Title: Nasal High Flow (NHF) therapy use following hospitalization for an exacerbation of COPD: A feasibility study

Acronym: N3ADS (Nasal high flow therapy 30 day readmission Study)

Study Phase: III

Sponsor: Fisher and Paykel Healthcare Limited, New Zealand

Principal Investigator: Doctor James FINGLETON

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1. REVISION HISTORY

Author	Revision	Date	Description of change
Janine Pilcher Sheng Feng	A	04/MAR/2015	First release, this revision of the document is also known as the REV_A_04MAR2015 referenced in the clinical research agreement and insurance agreement.
Janine Pilcher Sheng Feng	B	09/APR/2015	Revisions based on reviewer comments prior to NZ HDEC submission.
Janine Pilcher Sheng Feng	C	30/APR/2015	Revision to spirometry wording and time frame for recruitment
Janine Pilcher Sheng Feng Melanie Moylan	D	24/AUG/2015	Revisions based on review by Melanie Moylan (for detail see tracked changes document)
Janine Pilcher Melanie Moylan James Fingleton	E	20/NOV/2015	Revisions to oxygen titration methodology, time windows for phone calls and visits, event reporting, point of enrolment and training requirement. The clinical trials registration number has been added. Minor formatting changes to differentiate protocol from F&P internal documents. In addition, James Fingleton is to be made the new PI.

2. LIST OF ABBREVIATIONS

AE	Adverse Event
AECOPD	Acute Exacerbation of Chronic Obstructive Pulmonary Disease
COPD	Chronic Obstructive Pulmonary Disease
CIP	Clinical Investigation Plan
CRF	Case Report Form
ED	Emergency department/Emergency room
FEV1	Forced expiratory volume in 1 second
FVC	Forced Vital Capacity
GP	General Practitioner
IRB	Institutional Review Board
IEC	Independent Ethics Committee
NHF	Nasal High Flow
NZ	New Zealand
PI	Principal Investigator
SAE	Serious Adverse Event
SVC(in)	Slow Vital Capacity (inspiratory)
USA	United States of America

3. MONITORING ARRANGEMENTS AND DATA MANAGEMENT

3.1. Monitoring arrangements

Site/clinical monitoring to assure high quality trial conduct will be conducted by Fisher and Paykel Healthcare or its representative. "On site" monitoring of individual case histories, assessment of adherence to the protocol, ensure the ongoing implementation of appropriate data entry and quality control procedures, and general assessment of adherence to good clinical practices.

The monitor will be allowed, on request, to have access to all source documents needed to verify the entries on the CRF and other protocol-related documents; provided that subject confidentiality is maintained in agreement with international, national and local regulations. It will be the monitor's responsibility to inspect the CRF at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them.

The investigator's file will contain the protocol/amendments, financial disclosure form, CRFs and data clarification and query forms, HREC approval with correspondence, informed consent, staff curriculum vitae and authorization forms, screening and enrolment logs, and other appropriate documents/correspondence as per ICH/GCP and local regulations.

3.2. Data Management

Both physical and electronic copies of forms will be kept by the sponsor at FPH.

4. INVESTIGATOR INFORMATION

4.1. Primary Investigator

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4.5. Other

WHO Universal Trial Number (UTN): U1111-1158-9792
ClinicalTrials.gov Identifier: NCT02552732

5. SPONSOR INFORMATION

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6. DEVICE INFORMATION

6.1. Identification of the Medical Device

myAIRVO 2 is a humidifier with integrated flow generator that entrains room air and prescribed medical gases. The device then humidifies these gases through a chamber, which are delivered to the patient via a nasal cannula 'Optiflow+™' via a heated breathing tube, as depicted in figure1 below. Collectively both the device and the cannula deliver NHF therapy.

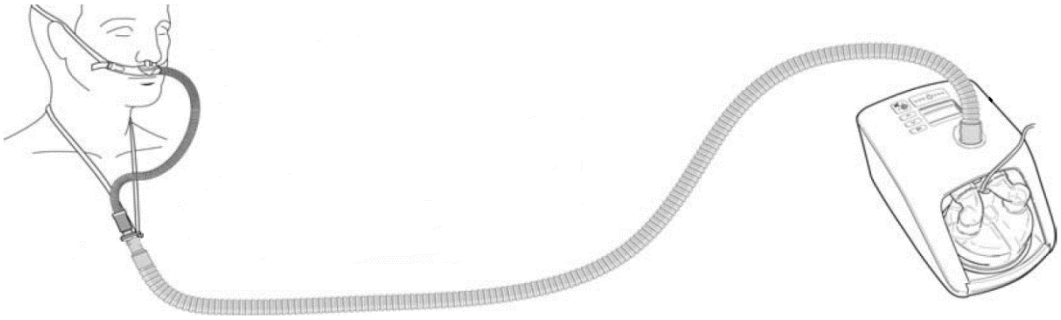

Figure 1 'myAIRVO 2 and Optiflow+ cannula'

myAIRVO 2 is designed to deliver heated and humidified gas over a range of temperature settings (31°C, 34°C and 37°C) and variable flow rates (10 to 60 L/min). These settings help preserve compliance with the treatment regimen.

6.2. Device Risk Analysis and Management

The AIRVO 2 series devices (including myAIRVO 2) are designed and released to market, in accordance to the FPH design control procedures incorporating a Risk Management File, and governed by the medical device industry Standards:

- ISO-13485:2003 (Quality Systems - Medical Devices - Particular Requirements); and
- ISO-14971:2007 (Application of Risk Management to Medical Devices).

7. JUSTIFICATION FOR A CLINICAL TRIAL

7.1. Synopsis

The aim of this feasibility study is to provide data for a subsequent randomized controlled trial to investigate if patient outcomes will be improved after an acute COPD exacerbation using domiciliary NHF compared to standard care. This feasibility study will investigate the following: process, resources, management and scientific aspects of delivering NHF as an adjunct therapy in COPD patients.

7.2. Literature Review

Chronic obstructive pulmonary disease (COPD) affects around 15% of the adult population of New Zealand, with AECOPD resulting in more than 9,000 hospital admissions per year.[1] The burden of COPD is recognized internationally with high admission and readmission rates reported in the United States of America (USA),[2] Europe[3 4] and Australia.[5]

There is increasing interest in the provision of NHF therapy to improve outcomes in patients with COPD. The myAIRVO 2 device is designed to deliver heated and humidified gases to provide respiratory support. Previous research in patients with COPD and bronchiectasis, has demonstrated to significantly reduce exacerbation days and time to first exacerbation, as well as improve lung function and quality of life.[6]

myAIRVO 2 may provide direct benefit to patients recovering from AECOPD by providing airway hydration, improving mucocilliary clearance[7] and increasing nasal temperature (to 37°C) which may reduce the risk of subsequent infection.[8] As well as improving clinical outcomes, NHF therapy may reduce readmission rates conferring significant economic benefits. In the USA, 21% of admissions to hospital with AECOPD are followed by readmission within 30 days, and the costs of a second hospital stay are consistently higher when compared with the original admission.[2] The proportion of patients that are readmitted within 30 days with a primary diagnosis of AECOPD in the USA is 7%.[2] This is similar to New Zealand data, where 8% of patients are readmitted with a primary diagnosis of AECOPD within 30 days of discharge, and 14% within 60 days (based on recent Wellington Regional Hospital audit data).[9]

In preparation for a randomized controlled trial powered to detect change in readmission rates, this study will inform an appropriate myAIRVO 2 prescription for COPD patients, recruitment rate projection and aspects of the trial design that need to be changed to increase the quality of data collection and patient compliance.

Should NHF therapy be demonstrated as an effective and well tolerated intervention to reduce hospital readmissions and improve symptoms following AECOPD, NHF therapy could be considered an effective and routine treatment option on discharge.

7.3. Preclinical Testing

Appropriate pre-clinical testing and data evaluation was carried out as a part of the product release for the AIRVO 2 series. The AIRVO 2 series is cleared for both hospital and home use by the FDA, and as this study only involves unmodified devices used as per intended use, further preclinical/safety testing is not required for this feasibility study.

7.4. Previous Clinical Experience

The AIRVO 2 series has been and is currently used for delivering NHF therapy to COPD patients, worldwide (including New Zealand and USA), in health care and domiciliary settings since 2013.

7.5. Justification for Administration

Participants will be asked to use myAIRVO 2, for participants on domiciliary oxygen, the oxygen will be delivered via the device (see section 9.10.04). Participants will not be given a specific time period to wear the device, but encouraged to use the therapy every day as much as possible without impacting on their daily routines. The first day after discharge will be classed as day one of the study. NHF therapy will be monitored from day one for a period of 30 days.

For all participants NHF therapy will be initiated at 25L/min with a the temperature setting of 37°C. All participants have the ability to reduce the temperature setting to 34°C. In participants who are not prescribed oxygen there will be the further option to increase or decrease flow rates (up to 30L/min or down to 20L/min). These modifications are to assist with comfort and adherence. Patients who are prescribed domiciliary oxygen flow rates will remain constant to deliver a more consistent concentration of oxygen.

The outcomes of this study will inform the appropriate methodology for subsequent randomized control trials to investigate the efficacy of NHF therapy in the long-term management of COPD patients. Given this, therapy settings, compliance to the therapy in this feasibility study are modifiable to gain maximum understanding of therapy usage.

8. OBJECTIVES OF THE CLINICAL INVESTIGATION

8.1. Hypothesis

This is a feasibility study to assess the process, resources, management and scientific aspects of NHF therapy use following discharge from hospital post AECOPD. This will inform the randomized controlled trial design to ensure methodological robustness.

8.2. Objectives

The objectives of the study:

1. To estimate the duration of use of the device including the mean hours of use per day and number of days use, to inform an daily myAIRVO 2 prescription for the proposed randomized controlled trial
2. To estimate the proportions of potential participants who could proceed to the proposed randomized controlled trial
3. To estimate the proportions of potential participants who would require oxygen delivery through myAIRVO 2 in the proposed randomized controlled trial
4. To estimate aspects of the use of myAIRVO 2 after discharge and to in particular estimate patient ratings of ease of use, and the proportion of those who required changes to initial settings of temperature and flow, and the magnitude of these changes, to inform prescription design for the proposed randomized controlled trial
5. To estimate particular clinical outcomes relevant to the planned randomized controlled trial, including hospital readmission, Emergency Department (ED visit) and General Practitioner (GP) visit rates.

8.3. Population

One hundred patients admitted to hospital with an AECOPD. Participants will be recruited from two sites: Wellington Regional Hospital, New Zealand (20 participants) and Alana Healthcare, USA (80 participants). Please see section 9.8 for details of inclusion/exclusion criteria.

8.4. Risks & Benefits

NHF therapy delivered by myAIRVO 2 may provide direct benefit to patients recovering from AECOPD by providing overnight respiratory support, improvement in mucocilliary clearance[7] and increased nasal temperature (to 37°C) which may reduce the incidence of subsequent infection.[8]

myAIRVO 2 operates according to the principle of all active respiratory gas humidifiers by artificially conditioning inspiratory airflow with heat and humidity.

The risk of using an active humidifier are electric shocks, burns of the patient and tubing melt down. The risks stated above are associated with any medical device, which uses electrical power for heating/warming. These risks are minimized as myAIRVO 2 is CE marked and has FDA Premarket Approval (PMA) clearance. The use of the device is in accordance to the user instructions and participants will be instructed according to the user guide.

The risks of NHF therapy for patients who receive supplemental oxygen are inappropriate oxygen delivery, with the potential for hyperoxemia, carbon dioxide retention, or hypoxemia. These risks will be minimized by an initial oxygen assessment by the study physician, comprehensive education for participants and exclusion of participants who the investigator is concerned may be at risk of giving themselves incorrect oxygen delivery.

There is no contraindication known to the use of active humidifiers in patients.

8.5. Essential Requirements of the Relevant Directive

ICH GCP and Ethics Committee approval.

9. CLINICAL INVESTIGATION DESIGN

9.1. Type of Investigation

Feasibility study.

9.2. Controls

There is no control group required for this study.

9.3. Bias

The feasibility study is designed to inform a future randomized controlled trial. Therefore bias is not relevant for the outcomes of this study.

9.4. End Points

The following end points will be evaluated:

Primary outcome:
The primary outcome will be NHF use for 30 days following discharge after AECOPD. Use will be expressed as hours of myAIRVO 2 use per day over 30 days, as obtained by myAIRVO 2 electronic monitoring.

Secondary outcomes:

Other use variables:

i. Number of days of use, adjusted for number of days with myAIRVO 2 at home
ii. Average use per day of myAIRVO 2 during week 1, week 2, week 3 and week 4.
iii. Average use per day on days of myAIRVO 2 use

Withdrawals and exclusions:

i. Proportion of participants screened that were excluded
ii. Reason for exclusion
iii. Proportion of participants enrolled that were withdrawn
iv. Reason for withdrawal

Participants requiring oxygen delivery via myAIRVO 2:

i. Proportion of participants using domiciliary oxygen

Aspects of myAIRVO 2 use:

i. Proportion of participants who reported having reduced myAIRVO 2 flow settings from the initial flow
ii. Reduction in flow
iii. Proportion of participants who reported having increased myAIRVO 2 flow settings from the initial flow
iv. Increase in flow
v. Proportion of participants who reported having reduced myAIRVO 2 temperature setting from the initial setting
vi. NHF therapy Questionnaire results

Clinical outcomes

i. Proportion of participants with at least one hospital readmission within 30 days of discharge
ii. Reasons for hospital admissions (AECOPD, other respiratory cause or other cause)
iii. In those that had at least one hospital readmission:
    a. Number of readmissions
    b. Time to first hospital readmission
    c. Hospital readmission length
iv. Proportion of participants with at least one ED visit within 30 days of discharge
v. Reason for ED visits (AECOPD, other respiratory cause or other cause)
vi. In those that had at least one ED visit:
vii. Number of ED visits
viii. Time to first ED visit
ix. Proportion of participants with at least one GP visit within 30 days of discharge
x. Reason for GP visits (AECOPD, other respiratory cause or other cause)
xi. In those that had at least 1 GP visit within 30 days of discharge: number of GP visits
xii. LACE Index for hospital admissions
xiii. Lung function measurements (FEV_1, SVC_{in} and FVC) at day 1 and 31.

* An ED visit is counted if the patient went to ED for assessment and was not subsequently admitted to a hospital ward.

9.5. Variables

i. myAIRVO 2 electronic monitoring data (device usage)
ii. Number of exclusions
iii. Number of withdrawals
iv. Domiciliary oxygen use
v. Aspects of myAIRVO 2 use
vi. Clinical outcomes

9.6. Measurements

i. myAIRVO 2 electronic monitoring
ii. 30 day NHF therapy Diary
iii. NHF therapy Questionnaire
iv. Recording of events: myAIRVO 2 use, exclusions, withdrawals, and clinical outcomes
v. Spirometry

9.7. Equipment

i. Case report forms and questionnaires will be in paper format.
ii. Spirometry data will be collected using a handheld spirometer (Jaegar pneumotac spirometer with J-Lab software)
iii. De-identified data (Participant ID only) will be recorded on the CRFs will be scanned to Fisher and Paykel, who will then enter it onto a secure electronic study database.

9.8. Inclusion / Exclusion criteria

Participants will be 18 years of age or older
Participants will be admitted to the respiratory ward(s) of either recruiting hospitals with AECOPD as the primary diagnostic reason for admission. They will be excluded if:

i. They are given a new domiciliary oxygen prescription during the current hospital admission
ii. The investigator believes the participant or their care giver will be unable to safely use myAIRVO 2 device following discharge
iii. They have any other condition which, at the investigator's discretion, is believed may present a safety risk or impact the feasibility of the study or the study results

9.9. Point of Enrolment

Participants will be considered enrolled and part of the study population at the time the inclusion and exclusion criteria have been met on the first visit in hospital. This will be after the Consent Form has been signed by both the Participant and Study Investigator.

9.10. Patient Procedure

9.10.1. Flowchart

The flowchart of the study is shown in Appendix 1.

9.10.2. Interventions

a. Participants will be split into 2 groups (those on a domiciliary oxygen prescription at the time of study entry and those who are not) with both groups receiving NHF therapy by myAIRVO 2. Participants will be encouraged to use myAIRVO 2 as much as possible (day and night) each day without impacting on daily living activities. Participants who are prescribed domiciliary oxygen will use NHF therapy via myAIRVO 2 with supplemental oxygen delivered via the device (section 9.10.04).

b. Interventions will be initiated from the time the participant is enrolled in hospital, to aid familiarization and acclimatization, and used until 30 days following discharge. Note the day of discharge is defined as Day 0.

c. By default, NHF will be set at 25L/min at 37°C. However, all participants are able to lower the delivered temperature to 34°C. For participants without a domiciliary oxygen prescription they can also increase/decrease the flow rate (up to 30L/min or down to 20L/min). Participants who have domiciliary oxygen flow rates are fixed in order to deliver a more consistent concentration of oxygen to maintain oxygen saturation.

9.10.3. Pre-discharge assessments and training

a. Participants will be approached at least one day prior to expected discharge to ensure familiarity with NHF therapy prior to discharge. Written informed consent will be obtained (see participant information sheets and consent forms).

b. Demographic data collection will include: Date of birth, gender, year of COPD diagnosis, presence of alpha1 antitrypsin deficiency, other respiratory conditions, current medications, pack year history (a pack year is defined as twenty cigarettes smoked every day for one year, for a calculator see http://smokingpackyears.com/), LACE index score and if domiciliary oxygen is prescribed. The Investigator will update the Medical History Log and Medication Log. The last recorded spirometric values in the participant's clinical records will also be documented.

c. Participant inclusion and exclusion criteria (Section 9.8) will be assessed, and ineligible patients excluded.

d. Participants will be allocated a myAIRVO 2 device and the device serial number will be recorded.

e. A training session on how to use myAIRVO 2 will be performed by the study investigator (Appendix 2). The participants' next of kin will be encouraged to be present at this session. Familiarization and acclimatization to the device and the therapy will also be conducted prior to leaving the hospital. Where possible any issues regarding the device or therapy will be addressed prior to discharge. The participant will also be given the myAIRVO 2 user manual and 'Quick guide sheet' to read prior to the home visit and a phone number to contact the investigator with any questions during business hours.

f. For participants on oxygen only: If possible, oxygen saturation testing on the participant's usual home oxygen flow will take place during the hospital admission. The participant will be placed on their home oxygen prescription while sitting at rest for at least 5 minutes. Should the participant's oxygen saturation levels on their prescribed oxygen be <88% or ≥95% they will be withdrawn from the study and referred for review of their home oxygen prescription.

g. The investigator will confirm with the participant preferably on day of discharge, if they would still like to continue in the study. The Investigator will update the CRF, including the Medical Contact Log, Medical History Log, Medication Log and AE/SAE forms as required. The device plus consumables and any participant paperwork required for the study will be made available prior to discharge or taken to the patients home on the day of or day after being discharged from the hospital..

9.10.4. Post-discharge methods

a. A home visit will be made by an investigator on the day of or day after discharge. The investigator will:

i. Ensure the equipment is set up correctly and reinforce the previous training on myAIRVO 2. (Appendix 1).
ii. Check participants will have the myAIRVO 2 user manual and the 'Patient summary sheet' as an easy reference for device use.
iii. Perform lung function tests using a spirometer (Jaegar pneumotac spirometer with J-Lab software) according to ATS/ERS Taskforce standards.[10] [11] Participants will not be required to withhold bronchodilator medication prior to testing. The drug, dose and time of the last administration prior to spirometry will be recorded. This will inform COPD severity of participants and baseline lung function measurements.

b. Participants on domiciliary oxygen will have oxygen saturations recorded on simple nasal prongs according to their existing prescription. NHF therapy will then be initiated and oxygen will be titrated through myAIRVO 2 to determine the flow of oxygen delivery required to achieve the same oxygen saturation level (Section 9.10.04).

c. myAIRVO 2 devices will electronically record data on the date and time the device was used. Should participants change the flow of their myAIRVO 2 device (participants without domiciliary oxygen only) or alter the temperature, they will be asked to document this in their diary.

d. On the 3rd, 7th, 14th and 21st and 28th day post discharge the investigator will contact the participant by phone. Participants will be asked:

i. If they are having any problems using myAIRVO 2.
ii. If they have needed to return to the hospital, the reason and length of their hospital visit. These details will be checked against hospital records. In addition, they will be asked if they have needed to visit their GP or other allied health care practitioners and the reason. The Investigator will complete the CRF and the medical history log, concomitant medications log, medical contact log, adverse event/ serious adverse event forms as required.

e. On the 31st day post discharge an investigator will perform a home visit or the participant will visit the study investigator at their clinic office.

i. When the investigator contacts the participant on day 28th day post discharge they will confirm with the participant the home /office visit time on the 31st day post discharge and that their last period of myAIRVO 2 use is to commence on day 30 (the day before the home/office visit).
ii. At the home/office visit the NHF therapy Questionnaire will be administered.
iii. Participants will be asked whether they have had any hospital admissions and the length and cause for any admissions. These details will be checked against hospital inpatient records. In addition they will be asked if they have visited their GP or other allied health care practitioners. The Investigator will complete the CRF and the medical history log, concomitant medications log, medical contact log, adverse event/ serious adverse event forms as required.
iv. Lung function will be performed using a spirometer (Jaegar pneumotac spirometer with J-Lab software) according to ATS/ERS Taskforce standards.[10] [11] Participants will not be required to withhold bronchodilator medication prior to testing. The drug, dose and time of the last administration prior to spirometry will be recorded. This will inform if lung function has improved during the study.
v. The myAIRVO 2 device and associated equipment will be collected from the participant.

9.10.5. **myAIRVO 2 domiciliary oxygen assessment and prescription**

a. The participant will have their prescribed domiciliary oxygen flow rate recorded.

b. Oxygen saturation levels will be measured (Point A) by oximetry after at least 5 minutes at rest using standard nasal prongs with oxygen administered according to their prescription (Flow A). Should the participant's oxygen saturation levels be <88% or ≥95% they will be withdrawn from the study and referred for review of their home oxygen prescription.

c. NHF therapy will then be administered to the participant by myAIRVO 2 set at a flow rate of 25L/minute with supplemental oxygen delivered at Flow A for at least 5 minutes whilst the participant is at rest. Oxygen saturation levels will then be recorded.

d. While myAIRVO 2 is delivering 25L/min flow, oxygen will be titrated via the device by 0.5L/min every 5 minutes until the oxygen saturation levels measured at Point A (i.e. with the portable oximetry probe after sitting at rest for at least 5 minutes using standard nasal prongs with oxygen administered at Flow A) are equivalent. This flow rate will be used for supplemental oxygen delivered during NHF therapy via myAIRVO 2 throughout the study period.

e. An explanation will be given to the participant in respect to the risks and symptoms of hyperoxia, hypoxia, and hypercapnea, how to use myAIRVO 2 with correct oxygen flow rates, and how to change the oxygen flow between myAIRVO 2 and their standard nasal prongs (if required). They will also be provided with the "'Quick guide sheet' specific to patients on domiciliary oxygen.

f. If there is any clinical concern, the participant will be withdrawn from the study at the Investigator's discretion. This may include, but is not limited to, concern regarding ability to maintain oxygen saturations within a safe range, the participant's ability to understand the risks and symptoms of hypercapnia and hypoxia, and the participant's ability to administer oxygen safely within the prescribed regimen.

9.10.6. Excluded participants

All participant exclusions will be documented on the Participant eligibility_screening log

9.10.7. Associated documents

Documents associated with this methodology include:

1. Consent form and participation information sheet for New Zealand participants
2. Consent form and participant information sheet for USA participants
3. Case report forms:
    a. CRF NZ
    b. CRF US
    c. Medical history log
    d. Concomitant medications log
    e. Adverse event (AE) form
    f. Serious adverse event (SAE) form
    g. Medical contact log
4. NHF therapy diary oxygen
5. NHF therapy diary no oxygen
6. NHF therapy questionnaire
7. Participant eligibility_screening log
8. Participant enrolment_withdrawal log
9. Fisher and Paykel myAIRVO 2 user manual
10. Patient summary sheet oxygen NZ
11. Patient summary sheet oxygen US
12. Patient summary sheet no oxygen NZ
13. Patient summary sheet no oxygen US
14. Data collection SOP
15. myAIRVO 2 electronic monitoring SOP
16. Equipment provision SOP
17. Equipment log
18. LACE Index

9.11. Withdrawal Criteria

Participants are able to stop the intervention at any time, without being withdrawn from subsequent portions of the study. Participants may withdraw from the entire study at any time without giving a reason. Participants may be withdrawn at the discretion of the Investigator for any reason that is believed may present a safety risk.

9.12. Number of Trial Subjects

100 (20 from NZ and 80 from USA sites, respectively) subjects.

9.13. Follow up Plan

The device will be used for 30 days at home post discharge of AECOPD. Participant contact by phone will occur on the 3rd, 7th, 14th and 21st and 28th day post discharge to check whether the participant has any problems

using myAIRVO 2. At the end of the 30 days a further home visit or office visit (participant preference) will occur, a questionnaire will be administered and the device collected. Participants are also able to contact investigators during the study period by phone for assistance. When study visits and phone calls fall outside of the working week these should be rescheduled to take place +/- 1 day of the specified date.

The level and duration of follow up should permit the demonstration of performance over a period of time sufficient to represent a realistic test of the protocol and the myAIRVO 2 device.

9.14. Foreseeable Complications

There are no foreseeable complications with recruitment or completion of the study in general. All units have already been prepared for trial. Complications relating to adherence to the study protocol and NHF therapy use are outcome measures of this study.

10. CLINICAL TRIAL DOCUMENTATION

10.1. Consent and Recruitment

NZ specific and USA specific information sheets and consent forms are to be used, as approved by their local regulatory body.

10.2. Case Report Forms

The CRFs are to be filled in by hand, see Data Collection SOP. CRFs are to be scanned to Fisher and Paykel who will then entered data into an electronic database.

10.3. Insurance Statement

A copy of the insurance statement is shown in Appendix 3. This is to document that compensation to subjects(s) for trial related injury will be available

10.4. Record of Deviations

This version of the protocol has was completed prior to participant recruitment, there are no deviations to date.

11. STATISTICAL CONSIDERATIONS

11.1. Description of the Statistical Design

As this is a feasibility study the primary outcome variable (9.4.1) will be expressed as the mean number of hours per day used, with standard deviation. The mean may be weighted for time in the study and allocated 95% confidence intervals for each by weighted regression.

Continuous outcomes 9.4.2-4, 9.4.11, 9.4.13, 9.4.18c, and 9.4.26 will also be expressed as mean, standard deviation. Means may be weighted for time in the study and allocated 95% confidence intervals for each by weighted regression.

For the mean number of hospital readmissions (9.4.18a), ED visits (9.4.21a) and GP visits (9.4.24) Poisson regression will be used.

Time to first hospital readmission (9.4.18b) and first ED visit (9.4.21b) will be analyzed by Kaplan-Meier survival estimates and CI for quantiles of survival, those who don't get admitted within the study time will be censored data.

Categorical outcomes 9.4.5-10, 9.4.12, 9.4.14, 9.4.16, 9.4.17, 9.4.19, 9.4.20, 9.4.22, 9.4.23 and 9.4.25 will be described by absolute numbers and proportions. Confidence intervals may be calculated for outcomes 9.4.5-10, 9.4.12, 9.4.14, 9.4.16, 9.4.19, and 9.4.22.

NHF questionnaire results (9.4.15) will likely be presented by mean, standard deviation and confidence interval, however if the data distribution is heavily skewed data may be presented as proportions.

11.2. Sample Size

The NZ site and USA site will recruit 20 and 80 patients, respectively. These values are based on an estimated drop-out rate of 20% and the requirement for a minimum of 80 patients in total to assess feasibility and provide robust information in respect of appropriate outcome measures.

11.3. Pass/Fail Criteria

There will be no pass/fail criteria as this is a feasibility study for evaluation of outcomes for subsequent trial design.

11.4. Statistical Termination

There will not be a statistical interim analysis. Therefore no criteria for termination on statistical grounds.

11.5. Statistical Procedure Deviations

Any deviation(s) from the original statistical plan will be described and justified in the protocol or final report, as appropriate.

11.6. Selection Criteria

For endpoint details see section 9.4. All participants who were screened to take part in the study will be included in the analysis of endpoint 2.b.i. All patients who were discharged with a myAIRVO 2 device to take home will be included in analysis of all other endpoints.

11.7. Statistical Data Management

As above. Data analysis will be with SAS 9.3

12. ADVERSE EVENTS AND TERMINATION

Fisher and Paykel Healthcare Data Safety Monitoring Board will review all SAE's.

12.1. Emergency Contact Details

Contact details below are for Investigator's to contact the Sponsor. SAEs will be reported to the Data Safety Monitoring Board within 24 hours:

Name: Stanislav Tatkov
Address: 15 Maurice Paykel Place, East Tamaki, Auckland 2013, NZ
Email: stanislav.tatkov@fphcare.co.nz
Phone: +64 9 574 0123 EXT 7938
Professional Position: Clinical Research Manager, F&P Healthcare

12.2. Foreseeable Adverse Events

Participants may wish to discontinue NHF therapy should they find it uncomfortable. Adverse events are expected, including death, hospital and Intensive Care Unit admissions and patient deterioration as part of disease progression.

12.3. Reporting Adverse Events

For the purposes of this study the following events will be considered to be serious adverse events (SAEs):

- Death
- Life-threatening event

- Permanently disabling or incapacitating event
- Hospitalisation or prolongation of hospitalisation. Hospitalisation for the purposes of SAE reporting is defined as an admission to hospital and does not include a presentation to the ED followed by discharge without admission or an admission for elective reasons
- Any event considered serious by the study investigator

SAEs will be reported to the Sponsor (Fisher and Paykel Healthcare) within 24 hours of the investigator becoming aware of the event on the study SAE form. Other adverse events will also be reported to the Sponsor within seven days.

Other adverse events (AEs) will be reported to the Sponsor (Fisher and Paykel Healthcare) within 7 days of the investigator becoming aware of the event on the study AE form.

Device deficiencies (related to the identity, quality, durability, reliability, safety or performance of a device) will be reported to the Sponsor (Fisher and Paykel Healthcare) in writing. If the investigator deems the event could have led to a serious adverse event, it must be reported within 24 hours of the investigator becoming aware it, otherwise it should be reported within 7 days. The sponsor will manage device deficiency reports as part of its ongoing post marketing safety review process and the investigator will supply the sponsor with additional safety information as required.

Adverse events and device deficiencies will be reported to the HDEC, IRB, Medsafe and FDA as required

12.4. Early Termination

Early termination may occur at the discretion of the Investigators for any reason that is believed may present a safety risk.

The following documentation is required if the appropriate party terminates a clinical trial.

12.4.1. Investigator

If the investigator terminates or suspends a trial without prior agreement of the Sponsor, the investigator should inform the institution, where required by the applicable regulatory requirements and the investigator/institution should promptly inform the sponsor and the IRB/IEC, and should provide the sponsor and the IRB/IEC a detailed written explanation for the termination or suspension.

12.4.2. Sponsor

If the Sponsor terminates or suspends a trial, the Sponsor should promptly inform the investigator. The investigator should then promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation for the termination or suspension.

12.4.3. Institutional Review Board (IRB) or Independent Ethics Committee (IEC)

If the IRB/IEC terminates or suspends its approval/favorable opinion of a trial the investigator should inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation for the termination or suspension.

13. PUBLICATION POLICY

The study sites, represented by the principal investigator (PI), will take responsibility to report the results in an appropriate scientific venue. Publication of the study outcomes will comprise the study as a whole and is encouraged by the sponsor regardless of outcome. The sponsor retains editorial rights to protect the sponsor's proprietary information and intellectual property.

14. APPROVAL

Signing the below approval indicates that the principle investigator(s) (PI) in each trial center and the sponsor agree to this version of Clinical Investigator Plan.

Primary Investigator Approval:

PI Name: _____

PI Signature: _____

Date (dd/mmm/yyyy): _____

Sponsor Approval

Sponsor Name: _____

Sponsor Signature: _____

Date (dd/mmm/yyyy): _____

15. REFERENCES

1. Martin P, Glasgow H, Patterson J. Chronic obstructive pulmonary disease (COPD): smoking remains the most important cause. N Z Med J 2005;118(1213):U1409.

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7. Gotera C, Diaz Lobato S, Pinto T, Winck JC. Clinical evidence on high flow oxygen therapy and active humidification in adults. Rev Port Pneumol 2013;19(5):217-27.

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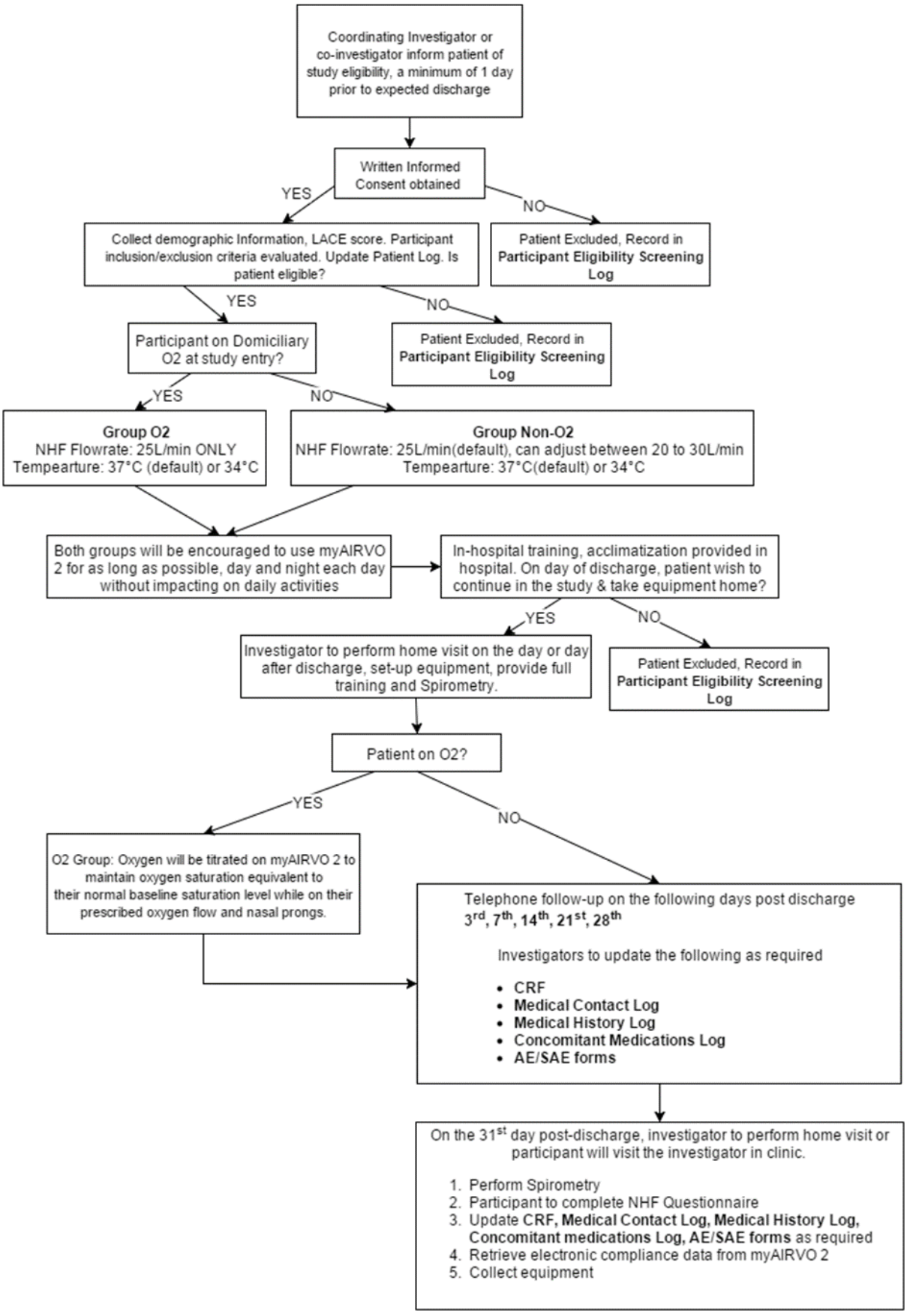
16. APPENDIX 1: FLOWCHART



17. APPENDIX 2: TRAINING SESSION REQUIREMENTS

Hospital Acclimatization/Familiarization session

Instruction	myAIRVO 2 manual reference
Familiarize and acclimatize participant to NHF therapy using myAIRVO 2, this should include a period of NHF use by the participant.	N/A
Explain warnings on page A-2 of myAIRVO 2	A-2
Explain how myAIRVO 2 works and what each of the consumables are for	A-3
Demonstrate switch on and startup of myAIRVO 2 and document participant's nasal cannula size (small, medium or large)	A-7
Instruct participant to change temperature setting and NOT activate junior mode	A-8 to A-9
Participants NOT on domiciliary oxygen: Demonstrate how to change target flow **OR** *Participants on domiciliary oxygen only:* Demonstrate how to connect oxygen tubing, explaining warnings for oxygen use & instruct participant NOT to change myAIRVO 2 flow setting	A-8 A-10
Demonstrate how to put myAIRVO on night mode	A-9
Give participant myAIRVO 2 manual and 'Quick guide' sheet	N/A

Full training Session at home visit:

Instruction	**myAIRVO 2 manual reference**
Explain warnings on page A-2 of myAIRVO 2	A-2
Re-explain how myAIRVO 2 works and what each of the consumables are for	A-3
Demonstrate startup of myAIRVO 2 including: - Position of AIRVO - Water chamber instillation, and that distilled water must be used - How to check water level and to avoid letting water run out - Installation of heated breathing tube	A-4 to A-6
Demonstrate how to switch on myAIRVO 2 including: - Switch on - Warm up screen - Connection of patient interface	A-7
Explain the drying mode and that should the participant wish to use myAIRVO 2 while it is in drying mode they can override it by pressing the main button twice or switching it off then on at the wall.	A-7
Participants NOT on domiciliary oxygen: Demonstrate how to change target flow **OR** *Participants on domiciliary oxygen only:* Demonstrate how to connect oxygen tubing, explaining warnings for oxygen use & instruct participant NOT to change MyAIRVO 2 flow setting	A-8 A-10
Instruct participant NOT to activate junior mode	A-8 to A-9
Demonstrate how to put myAIRVO 2 on night mode	A-9
Show participant where the alarms section is in the manual is and advise to: - Consider contact with investigator if the	A-11 to A-12

alarm sounds. - Contact with investigator MUST take place if the "Fault (E###) message is displayed	
Explain daily and weekly cleaning and maintenance regimens	A-13
Explain that there is a spare set of cannulas available should the participant soil theirs, and to contact the Investigator if more cannulas are needed	A-14
Instruct that the Filter in new and must NOT be removed, tampered with or replaced.	A-14
Ensure participant still has the 'Quick guide' sheet at front of myAIRVO 2 manual and reiterate that: - Participants can call during business hours with questions - myAIRVO 2 does NOT provide life support and should NOT be used to treat worsening symptoms, participant's should instead seek medical help - If unsure, do not use myAIRVO 2 until contact has been made with one of the Investigators - myAIRVO 2 should NOT be left running when not in use. The only exception to this is if the participant removes it for a very short period of time (e.g. to go to the bathroom or make a drink)	N/A

18. APPENDIX 3: INSURANCE CERTIFICATE

ACE Insurance Limited
CU 1-3, Shed 24
Princes Wharf
Auckland 1010
PO Box 734
Auckland 1140
New Zealand

+64 9 377 1459 *tel*
+64 9 303 1909 *fax*

Company Number: 104656
FSP Number: 35924

CERTIFICATE OF CURRENCY

Date of Issue: 27 March 2015 **Issuing Office**: New Zealand

To Whom It May Concern

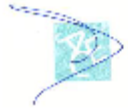
Insured:	Fisher & Paykel Healthcare Limited
Class:	Commercial General Liability (Claims made)
Policy Period:	From: 1 April 2015 at 4.00pm To: 1 April 2016 at 4.00pm
Policy Territory:	Worldwide as defined by the policy
Policy Number:	AGEL401312
Limit of Liability:	$10,000,000 any one Claim and in the aggregate in respect of the Products Hazard. Total: $10,000,000
Interested Party:	Medical Research Institute of New Zealand, Level 7, CSB Building, Wellington Regional Hospital, Riddiford Street, Newtown, Wellington 6021, New Zealand and Alana Healthcare 214 25th Ave N, Nashville, TN 37203, USA are noted as interested parties in respect of conducting the trial named Multicentre COPD Readmission Trial
Special Terms (if any):	Nil

This certificate hereby certifies that cover has been granted subject to the exceptions, terms and conditions and definitions of the Policy (as amended from time to time, including after the date of this Certificate of Currency).

Please refer to your agent, broker or the relevant ACE office for further information or a copy of the Policy.

ACE Insurance Limited has an "AA-" insurer financial strength rating given by Standard & Poor's (Australia) Pty Limited.

Signed at Auckland on behalf of ACE Insurance Limited:



ACE Insurance Limited – New Zealand Page 1 of 1