data set will contain all subjects, for whom hospital records were pulled and recorded.
- ITT: The intent-to-treat (ITT) population, a subset of the FAS, includes all subjects who satisfied all the inclusion criteria and none of the exclusion criteria. For Stage II of the study, patients who did not receive the MetaNeb® system will be excluded from the ITT population.

The ITT population will be the primary population for the analysis.

6.3 Analysis Methods – Primary and Secondary Endpoints

Primary Endpoint— Proportion of subjects who have a postoperative pulmonary complication

The proportion of subjects who have a PPC within 7 days of post-surgery hospital admission will be presented with 95% confidence intervals.

Incidence of each of the 4 components that contribute to the primary endpoints, will also be presented.

Secondary Efficacy Endpoints

Proportions of subjects will be presented for the following endpoints:

1. Requirement for invasive mechanical ventilation beyond Hour 48 from PSHA
2. Requirement for respiratory support beyond Hour 48 from PSHA
3. Readmissions to ICU and transfers to an elevated level of care within 7 days of PSHA during the initial hospital stay
4. Readmissions to ICU and transfers to an elevated level of care during the initial hospital stay
5. Readmissions to hospital after PSHA discharge

Mean, median, and standard deviation will be presented for the following endpoints:

1. ICU Length of Stay
2 Hospital Length of Stay
3 Time on mechanical ventilation
4 Time to extubation

6.4 Safety Data

6.4.1 Analysis Population

For Stage II, the safety population will be defined as subjects who were administered the MetaNeb® System.

6.4.2 Analysis Methods

All adverse device effects and device complaints will be tabulated for Stage II.

6.4.3 Clinical Adverse Device Effects and Device Complaints

During Stage II, the number (percent) of patients reporting an adverse device effect, and the number (percent) of device complaints reported will be presented.

For events with a partial start date, the year/month of the effect date will be compared to that of the MetaNeb® administration date to determine whether the event is treatment emergent.

The occurrence of the adverse device effect with the greatest severity will be used in the calculation of incidence by severity; adverse device effects will be classified by severity (mild, moderate and severe).

The incidence of serious adverse device effects (SADEs) will be presented. Details of each SADE will be listed, and includes subject ID, date of onset, duration, severity, and action taken with the study device.

The number (percent) of patients with a SADE that led to the discontinuation of the MetaNeb® administration or premature withdrawal from the study will be presented. A listing of the complaints and adverse device effects will also be presented.