Evaluation of The MetaNeb® System to reduce atelectasis assessed by chest x-ray

Protocol Number: CR-RR2016- 001
Status: Rev. C

Product: **The MetaNeb® System**

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Confidentiality Statement

Signature Page

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:

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List of Abbreviations

AARC	American Association for Respiratory Care
CF	Cystic Fibrosis
CHFO	Continuous High Frequency Oscillation
COPD	Chronic Obstructive Pulmonary Disease
CPEP	Continuous Positive Expiratory Pressure
CRFs	Case Report Forms
CRO	Contract Research Organization
FiO_2	Fraction of Inspired Oxygen
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICU	Intensive Care Unit
IPV	Intrapulmonary Percussive Ventilation
IRB	Institutional Review Board
LE	Lung Expansion
LPM	Liters Per Minute
MV	Mechanical Ventilation
O_2	Oxygen
PPC	Postoperative Pulmonary Complication
SpO_2	Oxygen Saturation
SOP	Standard Operating Procedure

Protocol Synopsis

Product Name:	**The MetaNeb® System**
Protocol Number:	CR-RR2016-001
Protocol Title:	**Evaluation of The MetaNeb® System to reduce atelectasis as assessed by chest x-ray**
Objective(s):	To evaluate the impact of use of The MetaNeb® System in clearance of atelectasis, as demonstrated by improvement in chest x-rays
Endpoints:	**Efficacy:** **Primary Endpoint:** • Chest x-ray assessed by Kelly Atelectasis Score [1] (Appendix 1) – Day 2 (approximately 48 hours) compared to baseline **Secondary Endpoint(s):** • Chest x-ray assessed by Kelly Atelectasis Score at Day 1 (approximately 24 hours) and at Day 4 (approximately 96 hours, or at discharge if discharge occurs before Day 4), compared to baseline • Chest x-ray improvement using a comparative scale (comparing baseline, Day 1, Day 2 and Day 4/discharge) • Oxygenation index (SpO_2/FiO_2 ratio) • Patient reported level of dyspnea - assessed by Modified Borg Dyspnea Scale (Appendix 2) • Change in patient respiratory status - subjective physician assessment –Respiratory Status Evaluation (Appendix 3) **Safety:** • Device-related adverse effects (adverse device effects) will be collected and evaluated.
Study Design:	The study will be a non-randomized open label study, with all subjects receiving treatment with The MetaNeb® System
Study Conduct:	The study will be conducted at one (1) site in the US.

Treatment of Subjects:	Subjects who qualify for enrollment in the study will receive therapy with The MetaNeb® System following the labeled instructions for the device. Details of the treatment including duration and frequency will be defined in treatment procedures.
Duration of Subject Participation:	Duration of treatment with The MetaNeb® System will be a minimum of 48 hours, or until the subject is discharged from the hospital (if discharge is earlier). Enrolled subjects will remain in the study through Day 4 or until the subject is discharged from the hospital, whichever occurs sooner.
Number of Subjects:	Up to approximately fifteen (15) subjects will be enrolled.
Study Population:	Post-surgical (thoracic, cardiac or abdominal surgery) non-mechanically ventilated patients with significant atelectasis, as documented by chest x-ray results.
Inclusion Criteria	Patients who meet all of the following inclusion criteria and no exclusion criteria will be included in the study: • Post-surgical (thoracic, cardiac or abdominal surgery) • Age $\geq$ 18 years • Significant atelectasis by chest x-ray • Patient meets indication for therapy intervention as defined by Recruitment and Airway Clearance Protocol (Respiratory Department Policy and Procedure) • Signed informed consent

Exclusion Criteria:	Patients who meet one or more of the following exclusion criteria will not be eligible for the study: • Cause of atelectasis suspected to be infectious or solid mass • Requirement for mechanical ventilation • Requirement for chronic supplemental oxygen • Hemodynamically unstable, as defined by need for vasopressor therapy • Anticipated need for mechanical ventilation or other poor clinical outcome, unrelated to atelectasis or secretion retention • Contraindication to MetaNeb® therapy (untreated tension pneumothorax) • Inability to perform MetaNeb® therapy using a mouthpiece • Anticipated hospital discharge within 24 hours
Methods:	Post-surgical patients with significant atelectasis confirmed by chest x-ray who require intervention and provide informed consent will be enrolled in the study. After enrollment, patients will be treated with The MetaNeb® System per a defined treatment regimen and within the approved product labeling. Details regarding therapy with The MetaNeb® System will be recorded. After collection of the baseline chest-ray, chest x-rays during the treatment period will be assessed starting with Day 1 (approximately 24 hours) after initiation of treatment with The MetaNeb® System. In the case multiple chest x-rays are performed on a single day, the one closest to 24 hours from the previous day's chest x-ray will be used for study purposes. Chest x-ray files will be sent to designated readers who are blinded to subject protected health information and/or date and time of chest x-ray. Chest x-rays will be scored using the Kelly atelectasis score. Chest x-rays will also be assessed using a comparative scale to evaluate intra-patient changes over time. Any device related adverse events which occur after study enrollment and initial MetaNeb® therapy will be recorded.

Subject Withdrawal:	Subjects may withdraw consent to participate in the study at any time. The subject may also be withdrawn from the study according to investigator judgement regarding the continued health or safety of the subject or related to inability or unwillingness to perform study therapy or procedures.
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. Shift tables from baseline to Day 1, Day 2, and Day 4/discharge will be tabulated for the Kelly atelectasis score and the patient reported level of dyspnea (modified Borg dyspnea scale). Proportions of subjects with improvement in atelectasis at Day 1, Day 2 and Day 4/discharge will be presented with ninety-five percent (95%) confidence interval. Time to a Kelly score of 1 in both lungs will be summarized with a Kaplan-Meier curve, with estimate of the median time and a 95% confidence interval. The oxygenation index will be summarized by calculating the mean and standard deviation at each time point, as well as for changes from baseline. Incidence of device-related adverse events (adverse device effects) will be tabulated.

1.0 Introduction

1.1 Background and Significance

Post-operative pulmonary complications (PPC) are associated with significant excess morbidity, mortality and healthcare expenditure. Atelectasis is an important cause and critical component of PPC [2-4]. Hypoxemia is a strong indicator of the presence of atelectasis [3]. The presence, progression or resolution of atelectasis can be confirmed and quantified by radiologic assessment [5,6].

Evidence from previous studies suggests that atelectasis can be effectively prevented or treated by early intervention including, but not limited to, lung expansion (LE) techniques and secretion clearance [3,4,7,8]. Such interventions should significantly mitigate progression to serious PPC.

1.2 Research Rationale and Supporting Evidence

The MetaNeb® System is an LE expansion device that has been cleared to market by the FDA for clearance of pulmonary secretions and for treatment or prevention of pulmonary atelectasis. The MetaNeb® 4 device is a Class II device, cleared to market April 25, 2013. It 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.

Devices similar to The MetaNeb® System have been evaluated in a number of clinical and laboratory studies and have been found to be safe and effective [9-25]. Clinical studies of The MetaNeb® System, however, are limited. One peer-reviewed publication 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 [26]. 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 Intrapulmonary Percussive Ventilation (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 [27]. 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 [28]. In a long-term care treatment protocol with intubated or tracheostomised patients on mechanical ventilation (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 [29]. 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 cystic fibrosis (CF) patients with severe pulmonary exacerbations and admitted for intravenous (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 [30]. 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 [31].

1.3 Rationale for the Proposed Study

Atelectasis is a complication in many hospitalized patients and is particularly common in patients recovering from cardiac and other thoracic and upper abdominal surgeries. It has been shown to be a precursor to other complications. The MetaNeb® System creates CPEP and CHFO for mobilization of secretions, lung expansion therapy, the treatment and prevention of pulmonary atelectasis. The proposed study is intended to evaluate the impact of this therapy in treating patients with significant atelectasis.

2.0 Study Objectives

The primary objective of this study is to evaluate the impact of use of The MetaNeb® System in clearance of atelectasis, as demonstrated by improvement in chest x-ray.

3.0 Study Design

3.1 Overview of Study Design

3.1.1 Design:

The study will be a non-randomized open label study. It is a pre-post study design with subjects serving as their own control. All subjects will receive treatment with The MetaNeb® System. The study will be conducted at one (1) site in the US.

The study will evaluate the impact of the therapy on chest x-ray scores and related clinical endpoints. Patients with evidence of significant atelectasis on chest x-ray will be enrolled. After assessing baseline status, therapy with The MetaNeb® System will be introduced and incorporated into the respiratory care treatment regimen. Outcomes will be assessed at regular intervals following the initiation of the therapy.

3.1.2 Procedure:

Up to approximately fifteen (15) patients will be recruited and enrolled from the ICU and/or general care floors. Eligible subjects will be patients who are not intubated, and who have developed clinically significant atelectasis (i.e. described in the radiologist report). Demographic data will be collected from the medical record of each subject at the time of enrollment.

Following enrollment in the study, subjects will receive treatment with The MetaNeb® System per a defined treatment regimen and within the approved product labeling. Treatments will be delivered on a defined schedule. Enrolled subjects will be treated for a minimum of 48 hours, or until discharge (if discharge from the hospital occurs before 48 hours).

Chest x-ray files at baseline (Day 0), for enrolled subjects, will be collected. Daily chest x-ray files for Day 1 (approximately 24 hours), Day 2 (approximately 48 hours) and Day 4 (approximately 96 hours) or discharge (if discharge occurs before Day 4) will be collected as they become available.

All chest x-rays will be logged by subject number, date and time, and event (i.e. Day 0, Day 1 and Day 2, Day 4/discharge) and assigned a number from a random number list. All chest x-rays, identified only by the assigned number will be placed in a file for review and scoring by the blinded radiologist(s).

Pulse Oximetry SpO_2 data along with the subject's oxygen support status (O_2 delivered in LPM or %) from the time corresponding to the baseline and the Day 4/discharge

chest x-rays will be collected. SpO_2/FiO_2 ratio will be calculated based on pulse oximetry and oxygen support corresponding to the time of each chest x-ray.

Pulse Oximetry SpO_2 data along with the subject's oxygen support status will also be collected from the patient record at the time closest to the beginning of each shift, for Day 2 and Day 3. SpO_2/FiO_2 ratio will be calculated based on pulse oximetry and oxygen support corresponding to the time closest to the beginning of each shift.

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

3.1.3 Product Description

The Product 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 and the treatment and prevention of pulmonary atelectasis. The device 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:

All enrolled patients will receive therapy for airway clearance and lung expansion procedures using The MetaNeb® System. Other airway clearance and/or lung expansion therapies will not be delivered during the study period. The treatment regimen for other respiratory care modalities will be that which is prescribed by the patient's health care team in the routine standard care of each patient (e.g. oxygen, aerosolized medications, etc.).

Exceptions to the above treatment protocol 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 (thoracic, cardiac or abdominal surgery) non-mechanically ventilated patients with evidence of significant atelectasis on chest x-ray, with an increasing need for respiratory support.

3.2.1 Inclusion Criteria:

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

- Age ≥ 18 years
- Significant atelectasis by chest x-ray
- Patient meets indications for therapy as defined by Recruitment and Airway Clearance Protocol (HOAG2013-0000002335/Version 4/Effective Date: 9/15/14)
- Signed informed consent

3.2.2 Exclusion Criteria:

Patients who meet any of the following criteria will be excluded from the study:

- Cause of atelectasis suspected to be infectious or solid mass
- Requirement for mechanical ventilation
- Requirement for chronic supplemental oxygen
- Hemodynamically unstable, as defined by need for vasopressor therapy
- Anticipated need for mechanical ventilation, or other poor clinical outcome, unrelated to atelectasis or secretion retention
- Contraindication to MetaNeb® therapy (untreated tension pneumothorax)
- Inability to perform MetaNeb® therapy using a mouthpiece
- Anticipated hospital discharge within 24 hours

3.3 Evaluation Criteria/Effectiveness

The therapy regimen (treatment with The MetaNeb® System) will be evaluated to determine if there is an improvement in chest x-ray scores after initiation of the therapy. The study will also evaluate if there is a corresponding improvement in the clinical respiratory status of the patients demonstrated by a decrease in the O_2 requirement and/or an improvement in oxygen saturation. Endpoints are described below:

Primary Endpoint:

Chest x-ray score improvement at Day 2 (approximately 48) hours after initiation of therapy with The MetaNeb® System.

Chest x-rays will be scored using the Kelly scoring system (Appendix 1) to assess the presence of atelectasis on Day 2, after initiation of therapy with The MetaNeb®

System. Scores for chest x-rays at Day 2 will be compared to the scores for chest x-rays taken at baseline. The Kelly score for each of the chest x-rays will be assessed by blinded reader.

The baseline chest x-ray for each subject is the qualifying x-ray that determined the presence of significant atelectasis.

Secondary Endpoint(s):

- Chest x-ray score improvement at Day 1 (approximately 24 hours) and at Day 4 (approximately 96 hours or at discharge, if discharge occurs before Day 4) after initiation of therapy with The MetaNeb® System.

  Scored using the Kelly score, as described above, to assess the presence of atelectasis.

- Chest x-ray improvement using a comparative scale after a minimum of forty-eight (48) hours of therapy with The MetaNeb® System.

  Chest x-ray improvement assessed using a comparative scale for baseline, Day 1, Day 2 and Day 4/discharge. Four chest x-rays for each enrolled subject (baseline, Day 1, Day 2 and Day 4/discharge), with date and time masked, will be sent to the radiologist for comparison. The radiologist will rank the four x-rays 1, 2, 3 or 4 (1 = least atelectasis, 4 = most atelectasis).

- Oxygenation index (SpO_2/FiO_2 ratio) at Day 1, Day 2 and Day 4/discharge compared to baseline

- Patient reported level of dyspnea (assessed by Modified Borg Dyspnea Scale – Appendix 2)

- Change in patient respiratory status (Respiratory Status Evaluation – Appendix 3)

  Physician observation and evaluation of patient respiratory status at time of enrollment (baseline) and on Day 2

Safety:

- Device-related adverse effects (adverse device effects) will be collected and evaluated.

3.4 Study Observations Table

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

Table 1. Study Observations

Day	Day 0 (Treatment Intiation)	Day 1 (Post Treatment Intiation)	Day 2 (Post Treatment Intiation)	Day 4 / Discharge (or Early Termination)
Selection Criteria / Enrollment	X			
Informed Consent	X			
Demographic Data	X			
Medical History	X			
Chest X-ray Score (Kelly)	X (Baseline)	X	X	X
Chest X-ray Ranking (Comparative)				X
O2 Requirement Collected at time of Baseline and Day 4 / Discharge Chest X-rays. Collected at beginning of each shift for Day 1 and Day 2	X	X	X	X
SpO_2 Collected at time of Baseline and Day 4 / Discharge Chest X-rays. Collected at beginning of each shift for Day 1 and Day 2	X	X	X	X
Borg Dyspnea Scale	X	X	X	
Respiratory Status Evaluation	X		X	
MetaNeb Treatments	X	X	X	X
Study Exit Form				X

3.4.1 Study Observations Table Detailed Description

Documentation of observations will be completed by study staff at the time of occurrence, from review of the patient's medical records and from scores and rankings for chest x-rays completed by radiologist review. 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 and Ethnicity, Gender.

Medical History: Admitting diagnosis, pulmonary history will be recorded from the patient medical record including: Asthma, CF, Bronchiectasis, COPD, Neuromuscular Disease, Obstructive Sleep Apnea or Other Pulmonary Condition(s).

Chest X-ray Score (Kelly): Chest x-ray files will be collected beginning with the enrollment chest x-ray (Day 0) and for Day 1, Day 2 and Day 4 or at time of discharge from the hospital (if earlier). All chest x-rays will be logged by subject number, date and time, and event (i.e. Day 0, Day 1, Day 2, Day 4/discharge) and assigned a number from a random number list. All chest x-rays, identified only by the assigned number, will be placed in a file and then reviewed and scored by the radiologist(s). Radiologist(s) will be blinded to subject and event.

Chest X-ray Ranking (Comparative): Chest x-ray files will be collected for each subject beginning with the enrollment chest x-ray (Day 0) and for Day 1, Day 2, and Day 4 or at time of discharge from the hospital (if earlier). The random number assigned to each chest x-ray (Day 0, Day 1, Day 2, Day 4) will be used to identify the time and date. The group of chest x-rays for each subject, identified only by the assigned number, will be placed in a file and then reviewed, compared and ranked by the radiologist(s). Radiologist(s) will be blinded to subject and event.

O_2 Requirement: The oxygen support status for each subject will be recorded for the time of the baseline and Day 4/discharge chest x-rays. The oxygen support status will also be recorded for the beginning of each shift for Day 1 and Day 2.

SpO_2: The oxygen saturation (based on pulse oximetry readings) for each subject will be recorded for the time of the baseline and Day 4/discharge chest x-rays. The oxygen saturation will also be recorded for the beginning of each shift for Day 1 and Day 2.

SpO_2/FiO_2 Ratio: The SpO_2/FiO_2 ratio (based on pulse oximetry readings and the O_2 requirement) for each subject will be calculated for the time of each chest x-ray. The SpO_2/FiO_2 ratio will also be calculated for the beginning of each shift for Day 0 – Day 2, or until the time of discharge from the hospital (if earlier).

Assessment of Dyspnea (Modified Borg Dyspnea Scale): An evaluation of each subject's dyspnea level will be assessed using patient response and a Modified Borg Dyspnea Scale. Evaluation will be completed by respiratory staff at the time of enrollment into the study (Day 0), and on a daily basis for Day 1 and Day 2, or at the time of discharge from the hospital (if earlier).

Respiratory Status Evaluation: An evaluation of each subject's respiratory status will be completed by the physician investigator at the time of enrollment into the study (Day 0) and on Day 2, or at the time of discharge from the hospital (if earlier).

MetaNeb® Treatments: All MetaNeb® treatments will be documented for each day beginning with enrollment (Day 0), Day 1 and Day 2, and through Day 4 or until the time of discharge from the hospital (if earlier).

3.5 Statistical Methods and Analysis

3.5.1 Sample Size Estimation:

The sample size for this study is a convenience sample. The study is designed to provide preliminary information on the benefits of the addition of the MetaNeb® System in treating pulmonary atelectasis and associated hypoxemia. Resulting data on the outcomes associated with The MetaNeb® System may help to provide definition of the effect size and variability and the number of subjects required for subsequent studies.

Subjects with a Kelly Score of one (1) or less in both lungs on the baseline (Day 0) chest x-ray will be excluded from the primary endpoint analysis and secondary endpoint analyses related to Kelly Score.

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 Endpoint:
The Kelly atelectasis score at Day 2 will be summarized with shift tables from baseline. Proportion of subjects showing an improvement from baseline will summarized.

Secondary Endpoints:

- The Kelly atelectasis score at Day 1 and Day 4/discharge will be summarized with shift tables from baseline.
- Time to a Kelly score of 1 in both lungs will be summarized with a Kaplan-Meier curve, with estimate of the median time and a 95% confidence interval.
- To address possible decrease in sample size over time, due to subjects' improvement and stoppage of use of The MetaNeb® System, the Kelly atelectasis score shift from baseline will also be tabulated using LOCF (last observation carried forward).
- Patient reported level of dyspnea (modified Borg dyspnea scale) will be tabulated for each time point.
- The oxygenation index will be summarized by calculating the mean and standard deviation at each time point, as well as for changes from baseline.

- Chest x-ray improvement using a comparative scale after a minimum of forty-eight (48) hours of therapy with The MetaNeb® System
- Oxygenation index (SpO_2/FiO_2 ratio) at Day 1 and Day 4/discharge compared to baseline
- Change in patient respiratory status (Borg Dyspnea Scale – Appendix 2)
- Physician observation and evaluation of patient respiratory status at time of enrollment (baseline) and on Day 2 (Respiratory Status Evaluation – Appendix 3)

Safety:
Incidence of device-related adverse events (adverse device effects) will be tabulated.

4.0 General Study Information

4.1 Technical Support for Product

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:

Informed consent must be obtained from all subjects 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, and subjects will be given a copy of their signed informed consent.

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 Brian Becker by phone: 651-490-6885 (office) PI [redacted] or email: brian.becker@hill-rom.com.

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 and followed under the current protocol.

5.4 Materials Provided by the Sponsor

The Sponsor will supply The MetaNeb® System devices to the institution.

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 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 (SADE) and unanticipated adverse device effects (UADE) should be reported immediately to the Sponsor and 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, as applicable.

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 review and given written approval for the 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 study visit 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.

Ownership and guidelines for use of the data generated by this clinical study will be in compliance with the terms specified in the Clinical Research Agreement.

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Appendix 1

Kelly Atelectasis Scoring System

Atelectasis score

Scoring index Dysphagia Analgesia Atelectasis Oesophagitis Wound symptoms ECOG Karnovsky Empyema

We are grateful to Barry Kelly, Department of Radiology, Royal Victoria Hospital for assistance with developing this scoring system. We have used it to score chest Xray findings in studies on sputum retention post thoracic surgery. Each lung is scored separately.

Score	Description
0	Normal
1	Linear atelectasis
1.25	a: one third of hemidiaphragm
1.50	b: two thirds of hemidiaphragm
1.75	c: all of one hemidiaphragm
2	Lobar consolidation
3	Lobar collapse
4	Bronchial consolidation (whole lung, bronchopneumonia etc)

Source: http://www.mactheknife.org/Scoring_systems/Atelectasis.html

Appendix 2

Modified Borg Dyspnea Scale

Modified Borg Dyspnoea Scale

0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight
3	Moderate — Exercise Training Zone
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Patient Instructions for Borg Dyspnoea Scale

"This is a scale that asks you to rate the difficulty of your breathing. It starts at number 0 where your breathing is causing you no difficulty at all and progresses through to number 10 where your breathing difficulty is maximal. How much difficulty is your breathing causing you right now?"

Appendix 3

Respiratory Status Evaluation

MetaNeb® Study: Respiratory Status Evaluation

Evaluate Patient's Pre-MetaNeb® therapy status based on the parameters listed below. Using these judgments as baseline reference points, score patient's respiratory and general health status following day two of MetaNeb® therapy.

☐ worse (1) ☐ unchanged (2) ☐ improved (3)

	Pre-treatment evaluation notes	Day 2 (48 Hour) Score	Comments
1) Lung assessment: Percussion • Resonance over hyperinflated areas • Dullness over consolidated areas • Location and excursion of diaphragm		☐ Worse (1) ☐ Unchanged (2) ☐ Improved (3)	
2) Lung Assessment: Auscultation • Sounds of normal air entry • Adventitious breath sounds (e.g. rhonchi, rales, pleural rub, stridor, decreased breath sounds) • Quality of breath sounds (e.g. bronchial, bronchovesicular, vesicular) • Inspiration/expiration ratio • Degree of air entry throughout chest (equal/unequal)		☐ Worse (1) ☐ Unchanged (2) ☐ Improved (3)	
3) Cough Assessment • Quality (effectiveness) • Severity • Frequency		☐ Worse (1) ☐ Unchanged (2) ☐ Improved (3)	
4) Secretion Assessment • Quantity • Consistency • Ease of clearance • Abnormal color/purulence		☐ Worse (1) ☐ Unchanged (2) ☐ Improved (3)	
5) Oxygenation • Skin color • SaO_2 • PaO_2 (if available)		☐ Worse (1) ☐ Unchanged (2) ☐ Improved (3)	
6) Work of Breathing • Respiratory rate/rhythm • Respiratory excursion/accessory muscle use • Breathing pattern		☐ Worse (1) ☐ Unchanged (2) ☐ Improved (3)	
7) Other Observations • General appearance • Mental acuity • Respiratory pain		☐ Worse (1) ☐ Unchanged (2) ☐ Improved (3)	