A pilot study to evaluate the use of the MN4000 for treatment of cystic fibrosis (CF) and motor neuron disease (MND) patients in the home setting

Protocol Number: CR-RR2016- 002
Status: Rev. A

Product: **MN4000**

Sponsor:
Hill-Rom Company, Inc.
Two Prudential Plaza, Suite 4100
180 N. Stetson Avenue
Chicago, IL 60601

Study Manager:

Brian Becker, MEd, RRT
Senior Manager, Clinical Research,
Hill-Rom Company, Inc.
1020 West County Road F
Saint Paul, MN 55126
PI [redacted]
brian.becker@hill-rom.com

PI [redacted]
Manager, Clinical Research,
Hill-Rom Company, Inc.
PI [redacted]

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	PI [redacted]	Date: 1-26-2017

Table of Contents

List of Abbreviations

AARC	American Association for Respiratory Care
ADE	Adverse Device Effects
ALS	Amyotrophic Lateral Sclerosis
ALS-FRS	Amyotrophic Lateral Sclerosis Functional Rating Scale
CF	Cystic Fibrosis
CFQ-R	Cystic Fibrosis Questionnaire - Revised
CHFO	Continuous High Frequency Oscillation
COPD	Chronic Obstructive Pulmonary Disease
CPEP	Continuous Positive Expiratory Pressure
CRFs	Case Report Forms
CRO	Contract Research Organization
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in One Second
FVC	Forced Vital Capacity
FEV_1/FVC	Ratio - Forced Expiratory Volume in One Second over total Forced Vital Capacity
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IPV	Intrapulmonary Percussive Ventilation
IRB	Institutional Review Board
LE	Lung Expansion
NMD	Neuromuscular Disease
MV	Mechanical Ventilation
MIP	Maximal Inspiratory Pressure
MND	Motor Neuron Disease
O_2	Oxygen
PAP	Positive Airway Pressure
PEP	Positive Expiratory Pressure
QOL	Quality of Life
SADE	Serious Adverse Device Effects
SpO_2	Pulse Oximetry Oxygen Saturation
SOP	Standard Operating Procedure
UADE	Unanticipated Adverse Device Effects
VC	Vital Capacity

Protocol Synopsis

Product Name:	**MN4000**
Protocol Number:	CR-RR2016-002
Protocol Title:	**A pilot study to evaluate the use of The MN4000 for treatment of cystic fibrosis (CF) and motor neuron disease (MND) patients in the home setting**
Objective(s):	To evaluate the use of the MN4000 to treat cystic fibrosis (CF) and motor neuron disease (MND) patients in the home setting
Endpoints:	**Primary Endpoint:** • Patient and/or caregiver satisfaction with therapy (Therapy Use Rating Scale) **Secondary Endpoints:** • Mean adherence to prescribed treatment regimen • Pulmonary Function Measures All Subjects: - Force Expiratory Volume – one second (FEV_1) CF patients only: - Forced Vital Capacity (FVC) - FEV_1/FVC MND patients only: - Slow Vital Capacity (SVC) - Resting Oxygen Saturation – pulse oximetry (SpO_2) - Maximal Inspiratory Pressure (MIP) - Peak Cough Flow • ALS-Functional Rating Scale (ALS-FRS) (MND Patients Only) • Cystic Fibrosis Questionnaire - Revised (CFQ-R) (CF patients only)

	• Exacerbations of pulmonary disease (hospitalization and/or antibiotics for respiratory infection or complication)
Study Design:	The study will be a non-randomized, open label pilot study with all subjects receiving treatment with the MN4000
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 MN4000 following the labeled instructions for the device. The prescribed treatment regimen including duration will be documented.
Duration of Subject Participation:	Each study subject will be treated with the MN4000 and will remain in the study for a period of approximately three months.
Number of Subjects:	A total of approximately 10 subjects will be enrolled.
Study Population:	Patients with CF or MND will be enrolled in the study.
Inclusion Criteria	Patients who meet all of the following inclusion criteria and no exclusion criteria will be included in the study: • Documented diagnosis of CF or MND • Age $\geq$ 18 years • Signed informed consent
Exclusion Criteria:	Patients who meet one or more of the following exclusion criteria will not be eligible for the study: • Requirement for continuous mechanical ventilation • Anticipated requirement for hospitalization within the next three months • History of pneumothorax within past 6 months • History of hemoptysis requiring embolization within past 12 months • Inability to perform MN4000 therapy using a mouthpiece (e.g. inability to create adequate mouth seal) • Inability to perform MN4000 therapy as directed • Inability or unwillingness to complete study visits or provide follow-up data as required by the study protocol

Methods:	Patients with CF and MND who require regular home airway clearance therapy will be enrolled in the study. After enrollment, demographic data and pulmonary related medical history data will be collected. Enrolled patients will be prescribed therapy with The MetaNeb® System for Homecare environment (The MN4000) within the approved product labeling. The MN4000 will be the primary airway clearance device for these patients during the study period. Details regarding therapy adherence with the MN4000 will be reported by the subject/caregiver for each day of therapy. Adherence to the prescribed therapy regimen and patient/caregiver satisfaction with the therapy (i.e. surveys regarding therapy effectiveness and ease of use) will be assessed. Pulmonary function, using measures appropriate for each population, will be assessed for each subject at baseline, after one (1) month and after three (3) months of home therapy with the MN4000. Results from the MN4000 therapy period will be compared to the baseline period, during which the subject received his/her regular airway clearance regimen. For patients with a diagnosis of CF, a quality of life survey will be administered. Respiratory status for patients with MND will be assessed using the ALS Functional Rating Scale. Airway Clearance Satisfaction surveys will be conducted at baseline, after one (1) month, and after three (3) months of therapy with the MN4000. Results from the MN4000 therapy period will be compared to the baseline period, during which the subject received his/her regular airway clearance regimen. Any device related adverse events which occur after study enrollment and initial MN4000 therapy will be recorded. Any equipment related complaints which occur after study enrollment and initial MN4000 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. Incidence of adverse device effects (ADEs) will be tabulated. Incidence of device-related complaints will be tabulated.

1.0 Introduction

1.1 Background and Significance

Airway clearance therapy is a key component of the care of many patients with chronic respiratory disease such as cystic fibrosis (CF). In addition, patients with neuromuscular weakness disorders such as motor neuron disease (MND) develop pulmonary complications as a result of low lung volume and inability to cough effectively. Airway clearance along with lung expansion and cough therapy are often prescribed in these patients to help maintain lung volume and avoid respiratory infections.

Evidence from previous studies involving The MetaNeb® System suggest that continuous high frequency oscillation (CHFO) and continuous positive expiratory pressure (CPEP) therapy will provide effective airway clearance and/or lung expansion therapy when used consistently as a primary home therapy.

1.2 Research Rationale and Supporting Evidence

The MetaNeb® System for Homecare environment (The MN4000) has been developed specifically for use in the home setting, for patients that have chronic respiratory disease and require regular airway clearance and/or lung expansion therapy. To-date, there have been no formal clinical studies of the device. However, there have been case reports and a few small studies of The MetaNeb® System, which is the acute care version of the MN4000. 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 to the alternative therapy [1]. Hsieh, et al. evaluated the impact of CPEP and CHFO using The MetaNeb® System in a group of anatomic lung resection patients. CPEP and CHFO therapy was compared to respiratory therapist driven protocol administered positive airway pressure (PAP) and positive expiratory pressure (PEP), the current standard of care. Results showed that CPEP and CHFO therapy resulted in significant improvement in vital capacity (VC) over time compared to standard positive pressure devices [2]. 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. Results support safety and feasibility and suggest that CHFO may be beneficial by improving lung compliance in patients with secretion-induced atelectasis [3].

One additional peer-reviewed publication involves 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 [4]. A number of additional abstracts and other reports have been presented or published that suggest that The MetaNeb® System is effective tool for mobilization of secretions and use of the therapy results in improvement in chest x-ray. 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 lung expansion (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 [5]. 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 [6]. 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 [7].

1.3 Rationale for the Proposed Study

Many patients with chronic respiratory disease require regular airway clearance therapy to mobilize secretions and to decrease the risk of pulmonary infections. Additionally, some patients (e.g. patients with neuromuscular disease) are prone to developing atelectasis and require therapy to maintain lung volume. The MetaNeb® System has been shown in anecdotal reports and preliminary studies to provide effective airway clearance and lung expansion therapy in a variety of patients in the acute care setting. The MN4000 is now available to provide this therapy in the homecare environment. The MN4000 creates CPEP and CHFO for mobilization of secretions, lung expansion therapy and the treatment and prevention of pulmonary atelectasis. The proposed study is intended to evaluate the impact of this therapy in treating patients with a need for daily airway clearance and/or lung expansion therapy in the home setting.

2.0 Study Objectives

The primary objective of this study is to evaluate the use of the MN4000 at the primary therapy for regular home airway clearance and lung expansion in patients with CF and MND.

3.0 Study Design

3.1 Overview of Study Design

3.1.1 Design:

The study will be a non-randomized open label pilot study. It is an observational design. All enrolled subjects will receive treatment with the MN4000. The study will be conducted at one (1) site in the US.

The study will evaluate subject satisfaction with the therapy and adherence to the therapy, and will also collect clinical outcome data. Adult patients with CF or MND who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled in the study. After assessing baseline status, therapy with the MN4000 will be introduced and incorporated into the home respiratory care treatment regimen. Outcomes will be assessed before, during and after the MN4000 treatment period.

3.1.2 Procedure:

Approximately ten (10) patients will be enrolled from CF and NMD clinics. Eligible subjects will be adult patients who are able to perform MN4000 therapy using a mouthpiece and who meet all inclusion and none of the exclusion criteria. Informed consent will be obtained. Demographic and medical history data will be collected from the medical record of each subject at the time of enrollment.

Baseline Clinic Study visit: At the Baseline Clinic Visit, a Therapy Use Rating Scale questionnaire will be completed by each subject and/or caregiver. Routine pulmonary function testing will be completed per standard clinic visit protocol. FEV_1, will be collected and documented for all study subjects. FVC and FEV_1/FVC will be collected and documented for CF subjects. SVC, Resting SpO_2, MIP and Peak Cough Flow will be collected and documented for MND subjects.

Population specific assessments will be conducted, as appropriate, during the Baseline Study Visit.

- A quality of life assessment will be completed by all CF subjects at Baseline Study Visit using the Cystic Fibrosis Questionnaire – Revised (CFQ-R) [8].
- The level of disability will be assessed for all MND subjects using The ALS-FRS [9].

Exacerbations that occurred in the three-month period prior to the Baseline Clinic Study Visit will be documented.

During the Baseline Study Visit, all subjects will be trained in the use of the MN4000. Following that visit, a MN4000 device will be delivered to the home of each study subject by a Hill-Rom designated trainer.

Home Training on the MN4000: The Hill-Rom designated Trainer will set up the device and review operation and treatment protocol at the time the device is delivered. Study subjects and caregivers will be instructed to use the device as their primary airway clearance and lung expansion therapy for a period of three months.

Adherence Documentation: During the three-month follow-up period, adherence to the daily prescribed therapy regimen will be assessed. Subjects/caregivers will be asked to provide adherence information for each day during the 90-day study period.

30-day and 90-day follow-up Study Clinic Visits: All subjects will be scheduled to complete a follow-up study clinic visit approximately one month after initiating therapy and again at the time of their routine clinic visit approximately three months after initiating therapy with the MN4000. During these study visits, the Therapy Use Rating Scale questionnaire will be completed by each subject and/or caregiver. Routine pulmonary function testing will be completed per standard clinic visit protocol. FEV_1, will be collected and documented for all study subjects. FVC and FEV_1/FVC will be collected and documented for CF subjects. SVC, Resting SpO_2, MIP and Peak Cough Flow will be collected and documented for MND subjects. The CFQ-R and The ALS-FRS will be collected for the CF subjects and the MND subjects respectively. Exacerbations that occurred since the previous clinic study visit will be documented.

3.1.3 Product Description

The MN4000 is an airway clearance and lung expansion therapy device that has been cleared to market by the FDA as The MetaNeb® System for Homecare environment, for clearance of pulmonary secretions and for treatment or prevention of pulmonary atelectasis. It is a Class II device, cleared to market on March 17, 2016 under premarket notification 510(k) K151689 as The MetaNeb® 4 System with application for homecare environment. It is commercially marketed as the MN4000. The device consists of a pneumatic compressor and an air pulse generator that delivers CHFO and 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 MN4000 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 their regular home airway clearance and lung expansion using the MN4000. Other airway clearance and/or lung expansion therapies will not be performed during the three-month study period. The treatment regimen for other respiratory care modalities (e.g. aerosolized medications) will be that which is prescribed by the patient's health care team in the routine standard care of each patient.

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 CF and adult MND patients.

3.2.1 Inclusion Criteria:

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

- Documented diagnosis of CF or MND
- Age ≥ 18 years
- Signed informed consent

3.2.2 Exclusion Criteria:

Patients who meet one or more of the following exclusion criteria will not be eligible for the study:

- Requirement for continuous mechanical ventilation
- Anticipated requirement for hospitalization within the next three months
- History of pneumothorax within past 6 months
- History of hemoptysis requiring embolization within past 12 months
- Inability to perform MN4000 therapy using a mouthpiece (e.g. inability to create adequate mouth seal)
- Inability to perform MN4000 therapy as directed
- Inability or unwillingness to complete study visits or provide follow-up data as required by the study protocol

3.3 Evaluation Criteria/Effectiveness

The MN4000 will be evaluated to determine patient and/or caregiver satisfaction with therapy along with adherence to prescribed therapy in the home setting over a period of three months. The study will also evaluate the clinical respiratory status of the patients during the three-month treatment period. Endpoints are described below.

Primary Endpoint:

- Patient and/or caregiver satisfaction with therapy

  Patient and/or caregiver satisfaction with therapy will be evaluated using a Therapy Use Rating Scale questionnaire. The Therapy Use Rating Scale is an assessment of patient/caregiver satisfaction with the therapy and their subjective assessment of the benefit of the therapy.

Secondary Endpoint(s):

- Mean adherence to prescribed therapy regimen

  Use of the MN4000 will be evaluated, collecting daily treatment usage information from study subjects and/or caregivers to determine the level of adherence to the prescribed therapy regimen.

- Pulmonary function measures

  Results of pulmonary function testing that are performed during routine clinic visits will be collected from each subject's medical record.

  FEV_1 will be collected for **all subjects**

  The following pulmonary function measures will be collected for **CF subjects only**:

  - FVC
  - FEV_1/FVC

  The following pulmonary function measures will be collected for **MND subjects only**:

  - SVC
  - Resting SpO_2
  - MIP
  - Peak Cough Flow

- Level of Disability Assessment – **MND Subjects Only**

  The level of disability will be assessed using The ALS-FRS. This is a validated questionnaire that evaluates progressive level of disability for MND patients.

- Quality of Life (QOL) Assessment -- **CF Subjects Only**

Quality of life will be assessed in patients with cystic fibrosis using the CFQ-R. The CFQ-R is a validated instrument designed to evaluate quality of life in adolescents and adults with CF.

- Exacerbations of pulmonary disease (hospitalization and/or antibiotics for respiratory infection or complication)

  Exacerbations of pulmonary disease will be defined as respiratory infections that result in requirement for hospitalization and/or antibiotics to treat the respiratory infection or complication. Hospitalizations that are part of routine care (e.g. hospital admissions for annual "tune-up") or antibiotics that are part of the regular treatment regimen will not be documented as exacerbations.

3.4 Study Observations Table

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

Table 1. Study Observations

Day	Baseline Clinic Visit	30 Days Clinic Visit	90 Days Clinic Visit or Early Term.
Selection Criteria / Enrollment	X		
Informed Consent	X		
Demographic Data	X		
Medical History	X		
Therapy Use Rating Scale (A/W Clearance Satisfaction)	X (eval of current therapy)	X	X
Pulmonary Function Measures *Specific tests for MND and CF Subjects*	X	X	X
CFQ-R (CF patients only)	X	X	X
ALS-FRS (MND patients only)	X	X	X
Exacerbations	X	X	X
MN4000 Treatments		Documented on a daily basis ← →	
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 questionnaires. A detailed description of documentation requirements for each parameter is below.

Selection Criteria/Enrollment: Inclusion and exclusion criteria will be reviewed and documented at the time of enrollment for all study subjects.

Informed Consent: Signed informed consent will be obtained from all subjects or legally responsible caregivers by the principle investigator or his/her representative, prior to enrollment in the study.

Demographic Data: The following data will be recorded from the patient medical record after enrollment in the study (at baseline): Age, Height, Weight, Race and Ethnicity, Gender.

Medical History: Pulmonary medical history will be recorded from the patient medical record after enrollment in the study (at baseline), including: CF. Neuromuscular Disease, Asthma, Bronchiectasis, COPD, Obstructive Sleep Apnea or Other Pulmonary Condition(s).

Therapy Use Rating Scale: The Therapy Use Rating Scale questionnaire will be administered at baseline, after one month of therapy with the MN400 System and after three months of therapy with the MN4000.

Pulmonary Function Measures: Standard spirometry measures that are collected at routine clinic visits (described in section 3.3) will be collected at baseline, after one month of therapy with the MN400 and after three months of therapy with the MN4000.

Cystic Fibrosis Questionnaire - Revised (CFQ-R): The CFQ-R will be administered to **CF subjects** during each study clinic visit, at baseline (evaluating current therapy), after one month of therapy with the MN400 System and after three months of therapy with the MN4000.

ALS-Functional Rating Scale (ALS-FRS): The ALS-FRS will be administered to **MND subjects** during each study clinic visit, at baseline (evaluating current therapy), after one month of therapy with the MN4000 and after three months of therapy with the MN4000.

Exacerbations: Exacerbations of pulmonary disease (defined as hospitalization and/or antibiotics for respiratory infection or complication) will be collected and documented for the three-month period prior to the baseline study clinic visit and for the time period since the last study visit for the one-month and three-month study visits.

MN4000 Treatments: MN4000 treatments will be documented to determine adherence to the prescribed therapy regimen. Treatment data will be collected from study subjects or caregivers for adherence reporting. Subjects will be asked to respond to simple adherence questions.

3.5 Statistical Methods and Analysis

3.5.1 Sample Size Estimation:

The sample size for this study is a convenience sample. Resulting data on the outcomes associated with the MN4000 may help to provide definition of the effect size and variability and the number of subjects required for subsequent studies.

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:

- Results of the Therapy Use Rating Scale will be summarized.

Secondary Endpoints:

- Mean adherence to prescribed therapy regimen will be summarized.
- Pulmonary function test results will be summarized.
- ALS-Functional Rating Scale (ALS-FRS) results will be summarized for MND subjects.

- Cystic Fibrosis Questionnaire – Revised (CFQ-R) results will be summarized for CF subjects.
- Exacerbations of pulmonary disease that occur during the study period will be summarized.

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 (ADE), 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: PI [redacted]
or email: brian.becker@hill-rom.com.

A complaint is defined as any written, electronic or oral communication that alleges deficiencies related to the identity, design, quality, durability, reliability, safety, effectiveness or performance of the device after its release for distribution.

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.

An adverse event (AE) is defined as any untoward medical occurrence, unintended disease or injury or untoward clinical signs (including abnormal lab findings) in subjects, users or other persons, whether or not related to the investigational medical device.

Events that do not meet the definition of AE include:

- Medical or surgical procedure (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen
- The disease/disorder being studied, or expected progression, signs or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

Disease-related events and/or disease-related outcomes that do not qualify and should not be reported as serious adverse events (SAEs):

- Any worsening in physical function and disease state, such as expected progression of pulmonary disease in CF or expected loss of ambulatory function in NMD, unless worse than expected for the individual
- Any other illness, or change in function that is expected in the usual course of the patient's disease, unless worse than expected for the individual

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 MN4000 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 shall be familiar with the appropriate use of the MN4000 device and any other information provided by the Sponsor.
- The Investigator shall provide adequate staff to conduct and complete the study within the agreed study time period. The Investigator shall ensure that all persons assisting with the study are adequately informed about the protocol, the MN4000 device and their study related duties.
- A qualified physician delegated as the Investigator will be responsible for all study related duties and functions. During a subject's participation, the Investigator/Institution shall ensure that adequate medical care is provided to the patient for any adverse event.
- The Investigator shall have written and dated approval from the IRB for the protocol, informed consent 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 shall conduct the study in compliance with the protocol agreed to by the Sponsor. The Investigator shall sign the protocol or

alternative contract to confirm agreement. The Investigator shall 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 MN4000 devices that are placed with the Investigator/Institution. When it is allowed, the Investigator may delegate Device accountability to another appropriate individual on the study team. 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 MN4000 device should be stored as specified by the Sponsor and applicable regulatory requirements. The Investigator shall ensure that the individual Device is demonstrated and/or used in accordance with the approved protocol and device manual/instructions for use. If appropriate and applicable, the Investigator or designee shall explain the correct use of the MN4000 device to each patient.

- In obtaining and documenting informed consent, the Investigator must comply with the applicable regulatory requirements and shall 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, shall disclose any financial interests that could affect the reliability of the data.

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

- The Investigator shall 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 shall 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) shall be reported immediately to the Sponsor and per the local IRB's reporting policy at that site. The initial reports shall be followed by more detailed reports if more information becomes available. If the study is

terminated prematurely or suspended for any reason, the Investigator shall 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 shall use an unambiguous patient identification code that allows for de-identification of all the data reported for each patient.

- The Sponsor shall 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 shall 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 shall 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 shall 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 shall 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.

11.0 References

1. Patel P, Garcia JA, 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?*, in *North American Cystic Fibrosis Conference 2013*. 2013, Pediatr Pulmonol. p. 359.

2. Morgan S, Honick C., Willford L, et al. *Continuous high frequency oscvillation therapy in mechanically ventilated patients in the pediatric intensive care unit*. in *AARC Congress 2014*. 2014. Las Vegas, NV.

3. Hsieh J, Prickett M, Willis N, et al. A comparison of positive pressure modalities in respiratory therapist driven protocol for patients post anatomic lung resction. Respir Care, 2014. 59(10): p. OF2.

4. Ortiz-Pujols, S., et al., *Chest high-frequency oscillatory treatment for severe atelectasis in a patient with toxic epidermal necrolysis.* J Burn Care Res, 2013. **34**(2): p. e112-5.

5. Withers L, Finch GC, Price KJ, er al. *Use of a progressive pulmonary protocol in an oncology intensive care unit*, in *Resp Care Open Forum 2009*, Resp. Care, 2009.

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

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

8 Modi AC, Quittner AL. *Validation of a disease-specific measure of health-related quality of life for children with cystic fibrosis.* J Pediatr Psychol. 2003 Dec;28(8):535-45.

9 Cedarbaum JM, Stambler N, Malta E, et al., The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). J Neurol Sci. 1999. 169(1-2): 13-21.