Title: Evaluating High Flow Humidification Therapy in Patients with Cystic Fibrosis

NCT #: NCT02129803

Document date: May 25, 2016

Document Type: Protocol and Statistical Analysis Plan

Evaluating High Flow Humidification Therapy in Patients with Cystic Fibrosis

Protocol Number: HM20002205
NCT02129803

Sponsor: Virginia Commonwealth University

Funding Support: Fisher & Paykel Healthcare

Investigators: Bruce K. Rubin, MEngr, MD,MBA, FRCPC (Principal Investigator)
H. Joel Schmidt, MD (Co-Principal Investigator)
Michael S. Schechter, MD, MPH (Sub-Investigator)
Nauman A. Chaudary, MD (Sub-Investigator)
Ronald W. Williams, Jr., MD (Sub-Investigator)

Sites: Children's Hospital of Richmond at VCU/VCU Medical Center
Main Hospital, 7th Floor – Pediatric Services
1250 East Marshall Street
Richmond, Virginia 23298-5051, United States

Children's Hospital of Richmond at VCU
Children's Pavilion
1000 East Broad Street
Richmond, Virginia 23298-0270, United States

VCU Medical Center
Critical Care Hospital, 3rd Floor
1213 East Clay Street
Richmond, Virginia 23298-5071, United States

VCU Health Systems
3470 Mayland Court
Henrico, Virginia 23233-1468, United States

INTRODUCTION

Mucus secretion and clearance is the primary physical defence of the airway epithelium.[1] Although mucus plays a defensive role, secretion retention is a common but serious problem in patients with chronic lung disease such as cystic fibrosis (CF).[3] Poor ion transport and rapid respiratory rate are thought to play a role in secretion hypohydration in the CF airway and this is thought to contribute to poor mucus clearance, increasing pulmonary symptoms (pulmonary exacerbation), poor sleep quality and a reduction in quality of life (QoL).[4] We have recently shown that high-flow, heated and humidified air delivered by a nasal cannula (HHNC) improves mucociliary clearance and clinical outcomes in young children requiring chronic mechanical ventilation.[5] To date, nocturnal HHNC (without supplemental oxygen) therapy has not been studied in individuals diagnosed with CF but previous laboratory research suggests that this could be safe and beneficial.[6]

HYPOTHESIS

It is hypothesized that HHNC delivered at 20 liters per minute (LPM) via Optiflow™ cannula and AIRVO™2 device may favorably affect the physical properties of the sputum and improve the subject's ability to clear secretions, resulting in beneficial clinical effects and improved quality of life.

STUDY OBJECTIVES AND ENDPOINTS

Primary Objectives

- To evaluate the effectiveness of 20 LPM HHNC therapy (Optiflow™ cannula and AIRVO™2 device) – experimental therapy versus 5 LPM HHNC therapy (Optiflow™ cannula and AIRVO™2 device) – control therapy on physiological outcomes in hospitalized subjects with cystic fibrosis during an acute exacerbation.

Secondary Objectives

- To determine if the experimental therapy has an effect on Quality of Life as measured by the Cystic Fibrosis Questionnaire - Revised (CFQ-R) compared to control therapy
- To determine the effect of the experimental therapy on sleep duration using actigraphy (Actiwatch® 2) and subjective sleep quality measured by the Leeds Sleep Evaluation Questionnaire (LSEQ) compared to control therapy
- To determine the effect of the experimental therapy on Quality of Life in respect to nasal dysfunction as measured by the Sino-Nasal Outcome Test (SNOT-20) compared to control therapy
- To determine the effect of the experimental therapy on comfort and ease of use using the non-validated comfort survey (VAS score) compared to control therapy

Primary Endpoints

- Change in sputum volume, cough transportability and hydration (% solids)
- Change in FEV_1 % predicted from admission to end of study.

STUDY DESIGN

The study is a single-center, randomized pilot study to evaluate the clinical effectiveness 20 LPM HHNC (Optiflow™ cannula and AIRVO™2 device) experimental therapy, versus 5 LPM HHNC (Optiflow™ cannula and AIRVO™2 device) control therapy, on specified outcomes in hospitalized subjects with cystic fibrosis during acute exacerbation.

Potential subjects will be identified in clinic before admission to the Children's Hospital of Richmond at VCU (CHoR) or Virginia Commonwealth University Medical. If potential subjects are not identified in clinic, they will be introduced to and informed of the study by a member of the study team within 24 hours of hospital admission.

Assent from a subject will be obtained if they are aged 10 to 17 years along with informed consent from the eligible subject's parent or legal guardian. Informed consent will be obtained from subjects aged 18 years or older. All informed consent/assent discussions will take place in a private room and be documented according to the Pediatric Research Office's 'Informed Consent Process Cover Sheet'. Potential subjects and family members will be given as much time as necessary to determine if they would like to participate in the study. No study team member will be present during this period to minimize any possible coercion.

After informed consent is obtained the subject will be assigned a unique 'Subject Identification Number.' This number will consist of 'VCUFP##', where the first subject will be 'VCUFP01', the second 'VCUFP02', and so forth. This unique identifier will be used instead of the subject's name, birth date, etc., to identify the subject for all study records and data.

After Subject Identification Number assignment is performed, randomization will occur. The study team will use the website www.randomization.com to randomize 30 study conditions (15 experimental and 15 control). The Study Coordinator will follow the randomization table chronologically as new subjects are consented.

This study is designed to accommodate 30 subjects (15 subjects per group) (Table 1). The study population will be determined from previously diagnosed CF patients who receive their CF care at CHoR and Virginia Commonwealth University. Subjects will be aged 10 years and older who are experiencing a CF exacerbation that requires hospital admission and therapy.

Table 1
STUDY DESIGN

Study Group	Assigned Intervention	Total Number of Subjects
Control Therapy	Low-Flow, 5 LPM (via Optiflow™ cannula) Heated (34°C), humidified air	15
Experimental Therapy	High-Flow, 20 LPM (via Optiflow™ cannula) Heated (34°C), humidified air	15

If a subject requests to withdraw from the study at any point, they are asked to inform the study doctor. Withdrawal from the study will not affect standard treatment the subject will receive for their CF exacerbation or ongoing treatment they may require. Upon withdrawal, the subject will forfeit any compensation for study participation.

Study subjects may be involuntarily removed from the study if the study doctor believes that they are not complying with the study protocol and/or the study doctor believes it is in the best interest of the subject to stop participation.

Study devices/equipment

The experimental therapy will be administered using Optiflow™ nasal cannula with the AIRVO™2 humidifier. The AIRVO™2 device will heat and humidify ambient air and the Optiflow™ nasal cannula will deliver the heated (approximately 34°C) and humidified air via the nares at a flow of 20 LPM.

Fisher & Paykel Healthcare manufactures the Optiflow™ nasal cannula and the AIRVO™2 device. The Optiflow™ nasal cannula and AIRVO™2 device are being provided by Fisher & Paykel Healthcare for the study with no cost to the study subject. In addition, the subject will not be subjected to any further costs associated with the study. The study devices will only be able available for use by the subjects that are enrolled in the study. The subject will be required to return the study device at the conclusion of the subject's study involvement, or when the subject is discharged from the hospital (whichever occurs first).

The control therapy will be administered using Optiflow™ nasal cannula with the AIRVO™2 device. The nasal cannula will deliver heated (approximately 34°C) and humidified air into the subject's nares at a flow of 5 LPM. This aims to mask the experimental and control therapy from the subjects and investigators.

Subjects will be educated by the study coordinator on how the device works and how to set up the nasal cannula appropriately. Subjects will be instructed to sleep with the designated nasal cannula and device as instructed during their hospitalization, for a maximum of five nights. The time the device is placed in the subject's nares and the time when the device is turned on will be recorded regardless of the intervention group to which the subject is assigned. The nursing staff will be instructed to check that the individual is wearing the device (either experimental or control) appropriately throughout the entire night. Should the nursing staff notice the nasal cannula being worn incorrectly the nurse will attempt to correctly reposition without disturbing the subject or if this is not successful the subject will be awakened to ensure correct cannula placement. Following the overnight intervention, the nasal cannula will be removed from the device and washed with warm water and mild dish washing detergent. After rinsing with clean water the nasal cannula will be stored in a clean zip locked bag taped to the device during periods of non-use.

At study conclusion for each subject (Table 2. Study Procedures), the device will be cleaned and sanitized per manufacturer's guidelines. While not in use, the devices will remain clean/sanitized and stored appropriately within in the hospital facility.

Eligibility Criteria

Individuals must meet all of the inclusion criteria listed below in order to be considered as a potential study subject.

Inclusion Criteria:

- Confirmed diagnosis of CF
- Hospital admission for acute pulmonary exacerbation of CF
- 10 years of age or older
- Is able to comply with the procedures scheduled within the protocol
- Provide informed consent/assent

If an individual is eligible as defined by the inclusion criteria but is found to meet any of the exclusion criteria listed below, they will not be permitted to enroll in the study.

Exclusion Criteria:

- Receipt of any aerosolized experimental or investigational drugs within 1 month of enrollment
- History of ENT surgery, nasal bleeding or nasal polyps within 6 months of starting study
- Requires supplemental oxygen
- History of obstructive sleep apnea
- History of pressure headaches requiring therapy within 1 month of enrollment
- Other medical or psychological conditions in which the study doctor(s) believe(s) would inhibit the individual from being an appropriate study subject.
- Has any contraindications to HHNC as listed below:
    - Maxillofacial trauma
    - Complete nasal obstruction
    - Presence of suspected base of skull fracture
- Any contraindication that applies to CPAP/ NIV therapy

STUDY PROCEDURES

The study requires clinical observations and overnight intervention therapy for/up to the first 5 nights of hospitalization. The study procedures to be performed on/by each subject enrolled in the study are outlined in Table 2.

Table 2
STUDY PROCEDURES

Time point	Procedure/Assessment
SCREENING (Day 0) **(In CF Clinic or within 24 hours of hospital admission)**	• Admission into the Children's Hospital of Richmond or MCV Hospital for adult subjects (hospital). • Introduction to study and review the study procedures/study device with the study coordinator and/or study doctor • Verification of inclusion/exclusion criteria and signing of Informed Consent Document. • Assignment of the unique Subject Identification Number • Review of medical history and treatment records • Baseline tests (as part of standard of care as medically indicated) • Completion of the Leeds Sleep Evaluation Questionnaire (LSEQ) by subject. • Completion of the CF-specific health related quality of life survey (Cystic Fibrosis Questionnaire – Revised (CFQ-R) by subject. • Completion of the Sino-Nasal Outcome Test (SNOT-20) by subject. • Sputum sample collection (if possible) • Randomization to intervention - either: 'Control Therapy' (*Low Flow, heated and humidified air delivered at 5 LPM via Optiflow™ cannula and AIRVO™2 device))* or 'Experimental Therapy' *(High-Flow, heated and humidified air delivered at 20 LPM via Optiflow™ cannula and AIRVO™2 device)*
BASELINE Day 1 (Approximately 9:00 AM)	• The device will be turned off (unless the subject has awakened earlier, in which case the subject can turn off the device when they wake). • Sputum sample will be collected (where possible) or collection of previously produced sputum to research laboratory by study coordinator by 10:00 AM. • Study coordinator will ensure that the nasal cannula is removed from the device and washed with warm water and mild dish washing detergent and rinsed thoroughly with clean water. The study coordinator will then place the nasal cannula in a clean zip locked bag taped to the device until required. • Completion of the Leeds Sleep Evaluation Questionnaire (LSEQ) • Completion of the device comfort survey (VAS Score). • The study coordinator will collect the device log, and review the previous night's medical records (including any test results or medication dispensed).
TREATMENT PHASE Day 2 – 5 (PM)	• There will be no collection of produced sputum during this time. • There will be no surveys completed during this time. • The study coordinator and/or the study doctor will continue to review the subject's treatment and medication records.

Table 2
STUDY PROCEDURES

Time point	Procedure/Assessment
	• Subjects will be allowed to go to sleep at whatever time they choose but must turn on the device before sleep onset and leave it on throughout the sleep period. • The nursing staff will be instructed to ensure the subject continues to wear the device during the night. If for some reason the device comes off, or is turned off, the nurse will record the event and will attempt to correctly reposition without disturbing the subject or if this is not successful the subject will be awakened to ensure correct cannula placement. ***If the subject is discharged between Day 2 – Day 5, then the date of discharge will follow the 'Discharge' study procedure in place of the 'Treatment Phase' study procedure***
DISCHARGE Day 6 (AM)* ***(*or earlier if discharged prior to 5 days of treatment)***	• The device will be turned off (unless the subject has wakened earlier), in which case the subject can turn off the device when they wake. • Sputum sample will be collected (where possible) or collection of previously produced sputum to research laboratory by study coordinator by 10:00 AM. • Subject will remove Actiwatch® 2 and Study Coordinator will download Actiwatch® 2 data • Completion of the Leeds Sleep Evaluation Questionnaire (LSEQ) by subject • Completion of the CF-specific health related quality of life survey (Cystic Fibrosis Questionnaire – Revised (CFQ-R) by subject • Completion of the Sino-Nasal Outcome Test (SNOT-20) by subject • Completion of the device comfort survey (VAS Score) by subject. • The study coordinator will collect the device log, and review the previous night's medical records (including any test results or medication dispensed). • A follow-up appointment in the CF clinic will be scheduled according to the study doctor's recommendations (as part of standard care). • The subject will be reminded to call the study coordinator or the study doctor if there are any new problems, questions or concerns once discharged from the hospital.
Clinical Follow-up Appointment	• The study coordinator and/or the study doctor will review the medical history and treatment records. • Baseline tests (as part of standard of care as medically indicated) • Completion of the Leeds Sleep Evaluation Questionnaire (LSEQ) by subject • Completion of the CF-specific health related quality of life survey (Cystic Fibrosis Questionnaire – Revised (CFQ-R) by subject • Completion of the Sino-Nasal Outcome Test (SNOT-20) by subject • Sputum sample collection (if possible). The sputum will be delivered to the research laboratory by the Study Coordinator • Study compensation

DATA HANDLING AND RECORD KEEPING

Power Calculation

No studies have evaluated the effect of high-flow HHNC therapy to improve sinopulmonary symptoms in CF. Thus, the current study is designed as a pilot study that is likely to be underpowered to reach significance.

Electronic Database Capture

Study data will be collected and managed using REDCap (Research Electronic Data Capture). REDCap is a secure web application designed to support data capture for research studies, providing user-friendly web-based case report forms, real-time data entry validation (e.g. for data types and range checks), audit trails and a de-identified data export mechanism to common statistical packages (JMP, SAS). REDCap also includes a powerful tool for building and managing online surveys. The database is hosted by VCU under award number UL1RR031990 from the National Center for Research Resources and NIH Roadmap for Medical Research, National Institutes of Health.

Only the study coordinators and the research assistants will have access to this password protected database.

With the exception of the 'Informed Consent/Assent' pages in the REDCap database, all subsequent pages will only identify the subject by the Subject Identification Number.

All hard copies of the signed Informed Consent/Assent documents will be kept in locked cabinet which is located in the study coordinator's locked office. A copy of the signed Informed Consent/Assent will be scanned into the subject's electronic medical record. Any other paper records that may be generated during the course of the study will be de-identified and labeled with the individuals Subject Identification Number and kept separated from the consent forms and locked in a cabinet in the study coordinator's locked office.

OnCore

OnCore is a clinical trial management systems (CTMS) which will be used for recording and tracking regulatory approvals, staff training and safety management (SAE tracking and IRB reporting). The CTMS system was developed by Forte Research and widely used across academic research universities nationwide. The program is a secure web-based system hosted by both the VCU and MCV health systems. Only fully-trained, credentialed employees of VCU have access to this database. The study coordinator will be the only individual (besides individuals that manage OnCore) with access to data entered for this study into the OnCore database.

SPUTUM SAMPLE COLLECTION AND PROCESSING

Sputum collection is needed for evaluation of biophysical properties.

The study coordinator will ask the study subject to cough sputum into a provided, sterile sample cup at 9:00 AM according to the schedule of events outlined in Table 2. Study Procedures. If the subject is able to produce sputum before this time, they will be provided the sterile sample cup and the sputum collected. All sputum samples will be transported on ice to the research laboratory as soon as possible on the day of screening and at follow-up. At baseline, intervention, and discharge, sputum will be delivered to the research laboratory on ice by 10:00 AM.

All sputum samples will be identified by the Subject Identification Number and the applicable time-point only.

SPUTUM SAMPLE ANALYSIS

All collected sputum samples will be used for cough transport and mucus hydration measurements.

In vitro cough transportability

A simulated cough machine is used to measure the airflow-dependent clearability of sputum. A model Plexiglas "trachea", rectangular in cross section (1.2 x 2 cm) is connected to an 8 L tank containing air pressurized to 8 psi giving a flow of about 11 L/s. A solenoid controls air release through a flow constrictive element used to mimic the airflow pattern of a natural cough. A sinusoidal constriction (length 7.7 cm and height 8 mm) is used to decrease the airway diameter while minimizing the turbulence (Reynolds number) of the system. A sample, 40 µl in volume and 0.5 mm in depth, is placed in a thin line across the base of the Plexiglas trachea. The bulk transport of the sample is measured in mm after a single cough maneuver. Three successive measurements are made and the results averaged (3).

Mucus hydration (% solids), and mucus density

A mucus sample is weighed in a microbalance and dried for 4 hours in a lyophilizer. The dried sample is then reweighed in order to calculate the percent solids composition. The density of the mucus is also calculated by dividing the weight of the sample by the volume. As the density of mucus should be 1.00 ± 0.15, this measurement is used as a check on the validity of the hydration measurement.

SLEEP DURATION ANALYSIS

Actigraphy provides a precise measurement of the motion of the part of the body to which a device is attached. Sleep/wake patterns will be recorded using the Actiwatch® 2. The data collected by the Actiwatch® 2 will provide objective and reliable data of the subject's sleep/wake patterns during the study period without influence. The unique Subject Identification Number assigned at Day 0 will be the only identifier linking the subject and the actigraphy data. The device is similar in size to a wrist watch and is well-suited for use with younger subjects or those sensitive to wrist-worn devices. The data collected will be downloaded into a software program "Actiware". This software will be located on the Coordinator's password protected computer. The data will then be scored and analyzed into predetermined intervals that will identify the epoch as either periods of wake or sleep. Statistics including Time in Bed (TIB), Total Sleep Time (TST), Wake After Sleep Onset (WASO), Sleep Efficiency (SE), Number of Wake Bouts (NWB) and Sleep Onset Latency (SOL) can be tracked over the study period.

Data Analysis

Statistical analysis of data will be performed using the JMP Pro 10 statistics package (SAS Institute, Cary, NC). Normality of data distribution will be visually checked and normally distributed data will be compared using two-tailed t-test and ANOVA. A $p < 0.05$ will be considered statistically significant. All results will be presented as means + the standard error of the mean.

QUALITATIVE EVALUATION

One sleep and three separate quality of life evaluations will be administered at various time-points according to Table 2 - Study Procedures. The information provided by the questionnaires will be transposed into the REDCap database by the study coordinator. All paper documents will be de-identified, the only identifier is the Subject Identification Number, which is kept in a locked cabinet, in the study coordinator's locked office.

Leeds Sleep Evaluation Questionnaire (LSEQ)

The Leeds Sleep Evaluation Questionnaire (LSEQ) is a 10-item, subjective, self-report, 5-10 minute paper and pencil measure designed to assess changes in sleep quality over the course of a psychopharmacological treatment intervention. The scale evaluates four domains: ease of initiating sleep, quality of sleep, ease of waking and behavior following wakefulness using paper and pencil. Developers initially validated the LSEQ in individuals aged 18-49 years. In the evaluation "initiating sleep" and the "quality of sleep" factors were correlated with one another while "awakening from sleep" and "behavior following wakefulness" factors were also correlated. Of the validated scales available to use for this study the LSEQ appears to be the most appropriate given the study being conducted.

Cystic Fibrosis Questionnaire-Revised (CFQ-R)

The Cystic Fibrosis Questionnaire-Revised (CFQ-R) is health-related quality of life (HRQoL) measure for children, adolescents and adults with CF. Initially it was developed through interviews with CF patients and healthcare providers and various focus groups and has since undergone comprehensive reliability and validity testing. This revised questionnaire is one of the most widely used HRQoL tests for CF. The CFQ-R measures how well an individual functions in a variety of domains, including Physical Functioning, Vitality, Health Perceptions, Respiratory Symptoms, Treatment Burden, Role Functioning, Emotional Functioning, and Social Functioning. This questionnaire is written for the intended age group in regards to language and length of questionnaire.

The Sino-Nasal Outcome Test (SNOT-20)

The Sino-Nasal Outcome Test 20 (SNOT-20) is a validated, health-related quality of life (HRQoL) questionnaire designed to determine the impact of nasal dysfunction on an individual's social/emotional health. This test consists of 20 questions and asks patients to assess nasal symptoms, emotion, and activity on a scale of worsening symptoms scored 1 through 7 to provide a quantifiable score capable of disease severity.[1,2]

Non-validated device comfort survey (VAS score)

The non-validated device comfort survey used for this study will be conducted using a VAS score. The VAS (visual analog scale) will be used to measured characteristics, such as pain, that cannot be directly measured. The subject will be asked to point to a face depicting various levels of pain on a VAS that corresponds to the associated pain level when on HHNC and high-flow therapies.

ETHICS

Institutional Review Board

This protocol and any accompanying material to be provided to a potential subject (such as advertisements, information sheets, or descriptions of the study used to obtain informed consent) will be submitted to an IRB by the investigators and approval from the IRB must be obtained prior to starting the study. This approval will be documented in a letter to the investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and the date on which the committee met and granted the approval.

Any amendments made to the protocol after receipt of IRB approval must also be submitted to the IRB for approval prior to implementation, if appropriate or the study must be paused and no further recruitment made until approval of the amendments has been granted. All related correspondence and IRB approved documents will be retained in a regulatory binder located in a locked cabinet in the study coordinator's locked office.

Code of Conduct

This study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations for Medical Sciences 2002), Guidelines for Good Clinical Practice (International Conference on Harmonization 1996), and the Declaration of Helsinki (World Medical Association 2008). In addition, the study will be conducted in accordance with the protocol, the International Conference on Harmonization guideline on Good Clinical Practice, and applicable local regulatory requirements and laws.

All members of the study team have completed the necessary Collaborative Institutional Training Initiative at the University of Miami (CITI) training. This program also includes Good Clinical Practice training. All copies of the study team member's certificates of completion as well as their current medical license and Curriculum Vitae will be maintained in the study regulatory binder.

LITERATURE CITED

1. Pynnonen MA, Kim HM, Terrell JE. Validation of the Sino-Nasal Outcome Test 20 (SNOT-20) domains in nonsurgical patients. Am J Rhinology & Allergy. 2009 Jan-Feb;23(1):40-5

2. Rudnick EF, Mitchell RB. Long-term improvements in quality-of-life after surgical therapy for pediatric sinonasal disease. OTO HNS 2007;6:873-877.

3. Agarwal M, King M, Rubin BK, Shukla JB. Mucus transport in a miniaturized simulated cough machine: Effect of constriction and serous layer simulant. Biorheology. 1989; 26:977-88

4. Rubin BK. Mucus, phlegm, and sputum in cystic fibrosis. Resp Care, 2009;54:726-32.

5. McNamara DG, Asher MI, Rubin BK, Stewart A, Byrnes CA. Heated humidification improves clinical outcomes compared to a heat-and-moisture exchanger in children with tracheostomies. Respir Care. 2014;59:46-53.

6. Voynow JA, Rubin BK. Mucus, mucins, and sputum. CHEST 2009;135:505-512.