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

Protocol Number: CR-RR2015- 001
Status: Rev. C
Product: **The MetaNeb® System**

Sponsor: Hill-Rom Company, Inc.
PI

Study Manager:
PI
Manager, Clinical Research,
Hill-Rom Company, Inc.
PI

Confidentiality Statement

This protocol contains information that is proprietary to Hill-Rom, Company, Inc. This information is provided to you for the purpose of conducting a clinical study for Hill-Rom. You may disclose the contents of this protocol to your study personnel under your supervision and your Institutional Review Board(s) or Independent Ethics Committee(s) for the same purpose. You may not disclose the contents of this protocol to any other parties (unless such disclosure is required by government regulations or laws, in which case, Hill-Rom will be notified of the disclosure at least 5 business days prior to the disclosure) without prior written permission from Hill-Rom. Any supplemental information (e.g., protocol amendment) that may be added to this document is also proprietary to Hill-Rom and should be handled using the same disclosure procedure.

Investigator Agreement

I agree to conduct this study in accordance with the design and specific provisions of this protocol. Modifications to the study are acceptable only with a mutually agreed upon protocol amendment.

I agree to await Institutional Review Board approval for the protocol before initiating the study, to obtain consent from subjects (unless waived) prior to their enrollment (if required) in the study, to collect and record data as required by this protocol and case report forms, to prepare adverse event and study reports as required by this protocol and to maintain study documentation for the period of time required.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study. I agree to ensure all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receive the appropriate information throughout the study.

Investigator Signature:	Date:
Investigator Signature:	Date:

Table of Contents

List of Abbreviations

AARC	American Association for Respiratory Care
ACT	Airway Clearance Therapy
ASA	American Society of Anesthesiologists
CF	Cystic Fibrosis
CHFO	Continuous High Frequency Oscillation
CPAP	Continuous Positive Airway Pressure
CPEP	Continuous Positive Expiratory Pressure
CPT	Chest Physiotherapy
CRF	Case Report Form
CRO	Contract Research Organization
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICU	Intensive Care Unit
IPPB	Intermittent Positive Pressure Breathing
IPV	Intrapulmonary Percussive Ventilation
IRB	Institutional Review Board
IV	Intravenous
LE	Lung Expansion
LOMV	Length of Mechanical Ventilation
LOS	Length of Stay
MV	Mechanical Ventilation
NIV	Noninvasive Ventilation
NSQIP	National Surgical Quality Improvement Program
OSA	Obstructive Sleep Apnea
PPC	Postoperative Pulmonary Complication
PRF	Postoperative Respiratory Failure
RCT	Randomized Controlled Trial
SOP	Standard Operating Procedure

Protocol Synopsis

Product Name:	**The MetaNeb® System**
Protocol Number:	CR-RR2015-001
Protocol Title:	Evaluation of a practice change to include The MetaNeb® System to reduce postoperative pulmonary complications
Objective(s):	To determine if a therapy regimen including treatment with The MetaNeb® System has a positive impact on the rate of pulmonary complications that occur in high risk post-operative patients.
Endpoints:	**Primary Endpoint:** **Significant Postoperative Pulmonary Complication (PPC):** One or more of the following that occurs within seven (7) days of the post-surgical admission will be considered a Significant Postoperative Pulmonary Complication (PPC) • Patient Requires Prolonged Mechanical Ventilation (> 24 hours from post-surgical admission). • Patient requires prolonged respiratory support for > 24 hours from post-surgical admission • Diagnosis of Pneumonia Within Seven (7) Days • Readmission to ICU for pulmonary complications within seven (7) days of post-surgical hospital admission. **Secondary Endpoints:** • Requirement for invasive mechanical ventilation for > 48 hours • Requirement for respiratory support for > 48 hours • ICU Length of Stay (LOS) • Hospital Length of Stay (LOS) • Time on Mechanical Ventilation • Readmissions to ICU • 30-day Readmissions to Hospital
Study Design:	Non-randomized facility (or hospital) level pre-post intervention study

Methods:	The study will be conducted in two stages. 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 will be performed. In Stage II, a CHANGE IN PRACTICE will be made and patients will receive standard care with the addition of therapy with The MetaNeb® System. Demographic, clinical & outcome data will be collected for eligible patients during the two stages of the study. Study staff will collect data from the medical records, following a protocol determined schedule.
Treatment of Subjects:	The treatment protocol used for Respiratory Care during the STANDARD THERAPY period of the Study is that which was prescribed by the patient's health care team in the routine standard care of each patient. Respiratory Care therapies include those therapies that were ordered and/or were delivered for the care of patients as determined by standard hospital and/or Respiratory Care department policies and procedures. The STANDARD THERAPY period is one year prior to initiation of the study. Data will be collected retrospectively. The treatment protocol used for Respiratory Care (excluding airway clearance and lung expansion interventions) during the CHANGE IN PRACTICE period of the Study will include care and therapy prescribed by the patient's health care team in the routine standard care of each patient. 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. Use of The MetaNeb® System will follow the labeling of the device. During Stage II, therapy with The MetaNeb® System will be delivered per treatment procedures. Other standard airway clearance and lung expansion therapies typically delivered by Respiratory Therapy will not be delivered during Stage II.
Duration of Participation:	The Study will take approximately fifteen months to complete, from the time of study initiation through completion of data analysis. The duration of study participation for prospectively enrolled subjects will be the duration of each patient's hospital stay with follow-up thirty days after discharge from the hospital.

Number of Subjects:	The sample size will be approximately 400 patients, 200 in the retrospective STANDARD THERAPY group and 200 in the prospective CHANGE IN PRACTICE group.
Study Population:	The study population consists of adult post-surgical patients who have undergone thoracic, aortic or upper abdominal surgery who are at high risk for PPCs.

Inclusion/Exclusion Criteria:	Inclusion Criteria:
	
	Patients who meet all of the following criteria will be included in the study:
	
	• Age ≥ 18 years
	• Post-thoracic, -upper abdominal or -aortic surgery
	• Open surgical procedure
	• Incision at or above the umbilicus
	• High risk defined by:
	  • Documented ASA class ≥3
	
	  OR
	
	  • Documented ASA class 2 **AND** One or more of the following:
	  • Current smoker or smoking history within past 6 months
	  • History of COPD
	  • Documented obesity and/or BMI ≥ 30 kg/m^2
	  • Age ≥ 75
	
	Exclusion Criteria:
	
	Patients who meet any of the following criteria will be excluded (or will be exited) from the study:
	
	• Contraindication to Continuous High Frequency Oscillation (CHFO) therapy (e.g. untreated tension pneumothorax)
	• Minimally invasive, or ". . . scopic" procedure.
	• Spinal surgery involving a posterior approach
	• Surgery for organ transplant
	• Chronic invasive positive pressure ventilation (PPV)

Statistical Methods:	Descriptive summary statistics will be provided for demographics, the primary and secondary endpoints. Continuous data will be summarized with N, mean, median, standard deviation, min, and max. Categorical data will be summarized with the number and percent of patients in each category. Time to event data (ex. Time to readmission) will be summarized with methods appropriate for survival data including a Kaplan-Meier plot. Ninety-five percent (95%) confidence interval will be computed for the primary endpoint, the incidence of significant postoperative pulmonary complications. Incidence rates for various demographic subsets, surgery types, and different population subsets may be presented as outlined in the statistical analysis plan document, to be published prior to study completion. Stage I and Stage II incident rates will be compared for the purpose of identifying any statistical associations that can be attributed to use of The MetaNeb® System.

1.0 Introduction

1.1 Background and Significance

Post-operative pulmonary complications (PPC) are associated with significant excess morbidity, mortality and healthcare expenditure. The incidence of "important" PPCs, across all surgeries, is approximately 2-5% in the general surgical population. There are factors, however, that place certain patients, and patients with certain procedures, at considerably higher risk for PPCs. One of the key factors in development of PPCs is the type of surgery. Following upper abdominal and thoracic surgery, pulmonary complications are the most common surgical complications. Other risk factors include advanced age, American Society of Anesthesiologists (ASA) physical status classification score $\geq$ 2, functional dependency, congestive heart failure and chronic obstructive pulmonary disease. Of these, ASA score $\geq$ 2 and functional dependency have consistently been associated with a higher rate of significant PPCs such as post-operative respiratory failure (PRF). PRF requiring prolonged mechanical ventilation (MV) or re-intubation accounts for the majority of poor outcomes and high economic costs.[1-4] Other risk factors that have been associated with increased risk of PPCs include history of COPD, smoking history and BMI $\geq$ 30 kg/m^2. [1-5]

Although PPCs are an incompletely understood multifactorial syndrome, atelectasis is recognized as a critical component.[6] Evidence has shown that atelectasis is a common precursor and concomitant feature of PPCs. Nearly all patients undergoing major surgery experience some degree of transitory, clinically unimportant atelectasis, most of these patients do not require aggressive therapy. There is, however, a more urgent need to treat atelectasis in subpopulations of high-risk individuals, in order to prevent more serious complications including progression to PRF.[7]

A variety of strategies have been shown to reduce the risk for development of post-operative atelectasis to at least some degree. These include but are not limited to pain control, monitoring of respiratory-depressing medications, selective use of nasogastric decompression, secretion mobilization techniques and lung expansion (LE) therapies.[6-9] However, the generally poor quality of clinical trials to evaluate these methods provides only limited, inconclusive evidence of efficacy. Among published studies, LE using continuous positive airway pressure (CPAP) breathing, particularly when used in hypoxemic high-risk patients, is the only modality to date demonstrating comparatively strong evidence.[10,11] In a systematic review of qualifying randomized controlled trials (RCT), Lawrence et al sought to evaluate interventions intended to reduce the incidence of atelectasis, pneumonia and PRF following non-cardiothoracic surgery.[11] Their meta-analysis pooling all eligible studies to determine "strength of evidence" found that only LE therapy merited a grade of "A". These

LE therapy techniques included incentive spirometry (IS), deep breathing techniques, chest physiotherapy (CPT), intermittent positive pressure breathing (IPPB) and continuous positive pressure (CPAP). Although data did not permit identification of a "best" modality, they did allow the conclusion that all lung expansion therapies reduced PPC by > 50% compared with no treatment. Well-designed studies are needed to distinguish which LE approach has the greatest potential to optimize patient care, clinical outcomes and cost savings.

1.2 Research Rationale and Supporting Evidence

Among LE devices, Intrapulmonary percussive ventilation (IPV) devices have been in use for more than 25 years and are used widely in the acute care, post-surgical, and homecare setting. Such devices provide both LE and airway clearance therapy (ACT) for patients with obstructive and/or restrictive lung diseases and conditions. The safety and efficacy of IPV have been demonstrated in clinical and laboratory studies.[12-34]

The MetaNeb® System is an LE expansion modality that incorporates all the physiological effects of IPV while providing additional therapeutic advantages intended primarily to more effectively treat or prevent pulmonary atelectasis. Equipment consists of a pneumatic compressor that delivers continuous high-frequency oscillation (CHFO) and positive expiratory pressure (CPEP) to 1) facilitate clearance of mucous from the lungs; 2) provide lung expansion therapy and; 3) enhance delivery of aerosol therapy. This "triple" mode device can provide aerosol therapy while alternating between CPEP for lung expansion and CHFO for airway clearance. Supplemental oxygen therapy may also be delivered when used with compressed oxygen. The MetaNeb® System has been cleared to market by the FDA based on substantial equivalence to IPV. Clinical studies of The MetaNeb® System, however, are limited. The only peer-reviewed publication to date is a case report concerning a patient who on her 17th hospital day, following an adverse medication reaction, developed severe atelectasis secondary to toxic epidermal necrolysis (Stevens - Johnson Syndrome). After initiation of therapy with The MetaNeb® System, atelectasis was completely resolved by hospital day 21. The patient was discharged on hospital day 25 without further pulmonary complications.[35] In addition to this publication, however, a number of abstracts and other reports have been presented or published. An abstract presented at the American Association for Respiratory Care (AARC) Congress in 2009, found that patients participating in a progressive pulmonary protocol in an oncologic intensive care unit and who received LE therapy with either IPV or The MetaNeb® System had significantly better post- therapy chest x-ray results compared with patients treated with The Vest® System and EZ PAP.[35] An earlier case study report presented at the AARC Congress in 2006 described an 80-year-old post-thoracoscopic surgical patient in respiratory distress. The patient was treated with The

MetaNeb® System, expectorated large amounts of tenacious secretions, and after only 2 treatment sessions had improved breath sound. Chest radiographs showed improved aeration and there was a reduction in oxygen requirement.[37] In a long-term care treatment protocol with intubated or tracheostomised patients on MV, patients were treated with The MetaNeb® System for 10 minutes every 6 hours until decanulation or discharge. Quality improvement results showed improvement in the percentage of patients weaned from MV along with a decrease in the need for bronchoscopy.[38] Two more recent studies have been presented at conferences and await full-text publication. Patel et al. reported on a randomized parallel study comparing outcomes in 32 adult CF patients with severe pulmonary exacerbations and admitted for IV therapy. Patients were randomized to treatment with either The MetaNeb® System or The Vest® System for up to 14 days. In this setting, results were positive but comparable.[39] Morgan, et al. investigated the feasibility, safety and efficacy of CHFO administered via The MetaNeb® System to 59 invasively ventilated pediatric patients, between 2007-2012. A total of 528 treatments were evaluated. Preliminary results support safety and feasibility and suggest that CHFO may be beneficial by improving lung compliance in patients with secretion-induced atelectasis.[40]

1.3 Rationale for the Proposed Study

Preliminary and anecdotal evidence suggests that use of The MetaNeb® System may be effective in postoperative patients prone to atelectasis and PPCs. The proposed study is intended to evaluate the effectiveness of this therapy in reducing the incidence of these complications in comparison to standard treatment.

2.0 Study Objectives

The primary objective of this study is to determine if a therapy regimen including treatment with The MetaNeb® System has a positive impact on the rate of pulmonary complications that occur in high risk post-operative patients.

3.0 Study Design

3.1 Overview of Study Design

3.1.1 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.

3.1.2 Procedure:

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.

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. 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.

In Stage II, 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. During Stage II, data from approximately 200 patients will be collected from the medical records across the 3 sites.

Demographic, clinical & outcome data will be collected for eligible patients during the two stages of the study. Study staff will collect data from the medical records, following a protocol determined schedule.

Pre-surgery data will be collected for eligible patients in both stages. In both Stage I and Stage II, outcomes will be tracked for each day from the time of the post-surgical admission to the hospital unit through post-surgery day seven (7). Additionally, hospital length of stay (LOS) and total ICU LOS will be determined based on documentation of admission and discharge dates and times for all days of hospitalization. Length of time on mechanical ventilation (LOMV) will be determined based on documentation of initiation and discontinuation dates and times for all days

of hospitalization. LOS and LOMV data will be collected from the medical record upon discharge from the hospital. Hospital records will also be reviewed after 30 days to determine if readmission to the hospital occurred for any study patients.

A timeline showing data procedures and collection points is included as Table 1 Study Observations Table.

The estimated study enrollment is 200 patients in both stages. 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.

3.1.3 Product Description

The product added in Stage II, the CHANGE IN PRACTICE phase is The MetaNeb® System, a therapeutic device that provides airway clearance and lung expansion therapy. The MetaNeb® System is a marketed product, indicated for mobilization of secretions, lung expansion therapy, the treatment and prevention of pulmonary atelectasis and also has the ability to provide supplemental oxygen when used with compressed oxygen. The system has three therapy modes:

- CHFO (Continuous High Frequency Oscillation) – delivers aerosol therapy while providing oscillating pressure pulses to the airway
- CPEP (Continuous Positive Expiratory Pressure) – delivers aerosol therapy while providing continuous positive pressure to help hold open and expand the airways
- Aerosol – for delivery of aerosol only. In this mode, CHFO and CPEP are not available

3.1.4 Treatment Protocol(s):

Stage I: STANDARD THERAPY period:

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 retrospective data collection only. The purpose of Stage I is to estimate the incidence of postoperative pulmonary complications that occur in postsurgical patients who receive standard therapy.

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.

Stage II: CHANGE IN PRACTICE period:

The treatment protocol used for Respiratory Care during the CHANGE IN PRACTICE period of the Study will be that prescribed by the patient's health care team in the routine standard care of each patient. 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.

Respiratory Care therapies, including therapy with The MetaNeb® System, that are delivered during the first seven (7) days of 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.

3.2 Study Population

The study population consists of adult post-surgical patients who have undergone thoracic, aortic or upper abdominal surgery who are at high risk for PPCs.

3.2.1 Inclusion Criteria:

Patients who meet all of the following criteria will be included in the study:

- Age ≥ 18 years
- Post-thoracic, -upper abdominal or -aortic surgery
- Open surgical procedure
- Incision at or above the umbilicus
- High risk defined by:
    - Documented ASA class ≥3

OR

- Documented ASA class 2 **AND** One or more of the following:
  - Current Smoker or Smoking history within past 6 months
  - History of COPD
  - Documented Obesity and/or BMI $\geq$ 30 kg/m^2
  - Age $\geq$ 75

3.2.2 Exclusion Criteria:

Patients who meet any of the following criteria will be excluded (or will be exited) from the study:

- Contraindication to Continuous High Frequency Oscillation (CHFO) therapy (e.g. untreated tension pneumothorax)
- Minimally invasive or "…scopic" surgical procedure
- Spinal surgery involving a posterior approach
- Surgery for organ transplant
- Chronic invasive Positive Pressure Ventilation (PPV) therapy

3.3 Evaluation Criteria/Effectiveness

The CHANGE IN PRACTICE therapy regimen (which includes therapy with The MetaNeb® System) will be evaluated to determine if there is a decrease in the number of patients who experience Significant Postoperative Pulmonary Complications among the group of patients treated with The MetaNeb® System. Endpoints are described below:

Primary Endpoint:

Significant Postoperative Pulmonary Complication (PPC):

One or more of the following that occurs within seven (7) days of the post-surgical admission will be considered a Significant Postoperative Pulmonary Complication (PPC)

- **Patient Requires Prolonged Mechanical Ventilation:**
  Defined as patient requirement for invasive mechanical ventilation (MV) for > 24 hours (after hour 24) post-operatively. This includes patients that require re-intubation and MV after hour 24, regardless of length of time on MV in the first 24 hours postoperatively.

- **Patient requires prolonged respiratory support for > 24 hours from post-surgical admission**
  - Requirement for non-invasive ventilation (NIV) above patient's baseline requirement after hour 24, or continuous positive airway pressure (CPAP) above patient's baseline requirement after hour 24.
  - Requirement for O_2 therapy > 40 % FiO_2 or > 5 LPM via NC (and above patient's baseline) after hour 24 postoperatively.

- **Diagnosis of Pneumonia Within Seven (7) Days**
  - Physician documented pneumonia AND
  - Radiologists report indicating pneumonia / new or expanded infiltrate AND
  - Elevated or low Temperature (> 38º C or < 36 º C, or as defined by the site) and/or elevated white count above the upper level of normal as defined by the site

- **Readmission to ICU (or transfer to an elevated level of care) for pulmonary complications within seven (7) days of the post-surgical hospital admission**
  Defined as readmission to the ICU within seven days of post-surgical hospital admission or readmission to an elevated care unit such as special care or ICU step-down unit after being moved to a lower (e.g. general care) floor (e.g. patient discharged from ICU on day 4 at 0800 is readmitted to the ICU before day 8 at 0800).

Secondary Endpoints:

- **Requirement for invasive mechanical ventilation for > 48 hours within seven (7) days of the post-surgical hospital admission**
  Defined as patient requirement for invasive mechanical ventilation (MV) for > 48 hours (after hour 48) post-operatively. This includes patients that require re-intubation after hour 48, regardless of length of time on MV in the first 48 hours postoperatively.

- **Requirement for respiratory support for > 48 hours within seven (7) days of the post-surgical hospital admission**
  Respiratory support greater than the patient's baseline level for a period longer than 48 hours
  - Requirement for non-invasive ventilation (NIV) above patient's baseline requirement after hour 48 from post-surgical admission or continuous positive airway pressure (CPAP) above patient's baseline requirement after hour 48.
  - Requirement for O_2 therapy > 40 % FiO2 or > 5 LPM pm via Nasal Cannula (and above patient's baseline) after hour 48 postoperatively.

- **ICU Length of Stay (LOS)**

  ICU length of stay, during initial hospital stay, will be determined by calculating the number of days/hours spent in ICU. The following will be documented:

  - Time of admission to the ICU to actual time of initial discharge from the ICU during initial hospital stay
  - Total ICU days/hours (includes readmissions) during initial hospital stay

- **Hospital Length of Stay (LOS)**

  Hospital length of stay will be determined by calculating the number of days/hours spent in hospital. The following will be documented:

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

- **Time on Mechanical Ventilation**
  Time on mechanical ventilation, during the initial hospital stay, will be documented as follows:

  - Time to initial extubation from time of initial intubation, if initial intubation was placed after surgery; or from time of post-surgical admission, if intubation was in place prior to start of surgery
  - 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 post-surgical admission 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 post-surgical admission to the hospital unit until the time of initial hospital discharge.

- **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 readmission to ICU or elevated level of care events

- Number of patients requiring readmission to the ICU or to an elevated level of care

- **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 discharge for any study patient will be documented.

3.4 Study Observations Table

The study observations and documentation timeline is outlined in Table 1.

Table 1. Study Observations 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

* Informed consent will be obtained only for subjects in Stage II.

3.4.1 Study Observations Table Detailed Description

Documentation of observations will be completed by study staff based on review of the patient's medical records. A detailed description of documentation requirements for each parameter is below.

Demographic Data: The following data will be recorded from the patient medical record: Age, Height, Weight, Race, Gender, ASA score, Documented obesity and/or BMI ≥ 30 kg m2.

Medical History: Pulmonary history will be recorded from the patient medical record including: Asthma, Cystic Fibrosis, Bronchiectasis, COPD,
Neuromuscular Disease, Other Pulmonary Condition(s), Obstructive Sleep Apnea

Pre-surgery Respiratory Status: Pre-surgery respiratory status such as Invasive Mechanical Ventilation, Non-invasive Mechanical Ventilation, CPAP, Supplemental oxygen will be recorded.

Post-Surgery Data (day 0): Following surgery, the albumin level (if available in the medical record) and surgery type will be recorded.

Location: The post-surgery location of each patient upon return to the hospital unit or floor (ICU, General Care, etc.) will be recorded. The patient's location during the first seven days, or until the time of discharge from the hospital, whichever occurs first, will also be recorded at regular intervals based on entries in the medical record.

Respiratory Status: The respiratory status of each patient, following surgery will be recorded. Respiratory status during the first seven days, or until the time of discharge from the hospital, whichever occurs first, will also be recorded at regular intervals based on entries in the medical record. Respiratory status will include documentation of the mode of support, the device in use and the settings.

Respiratory Milestones: Key respiratory milestones that occur each day will be recorded based on entries in the medical record. These include 1) extubation, 2) re-intubation, 3) return to baseline respiratory support, 4) Diagnosis of Pneumonia and 5) Readmission to the ICU or an elevated level of care. These milestones will be recorded for each day until discharge from the hospital, or through day seven (7) following the day of surgery, whichever occurs first.

Respiratory Treatments: Standard respiratory treatments including CPAP therapy (non-continuous), IPPB, Nebulizer treatments, Chest physiotherapy, and others will be

recorded for each day until discharge from the hospital, or through day seven (7) following the day of surgery, whichever occurs first. Type of therapy and the number of treatments received on each day will be recorded.

During Stage II, each MetaNeb® therapy will be documented including time and duration of therapy and adherence to defined treatment regimen

Hospital Discharge Summary: A summary including date and time of discharge along with the location to which the patient is being discharged will be completed after discharge.

ICU Admission/Discharge Summary (Day 8 – Discharge): Dates and times of all ICU admissions, or admissions to a unit for an elevated level of care, along with discharges from those units, that occur between post-surgery day 8 and discharge from the hospital, will be documented.

Discharge Respiratory Summary (Day 8 – Discharge): Dates and times of each initiation and discontinuation of mechanical ventilation that occur between post-surgery day 8 and discharge from the hospital, will be documented.

30-day Readmission: Hospital medical records for each patient will be evaluated after 30 days post discharge, to determine if any hospital readmissions had occurred.

3.5 Statistical Methods and Analysis

3.5.1 Sample Size Estimation:

This study is designed to provide information on the benefits of the addition of the MetaNeb® System in reducing the incidence of postoperative pulmonary complications (PPCs) in high-risk subjects undergoing high-risk surgical procedures (upper abdominal, thoracic, aortic). The study will be conducted in 2 stages:

- Stage I: To update/confirm the estimate of the current incidence of PPC's with current Standard of Care Practice. Recent published articles suggest incidence rates between 5%-15%, depending on the patient population and type of surgery. This stage of the study will be a retrospective pre-intervention observational period, conducted at 2 - 4 hospitals/sites, with no intervention in the patients' post-surgical

management. Data from approximately 200 subjects will be collected. The incidence rate will be calculated, along with a 95% confidence interval.

- Stage II: To assess the impact of the MetaNeb® System on the incidence of PPC's. This stage of the study will be a prospective post-intervention period conducted in the same 2 - 4 hospital sites with an intervention involving use of the MetaNeb® System in addition to Standard of Care Practice.

3.5.2 Statistical Analysis:

- Summary statistics and data listings will be provided.

- Demographic data will be summarized. For continuous type data (e. g. Age), descriptive summary statistics (N, mean, median, standard deviation, min, and max) will be presented. For categorical variables (gender, race, etc.) the number and percent of patients in each category will be provided.

Primary Endpoints:
The incidence of significant postoperative pulmonary complications (as defined in section 3.3) along with 95% confidence interval will be generated. Additionally, the incidence rates will be summarized for various demographic subsets, by surgery type, and for different population subsets. The descriptive summary statistics for the subsets may be presented side-by-side for ease of comparison. The specific subsets to be summarized will be described in a separate document (the statistical analysis plan).

Secondary Endpoints:
The secondary endpoints as listed in section 3.3 will be summarized with descriptive summary statistics appropriate for continuous or categorical data, depending on the outcome being summarized:

1. Requirement for invasive mechanical ventilation for more than 48 hours.
2. Requirement for respiratory support for more than 48 hours
3. Length of ICU stay (ILOS)
4. Length of hospital stay (HLOS)
5. Time on mechanical ventilation
6. Readmission to ICU
7. Readmission to hospital

Stage I and Stage II results will be compared for the purpose of identifying any statistical associations that can be attributed to use of The MetaNeb® System.

4.0 General Study Information

4.1 Technical Support

Technical product support will be performed by Hill-Rom following routine service practices (contact details will be provided).

4.2 Record Retention

Records must be maintained for a period of up to three years after the latter of the following dates: the date the study is completed/terminated, or the date of the last regulatory approval. The Investigators or Institutions shall notify the Sponsor at least thirty (30) days prior to any planned destruction of records from this study.

All records will be kept confidential and the patient's name will not be released at any time. Code numbers will be used to de-identify patient information on the CRFs and other study-related documents.

5.0 Study Procedures

5.1 Informed Consent:

A waiver of informed consent will be requested for patients enrolled in the study in Stage I (retrospective review of data). Informed consent must be obtained from all subjects in Stage II prior to participation as per Federal Regulations and/or the qualifying Institutional Review Board (IRB). A blank copy of the IRB-approved form must be kept on-site and by the sponsor. The signed original for each subject must be kept in the study files.

5.2 Complaints and Adverse Events Reporting

During the study, any adverse device effect, device-related complaint or allegation of injury (of any type) must be reported to the Sponsor within 24 hours. Please contact PI

A complaint is defined as any written, electronic or verbal communication that alleges deficiencies related to the identity, design, quality, durability, reliability, safety, effectiveness or performance of the device. A serious injury is defined as an injury or illness that is life-threatening; results in permanent impairment of a body function or permanent damage to a body structure; or necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

Any device complaint and/or allegation of injury shall be reviewed, evaluated, and investigated by Hill-Rom Post Market Surveillance and reported to the appropriate Health Authority per current regulations. The Investigators are responsible for informing the Institutional Review Boards, as per their guidelines.

5.3 Deviations from the Study Protocol

A change (other than administrative) to any part of the study protocol must be mutually agreed upon by the Sponsor and the Investigator(s). The Investigator(s) will then submit an amendment to his/her/their institution's local IRB. Until the new protocol is approved, new patients will be included under the current protocol.

5.4 Materials Provided by the Sponsor

The Sponsor will supply all The MetaNeb® System devices to the institutions.

6.0 Investigator and Sponsor Responsibilities

6.1 Investigator's Responsibilities

The Investigator will comply with Good Clinical Practices (GCPs) and applicable regulatory requirements, as itemized below.

- The Investigator should be familiar with the appropriate use of The MetaNeb® System Device and any other information provided by the Sponsor.

- The Investigator should provide adequate staff to conduct and complete the study within the agreed study time period. The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, The MetaNeb® System Device and their study related duties.

- A qualified physician delegated as an investigator or sub-investigator will be responsible for all study related duties and functions. During a patients' participation, the Investigator/Institution should ensure that adequate medical care is provided to the patient for any adverse event.

- The Investigator should have written and dated approval from the IRB for the protocol, IC forms or waiver of informed consent, HIPAA authorization, patient recruitment procedures and any other written information for the conduct of the study and/or to be provided to patients.

- The Investigator/Institution should conduct the study in compliance with the protocol agreed to by the Sponsor. The Investigator should sign the protocol or alternative contract to confirm agreement. The Investigator should not implement any deviation or changes to the protocol without agreement with the Sponsor and prior review and agreement from the IRB, unless the deviation or change is to eliminate an immediate hazard to study patients.

- The Investigator/Institution is responsible for all MetaNeb® System Devices that are placed with the Investigator/Institution. When it is allowed, the Investigator may assign Device accountability to another appropriate individual. The Investigator or responsible individual shall maintain records of the Device delivery to the site, inventory at the site, the use by each patient, and the return to the Sponsor of unused Device or equipment. The MetaNeb® System Device should be stored as specified by the Sponsor and applicable regulatory requirements. The Investigator should ensure that the individual Device is demonstrated and/or used in accordance with the approved protocol. If appropriate and applicable, the Investigator or designee should explain the correct use of The MetaNeb® System Device to each patient.

- In obtaining and documenting informed consent (unless waived), the Investigator should comply with the applicable regulatory requirements and should adhere to GCP and the ethical principles that have their origin in the Declaration of Helsinki.

- The Investigator, per Title 21 Code of Federal Regulations Part 54, should disclose any financial interests that could affect the reliability of the data.

- The Investigator should ensure the accuracy, completeness, legibility and timeliness of the data reported to the Sponsor in the CRFs and required reports.

- The Investigator should maintain the study documents as required by the applicable regulatory requirements. Records must be maintained for a period of three years after the latter of the following dates: the date the study is completed/terminated or the date of the last regulatory approval based on the study data. The Investigator or Institution shall notify the Sponsor at least thirty (30) days prior to any planned destruction of records from this study.

- The Investigator should submit written summaries of the status of the study to the IRB annually, or as requested by the IRB, and upon completion of the Study.

- All serious adverse device effects should be reported immediately to the Sponsor, per the local IRB's reporting policy at that site. The initial reports should be followed by more detailed reports if more information becomes available. If the study is terminated prematurely or suspended for any reason, the Investigator should promptly inform the study patients and ensure appropriate therapy and follow-up is scheduled or documented for each patient.

6.2 Sponsor's Responsibilities

The Sponsor of the program is Hill-Rom Company, Inc. The Sponsor's, responsibilities are itemized below.

- The Sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written standard operating procedures (SOPs) to ensure that studies are conducted and that the data are generated, documented, and reported in compliance with the protocol, GCPs and applicable regulatory requirements. The Sponsor is responsible for securing an agreement from all involved parties to ensure direct access to all study-related sites, source documents, and reports for the purpose of monitoring and auditing.

- The Sponsor may transfer any or all of the study-related duties and functions to a Contract Research Organization (CRO), but the ultimate responsibility for the quality and integrity of the data resides with the Sponsor.

- The Sponsor should use an unambiguous patient identification code that allows for de-identification of all the data reported for each patient.

- The Sponsor should retain the essential documents as required by the applicable regulatory requirements. Records must be maintained for a period of three years after the latter of the following dates: the date the study is completed/terminated or the date of the last regulatory approval.

- The Sponsor should ensure the Investigator(s) selected for the study have the proper qualifications, training, and resources to perform the study adequately.

- The Sponsor shall provide the Investigator(s) with a protocol and an Investigator Brochure (or equivalent documentation) and allow sufficient time for the Investigator to review the information provided.

- The Sponsor should ensure timely delivery of the Device(s) to the Investigator(s); maintain records that document shipment, receipt, disposition, return and destruction (if applicable) of the Devices; maintain a system for retrieving Devices and documenting this retrieval; maintain a system for the disposition of unused Device(s) and for the documentation of this disposition.

- The Sponsor should ensure that it is specified in the protocol or other written agreement that the Investigator(s)/Institution(s) provide direct access to source documents for study-related monitoring, audits, IRB review, and regulatory inspection. The Sponsor should verify that each patient has consented in writing, to direct access to his/her original medical records for study-related monitoring, audit, IRB review and regulatory inspection, or that informed consent has been waived.

- The Sponsor is responsible for submitting reports of all recalls and device disposition to the IRB and the FDA.

7.0 Administrative Study Information

7.1 Pre-Study Site Visit

The Sponsor will visit the site and meet with the Investigator(s) to assess and confirm the site's ability to perform the study, store study equipment, and recruit patients.

7.2 Institutional Review

Prior to study initiation, the appropriate IRB must approve the observational study. It is the responsibility of the Investigators, in collaboration with the Sponsor, to provide the IRB with all necessary information to satisfy the individual Institution's requirements.

7.3 Investigator Records and Reports

Where required by applicable regulatory requirements, an investigator signatory will be obtained for the acceptance of the clinical study report. The Investigator(s) will be provided reasonable access to statistical results and tables and will be provided a summary of the study results.

7.4 Interim Monitoring and Closeout

Interim monitoring and close-out visits may be conducted by the Sponsor for quality assurance.

8.0 Changes Necessary after Study Initiation

If there are changes to the study plan or protocol, these changes will be agreed upon by the Sponsor, its acting representative (if appropriate), the Investigator(s), and the IRB before the changes are implemented. All changes must be documented.

9.0 Study Completion

See section 3.4 for timeline details. Upon completion of the study, a study exit form will be completed for each patient.

10.0 Confidentiality/Publication of the Study

Any information shared by the Sponsor regarding this clinical study is the property of the Sponsor. This protocol is considered proprietary information and should be kept confidential.

The data generated by this clinical study are the property of the Sponsor. These data may be used by the Sponsor, now and in the future, for presentation or publication at the Sponsor's discretion or for submission to regulatory agencies.

11.0 References

1 Gupta H, Gupta PK, Fang X, et al. Development and validation of a risk calculator predicting postoperative respiratory failure. Chest 2011; 140:1207-1215.

2 Dimick JB, Chen SL, Taheri PA, et al. Hospital costs associated with surgical complications: a report from the private-sector National Surgical Quality Improvement Program. J Am Coll Surg 2004; 199:531-537.

3 Zilberberg MD, Shorr AF. Prolonged acute mechanical ventilation and hospital bed utilization in 2020 in the United States: implications for budgets, plant and personnel planning. BMC Health Serv Res 2008; 8:242.

4 Khuri SF, Henderson WG, DePalma RG, et al. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. Ann Surg 2005; 242:326-341; discussion 341-323.

5 Agostini P, Cieslik H, Rathinam S, et al. Postoperative pulmonary complications following thoracic surgery: are there any modifiable risk factors? Thorax 2010; 65:815-818.

6 Restrepo RD, Braverman J. Current challenges in the recognition, prevention and treatment of perioperative pulmonary atelectasis. Expert Rev Respir Med 2015; 9:97-107

7 Rama-Maceiras P. [Peri-operative atelectasis and alveolar recruitment manoeuvres]. Arch Bronconeumol 2010; 46:317-324

8 Hans GA, Sottiaux TM, Lamy ML, et al. Ventilatory management during routine general anaesthesia. Eur J Anaesthesiol 2009; 26:1-8

9 Sabate S, Mazo V, Canet J. Predicting postoperative pulmonary complications: implications for outcomes and costs. Curr Opin Anaesthesiol 2014; 27:201-209

10 Branson RD. The scientific basis for postoperative respiratory care. Respir Care 2013; 58:1974-1984

11 Qaseem A, Snow V, Fitterman N, et al. Risk assessment for and strategies to reduce perioperative pulmonary complications for patients undergoing noncardiothoracic surgery: a guideline from the American College of Physicians. Ann Intern Med 2006; 144:575-580

12 Berlinski A, Willis JR. Albuterol delivery via intrapulmonary percussive ventilator and jet nebulizer in a pediatric ventilator model. Respir Care 2010; 55:1699-1704

13 Birnkrant DJ, Pope JF, Lewarski J, et al. Persistent pulmonary consolidation treated with intrapulmonary percussive ventilation: a preliminary report. Pediatr Pulmonol 1996; 21:246-249

14 Clini EM, Antoni FD, Vitacca M, et al. Intrapulmonary percussive ventilation in tracheostomized patients: a randomized controlled trial. Intensive Care Med 2006; 32:1994-2001

15 Dimassi S, Vargas F, Lyazidi A, et al. Intrapulmonary percussive ventilation superimposed on spontaneous breathing: a physiological study in patients at risk for extubation failure. Intensive Care Med 2011; 37:1269-1276

16 Fornasa E, Ajcevic M, Accardo A. Characterization of the mechanical behavior of intrapulmonary percussive ventilation. Physiol Meas 2013; 34:1583-1592

17 Gatani T, Martucci N, La Rocca A, et al. Management of localized pneumothoraces after pulmonary resection with intrapulmonary percussive ventilation. Ann Thorac Surg 2010; 90:1658-1661

18 Ides K, Vos W, De Backer L, et al. Acute effects of intrapulmonary percussive ventilation in COPD patients assessed by using conventional outcome parameters and a novel computational fluid dynamics technique. Int J Chron Obstruct Pulmon Dis 2012; 7:667-671

19 Natale JE, Pfeifle J, Homnick DN. Comparison of intrapulmonary percussive ventilation and chest physiotherapy. A pilot study in patients with cystic fibrosis. Chest 1994; 105:1789-1793

20 Nava S, Barbarito N, Piaggi G, et al. Physiological response to intrapulmonary percussive ventilation in stable COPD patients. Respir Med 2006; 100:1526-1533

21 Newhouse PA, White F, Marks JH, et al. The intrapulmonary percussive ventilator and flutter device compared to standard chest physiotherapy in patients with cystic fibrosis. Clin Pediatr (Phila) 1998; 37:427-432

22 Nicolini A, Mollar E, Grecchi B, et al. Comparison of intermittent positive pressure breathing and temporary positive expiratory pressure in patients with severe chronic obstructive pulmonary disease. Arch Bronconeumol 2014; 50:18-24

23 Paneroni M, Clini E, Simonelli C, et al. Safety and efficacy of short-term intrapulmonary percussive ventilation in patients with bronchiectasis. Respir Care 2011; 56:984-988

24 Reper P, van Looy K. Chest physiotherapy using intrapulmonary percussive ventilation to treat persistent atelectasis in hypoxic patients after smoke inhalation. Burns 2013; 39:192-193

25 Reychler G, Keyeux A, Cremers C, et al. Comparison of lung deposition in two types of nebulization: intrapulmonary percussive ventilation vs jet nebulization. Chest 2004; 125:502-508

26 Riffard G, Buzenet J, Guerin C. Intrapulmonary percussive ventilation superimposed on conventional mechanical ventilation: comparison of volume controlled and pressure controlled modes. Respir Care 2014; 59:1116-1122

27 Toussaint M, De Win H, Steens M, et al. Effect of intrapulmonary percussive ventilation on mucus clearance in duchenne muscular dystrophy patients: a preliminary report. Respir Care 2003; 48:940-947

28 Toussaint M, Guillet MC, Paternotte S, et al. Intrapulmonary effects of setting parameters in portable intrapulmonary percussive ventilation devices. Respir Care 2012; 57:735-742

29 Tsuruta R, Kasaoka S, Okabayashi K, et al. Efficacy and safety of intrapulmonary percussive ventilation superimposed on conventional ventilation in obese patients with compression atelectasis. J Crit Care 2006; 21:328-332

30 Vargas F, Boyer A, Bui HN, et al. Effect of intrapulmonary percussive ventilation on expiratory flow limitation in chronic obstructive pulmonary disease patients. J Crit Care 2009; 24:212-219

31 Yen Ha TK, Bui TD, Tran AT, et al. Atelectatic children treated with intrapulmonary percussive ventilation via a face mask: clinical trial and literature overview. Pediatr Int 2007; 49:502-507

32 Vargas F, Bui HN, Boyer A, et al. Intrapulmonary percussive ventilation in acute exacerbations of COPD patients with mild respiratory acidosis: a randomized controlled trial [ISRCTN17802078]. Crit Care 2005; 9:R382-389

33 Nino G, McNally P, Miske LJ, et al. Use of intrapulmonary percussive ventilation (IPV) in the management of pulmonary complications of an infant with osteogenesis imperfecta. Pediatr Pulmonol 2009; 44:1151-1154

34 Testa A, Galeri S, Villafane JH, et al. Efficacy of short-term intrapulmonary percussive ventilation in patients with chronic obstructive pulmonary disease. Disabil Rehabil 2014:1-5

35 Ortiz-Pujols S BL, Klatt-Cromwell C, et al. Chest high-frequency oscillatory treatment for severe atelectasis in a patient with toxic epidermal necrolysis. . J Burn Care Res 2013; 34:e112-115

36 Withers L FC, Price KJ, Nguyen QM. Use of a progressive pulmonary protocol in an oncology intensive care unit. In: Care R, ed. Resp Care Open Forum 2009

37 Bocci M GJ, Timons B, et al. A case study: The use of MetaNeb to improve secretion removal and reverse atelectasis. In: AARC, ed. AARC Open Forum. http://www.rcjournal.com/abstracts/2006/?id=of-06-113, 2006

38 Coleman E BB. Aggressive pulmonary secretion clearance intervention in long term care (LTC): A treatment protocol using the MetaNeb System. Advance for Long Term Care Management 2011

39 Patel P FL, Balekian A, et al. Is MetaNeb comparable to high frequency chest compression in the setting of a severe pulmonary exacerbation in adults with cystic fibrosis? North American Cystic Fibrosis Conference 2013: Pediatr Pulmonol, 2013; 359

40 Morgan S HC, Willford L, Turner D, Cheifetz IM. Continuous high frequency oscillation therapy in mechanically ventilated patients in the pediatric intensive care unit. AARC Congress 2014. Las Vegas, NV, 2014