# Vapotherm, Inc

**HVNI Ambulation Feasibility Study**

Confidential

| | |
|---|---|
| **Protocol Title:** | **Assessing clinical effect of HVNI on improving patient ambulation in acute care scenarios: a feasibility study** |
| **Protocol Number:** | RP-VTPF2018001Sci |
| **Revision:** | Rev 1.0 – January 30, 2019 |
| **Principal Investigator:** | Thomas Siler, M.D. |
| **Co-Investigators:** | TBD |
| **Sponsor:** | Vapotherm, Inc<br>100 Domain Drive<br>Exeter, NH 03833<br>1 (603) 658-0011<br>http://www.vtherm.com |

**Confidential**

Study site should keep protocol, all contents and related information confidential.

## Protocol Approval

### Investigator Statement

As Investigator of the study titled "Assessing clinical effect of HVNI on improving patient ambulation in acute care scenarios: a feasibility study" (the "Study"), I agree to:

(i) conduct the Study in accordance with: this Investigator Agreement; the Study's Protocol as approved by the IRB (the "Protocol"); all applicable laws and regulations; and any IRB or FDA conditions of approval;
(ii) await IRB approval for the Protocol before obtaining informed consents (if applicable);
(iii) ensure that all requirements for informed consent are met and not let any subject participate in the Study before obtaining that subject's informed consent (if applicable);
(iv) not make modifications to the Protocol without first obtaining consensus from the Vapotherm Science and Innovation team and necessary IRB approval;
(v) maintain Study documentation for the period of time as required by appropriate regulations; and
(vi) supply to the Sponsor, as part of this Investigator Agreement, my curriculum vitae.

**INVESTIGATOR**

Signature: _____

Printed Name: _____

Date: _____

**Glossary of Definitions and Terms**

High Flow Nasal Cannula (HFNC): Nasal cannula system that delivers flow rates of respiratory gas meeting or exceeding a patient's normal spontaneous inspiratory flow demand. HFNC systems must maintain adequate heating and humidification of the delivered gas to protect the airway tissues from dryness.

High Velocity Nasal Insufflation (HVNI): The use of HFNC with specified parameters including flow rates, fraction of oxygen, gas temperature and cannula interface dimensions to achieve a defined therapeutic effect.

Non-Invasive Positive Pressure Ventilation (NIPPV): Breathing assist where a mask is strapped tightly to a patient's face and bi-level pressure is administered at an established frequency to support a patient's minute ventilation.

Mechanical Ventilation (MV): Breathing assist that requires intubation and the delivery of forced positive pressure breaths at a set frequency.

Respiratory Failure: The inability to maintain sufficient arterial blood oxygen saturation and $CO_2$ levels during unassisted spontaneous breathing.

Pulmonary Rehabilitation: Exercise regimen for patients with compromised cardio-pulmonary function.

Vapotherm Transfer Unit (VTU): system composed of a roll stand, power source and gas supply that allows the Precision Flow to function independently of wall connections and therefore become mobile, facilitating therapy during ambulation.

Ambulatory Oxygen: A portable oxygen cylinder device allowing the patient to carry around their oxygen supply so as to breathe during routine mobility & exercises.

Pulse Oximetry Reading ($SpO_2$): Indirect measure of a patient's arterial blood oxygen saturation using pulse oximetry technology.

Resting $SpO_2$: $SpO_2$ value the patient demonstrated at rest, while sitting upright and connected to the patient monitors prior to the start of the study session. This value will be patient specific and reflect the patient's clinical status.

Desaturation $SpO_2$: The $SpO_2$ value considered to be the point of desaturation. This value is based on the desaturation requirement for reimbursement of oxygen therapy.

Ventilatory Work Effort / Work of Breathing (WOB): The physical, physiologic muscular demands of breathing manifested through the sign and symptoms of increased physical exertion, which include airway resistance, use of accessory muscles for inspiration or expiration.

Fraction of inspired oxygen ($FiO_2$; %): The percent of the delivered respiratory gas mixture that is oxygen, expressed as a fraction.

Ventilatory Rate (Respiratory Rate; RR): The number of breaths a subject takes per minute (breaths·min$^{-1}$).

Blood Pressure (BP): pressure of the blood in the circulatory system.

Heart Rate (HR): The number of heart beats per minute (beats·min$^{-1}$).

Modified Borg Scale (Borg): Dyspnea is an important measure of patient respiratory distress & pulmonary functional status. This scale allows for patients and clinicians to rate dyspneic status by using specific descriptors, on a scale of 0 (no dyspnea) to 10 (unbearable dyspnea). The modified Borg scale is also used for rating the subjective perceived exertion during exercise, while at the same workload.

Standard of Care (SOC): Site standard practices for the medical care of patients presenting with specific symptoms.

Case Report Form (CRF): The form used to record pertinent patient data to address the study aim. CRFs do not contain patient names or medical record numbers; rather they will be coded with a patient number and the site principal investigator at each center will maintain the key. The CRFs are the property of Vapotherm.

## I. Background and Significance

Hypoxemia and dyspnea are hallmark characteristics of patients with chronic pulmonary disease [1], and can be attributed to acute respiratory failure. Oxygen therapy is the first stage in the treatment and prevention of acute respiratory failure. This therapy is delivered through pressure (mechanical ventilation [MV], non-invasive positive pressure ventilation [NIPPV]) and flow-based (HFNC) modalities to support oxygenation and ventilation, and in many cases, NIPPV & HFNC have been demonstrated to provide comparable support [2-4]. The key difference in these modalities lies in a patient's functional respiratory drive – for the pressure-based therapies this is not a contraindication. However, oftentimes HFNC can be a stop-gap to & weaning-step from the invasive and betimes patient-intolerant pressure therapies [2,3,5,6]. Many areas of patient care commonly use oxygen therapy: intensive care, emergency department, surgical suite, hospice, home-care. Further, in many such cases ambulation and early mobility is used in concert with oxygen therapy, as exercise is linked to improved patient outcomes [7-9]. In fact, early mobility provides profound effects on physical health, strength, and mental health. Past studies with ambulatory oxygen evaluated patients with a need for oxygenation and ventilatory support during daily activity, including the following: chronic obstructive pulmonary disorder (COPD), interstitial lung disease (ARDS), pulmonary hypertension, pulmonary fibrosis, post-operative surgery, weaning from mechanical ventilation, and an inability to utilize normal lung inspiratory/expiratory mechanics [7-13]. In summary, early mobility and ambulation provides hospitals a cost-effective method to improve patient outcomes in a wide range of critical care settings. This feasibility study aims to evaluate the effect of high velocity nasal insufflation (HVNI) on patient ambulation and to compare HVNI to treatment as usual (TAU).

Ambulatory care oxygen denotes the use of supplemental oxygen during any form of mobility, exercise, and daily life activities [7]. Use of ambulatory oxygen in patients with respiratory distress has become prevalent as patients often desaturate (hypoxemic, <88%) during exercise & mobility assessments [7,8,14]. This desaturation, especially in patients with resting hypoxemia challenges, has been associated with reduced exercise tolerance, reduced $FEV_1$, and in chronic cases even increased patient mortality [10,11,13]. It is also used by patients on long-term oxygen treatment during any exercise [15]. In fact, pulmonary rehabilitation has become a standard of care (SOC) for patients with respiratory diseases, with evidence supporting the benefits of exercise to improved dyspneic, quality of life (QOL) outcomes, hospital resource allocation, psychosocial benefits, and cost-effectiveness [8]. The long-term benefits of using oxygen, in conjunction to ambulation, is still debated [16-18]. Clear episodic improvements have been demonstrated to improve exercise performance measures [7,8], reduce exercise dyspnea [1], improve recovery time [8,19], reduce WOB [8], reduce incidence of cardiopulmonary complications [20], and in some cases improve patient mental health [8,14]. Systematic reviews have also highlighted the correlation between longer hospital stays and greater chances for complications followed by lengthened rehabilitation due to muscle wasting, which may be ameliorated through early ambulation [7,8]. A study in COPD patients even suggested that a 4% desaturation during 6-minute-walk-tests (6MWT) may predict long-term mortality [11].

Multiple studies have demonstrated improved activity, performance, reduced dyspnea, and improved $SpO_2$ saturation as positive patient outcomes of ambulation during MV and non-invasive ventilation (NIV). In fact, early ambulation of patients requiring MV has been communicated as clinically useful as early as 1975 [21]. Previously, NIV has been shown to increase exercise tolerance, reduce exercise desaturation episodes, and thereby improve pulmonary rehabilitation [8,22]. Menadue et al. specifically explored NIV's effect on exercise in acute hypercapnic exacerbations of respiratory disease, and demonstrated that oxygen by NIV improved the

6MWT performance, reduced patient dyspnea, and improved $SpO_2$ saturations when compared to oxygen alone [23]. Studies by Jolley et al. [12,16,24], with MV, demonstrated that: (1) in surveys across 47 hospitals in Washington State higher activity levels were noted due to SOC practice from available (76%) site mobility protocols [24], and (2) adults in acute respiratory failure placed on MV, involved in early physical and occupational therapy, were strongly predictive of improved out-of-bed mobility outcomes [12]. Accordingly, the presence of endotracheal tubing during MV was negatively associated to out-of-bed mobility. A study by Nishiyama et al. in IPF patients without resting hypoxemia demonstrated that no benefit existed between air & oxygen (4LPM) in terms of exertional dyspnea & performance (6MWT), but noted that mobility assessments should be made on an individual basis [20]. In fact, mobility during MV is so prevalent and effective that Hodgson et al., in a systematic review of literature, developed consensus recommendations on safety parameters of ICU mechanically ventilated adults [25]. Looking back, these studies and others used endpoints from the following pool to assess improved outcomes: exercise performance, recovery time, $SpO_2$ saturation, clinician perception assessments, perceived dyspnea, perceived exertion, health status questionnaires, lung function by spirometry, heart rate, respiratory rate, work of breathing, and mobility assessment scoring (BMAT, MMS, mMRC) [7,8,12,26].

As literature has established the importance of ambulation and early mobility during hospital stay, especially in patients needing oxygen for daily activity, this study explores the potential benefit of HVNI during patient ambulation. Vapotherm's HVNI therapy is premised on the technical ability to create ideally conditioned respiratory gas, which is delivered nasally with an intent to support spontaneous ventilation as opposed to simple oxygen therapy [5,27]. Vapotherm technology is unique in its ability to provide this conditioned gas through a small-prong nasal cannula resulting in a high velocity without the well-known adverse effects related to drying and cooling of the nasal mucosa [28]. This high velocity nasal flow facilitates a well described mechanism of improving ventilatory efficiency by way of eliminating anatomical dead space of the upper airway [5]. The purging of the nasal cavity is important to alveolar gas exchange because the gas that is drawn to the respiratory regions of the lungs comes from the anatomical reservoir created by the flush, in the same way that oxygen conservation masks can incorporate reservoir bags to reduce the bulk flow requirements from the oxygen source to achieve the same oxygenation effect [5,29]. Based on mathematical modeling, physiologic studies and clinical observations, a flow rate of 4 to 8 $L \cdot min^{-1}$ through Vapotherm's neonatal cannulae, or 25 to 35 $L \cdot min^{-1}$ through Vapotherm's adult cannulae, would purge the anatomical reservoir of the upper airway in the window of time between breaths.

Vapotherm's humidification systems are specifically designed to tolerate a high back pressure in the humidification cartridge that is generated by passing these flow rates through small bore cannulae that result in the appropriate flow velocities (turbulent energy) [29]. Since 2000, Vapotherm HVNI has been used extensively and has been well studied and the clinical impact of this ventilation effect using Vapotherm's conventional cannula line is well described [5,28-31]. A multi-center recent randomized clinical trial also demonstrated the noninferiority of HVNI to NIPPV in the treatment of undifferentiated respiratory distress for patients presenting in the Emergency Department [2].

As Vapotherm Hi-VNI technology becomes more common-place in hospital standard of care & practice, HVNI therapy may also have a demonstrable effect on improving patient ambulation and mobility. Mobility represents a key factor in the timely improvement of patient health, and in end-of-life cases it can have a mental impact [8]. In addition to the patient benefits, ambulation and early ambulation & mobility can also reduce the patient hospital resource allocation and reduce the length of stay (LOS). Some hospitals have included patient ambulation metrics as a key success factor, and this also can play a role to stepping-down

the patients to less critical care environments. The goal of this study is to establish a low risk model, modified from the 6MWT, for patients with dyspnea: (1) evaluate the effect of HVNI on ambulation, and (2) assess the impact HVNI use may have on improved outcomes when compared to standard TAU (HVNI).

## II. Overall Study Objective

The **overall objective** of this study is to evaluate the ability of HVNI to improve patient ambulation relative to a treatment as usual (TAU).

The **hypothesis** is that HVNI therapy, when implemented in conjunction to ambulatory practices, will be more effective than TAU to improve patient mobility by reducing the patient's perceived dyspnea and exertion via maintaining oxygenation (reduced desaturation) and supporting ventilation (reduced work of breathing [WOB]).

To test this hypothesis, the study will be conducted with the following specific aims:

**Aim #1: Primary Outcome.** The primary endpoint is exercise performance, defined as the distance and duration of patient ambulation.

**Aim #2: Secondary Outcomes.** The secondary endpoints evaluate the patient recovery interval, defined as the recovery time (return time to baseline perceived dyspnea). Other endpoints will include: vital signs (heart rate [HR], respiratory rate [RR], blood pressure [BP]), arterial oxygen saturation ($SpO_2$), rated perceived exertion (RPE), and rated perceived dyspnea (RPD).

**Aim #3: Tertiary Outcomes.** The tertiary endpoints evaluate the clinician perception scores. For the clinician perceptions this will include: technical/clinical difficulties, patient comfort & tolerance, ease of use, monitoring & support for therapy, and expected/perceived patient outcomes.

These **endpoints** will establish the effect HVNI therapy may have on improving patient ambulation relative to TAU, while potentially demonstrating the effect of HVNI on hospital resource allocation and patient comfort.

**III. Subject Selection**

Subjects will be identified and recruited by study investigators. The feasibility study will take place at a clinical setting (e.g. hospital, academic center, out-patient facility), where testing can be performed with appropriate supervision and staff training to maintain patient safety. The test model is a modified 6MWT. Initial contact will be made by the study investigators, and the participants may or may not decide to enroll. Compensation will be provided to participants for enrollment into this study.

**Inclusion Criteria**

1. Adults over the age of 18 years
2. Demonstrated respiratory distress upon mild to moderate exertion (e.g. dyspnea upon standing, walking, etc.)
3. Candidate for clinical ambulation/mobilization
4. GOLD 4 spirometry or GOLD 3 with significant dyspnea on exertion with or without supplemental oxygen

**Exclusion Criteria**

1. Hypoxemia at resting baseline with $SpO_2$<88% with supplemental oxygen
2. Inability to provide informed consent
3. Pregnancy
4. Known contraindication to perform ambulation, per site SOC practices
5. Inadequate respiratory drive or any known contraindications to HVNI
6. Inability to use nasal cannula and HVNI therapy
7. Agitation or uncooperativeness
8. Determined by the attending clinician to be sufficiently unstable or unsuitable for this feasibility study

**IV. Study Design**

The study objective is to evaluate the ability of HVNI to improve patient ambulation relative to TAU by using a modified 6MWT model. The hypothesis is that HVNI therapy, when implemented in conjunction to ambulatory practices, will be more effective than TAU to improve patient by reducing the patient's perceived dyspnea and exertion via maintaining oxygenation (reduced desaturation) and supporting ventilation (reduced WOB).

This will be a feasibility study, performed as a prospective, crossover trial to evaluate the potential patient improvement during ambulation while on HVNI relative to TAU. Patients who fit the criteria for inclusion will perform ambulation for each study period: the baseline period (TAU) followed by the test period (HVNI). The clinical management will otherwise remain unchanged based on the site SOC practices. The patient $FiO_2$ and flow values will be recorded while on any supplemental oxygen. Subjects will wear appropriate gear and, when applicable, have mobile carts to provide supplemental oxygen therapy (e.g. HVNI VTU) during ambulation.

This feasibility study design focuses on three distinct phases: (1) baseline characterization, (2) performance measures of ambulation, and (3) clinician perceived satisfaction scores. The baseline characterization is to provide patient background, history, and initial relevant clinical evaluation from Aim 2. Performance

measures from Aims 1 & 2 will provide physiologic relevant indices before/during/after ambulation session and will be used for meaningful comparison between study arms. Lastly, Aim 3 will provide an overall assessment from the clinician perceived satisfaction scores.

This feasibility study will involve two study periods: baseline (TAU) and test (HVNI). Baseline period will be administered first, followed by the test period. Patients deemed in need of ambulation (per inclusion/exclusion criteria) will be enrolled into the study and will complete both study periods:

1. Treatment as usual (TAU) of standard practices (control arm) for ambulation at site
2. Vapotherm HVNI therapy (test arm) administered as described below during ambulation at site

This feasibility study will be conducted in a research facility and where testing can be performed with appropriate supervision and staff training to maintain patient safety. This current study uses a modified 6MWT ambulation test to evaluate the patient performance. Primary and secondary outcomes will be completed upon the completion of each study arm's ambulation test. Tertiary outcomes will be completed upon study. All respiratory interventions will be tracked during the study window, and disposition and mortality will be tracked for each patient.

## V. Subject Enrollment

Subjects will be solicited by research staff and consented prior to participation in this feasibility study (Aims 1-3). Once consented, the participants will complete all Aims during the course of participation in the study, per the TAU at each site. Compensation will be provided to participants for enrollment into this study.

### Sample Size:

To provide a sample data set, we will enroll up to 32 subjects to complete this feasibility assessment, with a calculated sample size of N=26 plus a 20% failure rate. This will provide sufficient initial data to inform the appropriate sample size of a follow-on randomized study.

This sample size was calculated through use of references that approximated similar studies [1,32]. McCarthy et al. found a mean difference of 42.93m with 95CI: 32.64 – 55.21m when evaluating patient ambulation with and without adjunctive therapy [32]. For this study, using a desired power of 90% with alpha=0.05, the sample size is estimated at 26 to show a difference in data between the control and test groups.

## VI. Study Procedures

This feasibility study is non-blinded by necessity, since the provided therapies have different devices. No randomization will be incorporated into this feasibility study design. The study arms will be performed as a crossover design, baseline performed first followed by the test period. Study model for the ambulation test is a modified 6-minute walk test. Figure 1 illustrates an overview of the study procedures. This feasibility study will evaluate the baseline, performance, recovery, and clinical assessment indices to demonstrate the effect between TAU and HVNI during ambulatory practice.

### Screening, Enrollment, & Management

Upon screening, subjects will be asked to participate in this study, and if so they will be consented prior to enrollment. Subjects are instructed that if at any time during the study they are free to stop the test and discontinue study participation. All study procedures will be explained to the subject.

Upon enrollment, appropriate study data will be collected (see below under Data Collection), including patient demographics, anthropometrics, and applicable history (LTOT user, positive-airway pressure therapy user, current respiratory therapy). Subjects will be managed by routine care while study data is captured as shown in the timeline below (Table 1). All decision making for patient ability to ambulate and continue study procedures will be made per standard practice at the site, using the judgment of the research team.

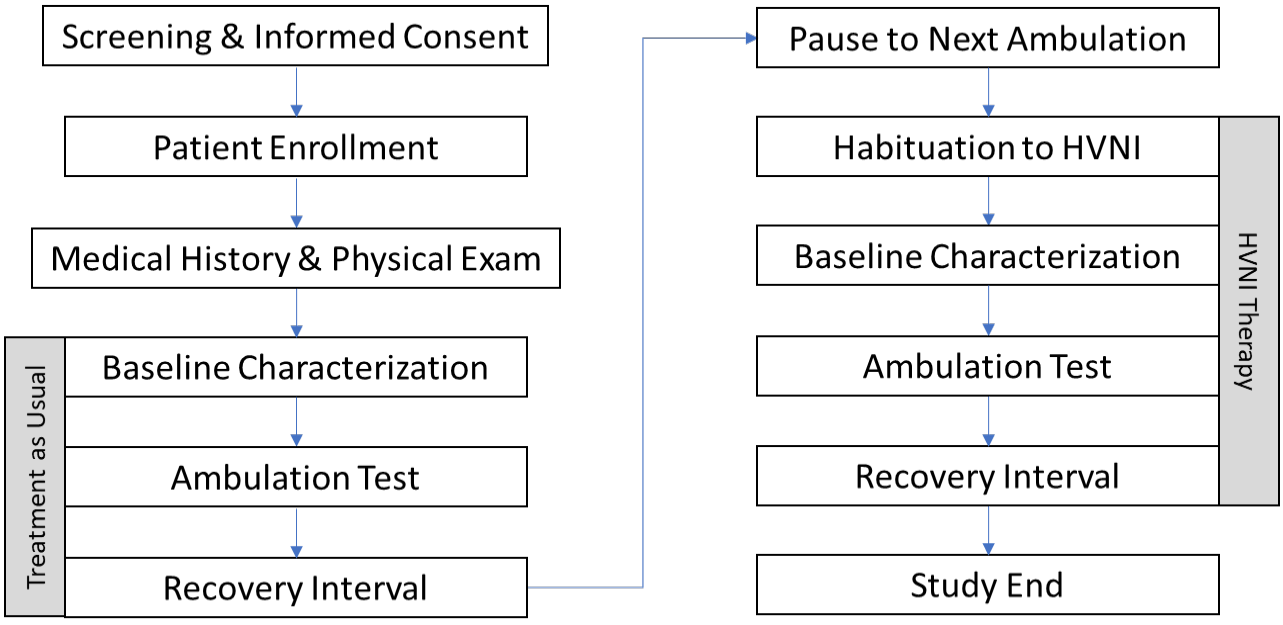


**Figure 1. Framework of the clinical study procedures discussed within this protocol.**

**Control Session**
The Control session is treatment as usual (TAU), without use of HVNI during any time of this study period.

The Control session will follow three phases (see Figure 1 & Table 1): Baseline Characterization, Ambulation Test, and Recovery Interval. After these phases are complete, the next ambulation exercise will be determined per standard practice and when deemed appropriate by investigator.

Prior to the Control Session baseline characterization, the subjects should wear comfortable clothing, appropriate walking shoes, and usual walking aids (cane, walker, etc.). No vigorous exercise should be performed 2 hours prior to the ambulation test [33].

Baseline Characterization Sitting down, the subject will be setup and prepared for the ambulation test with appropriate data recording devices and supplemental oxygen (not HVNI). The subject will be allowed to acclimate to the supplemental oxygen during this period of time. While subject is at rest, standing up, the following data will be collected (see Table 1): RR, HR, BP, $SpO_2$, and RPD (Modified Borg scale 0-10). For the RPD & RPE, the coordinator will record patient scores, the $FiO_2$ and flow settings for any supplemental oxygen provided to the patient before/during/after this baseline phase. TAU will not include HVNI in this study period. The Ambulation Test will be performed after the baseline characterization is. The definition for this ambulation test will be to walk until 18 minutes has elapsed or the patient is unable to continue. A timer will keep track of the test duration, and the clinician will keep track of the distance traveled during ambulation. At test start, test end, & 1-minute intervals the subjects will be asked to rate their RPE (Modified Borg scale 0-10). The subject vitals will be monitored during this ambulation test and recorded as follows: HR, RR, $SpO_2$. The ambulation test will end if the subject has completed 18 minutes, stops walking for more than 10 seconds, has to sit down, has any adverse events, or should the investigator deem necessary.

Recovery Interval will begin immediately following the end of the Ambulation Test. The subject will perform this recovery interval while safely seated. The time to return to the subject's resting-while-standing RPD score (Baseline) will be used as recovery time. At the end of the recovery interval, record the subject RR, HR, BP, $SpO_2$, and RPD & RPE. Any adverse events will be recorded. Any exacerbations from ambulation walk test will be recorded during the recovery interval. Record the recovery end time and date.

After the Recovery Interval is complete, all associated data will be collected including clinician perception/satisfaction scores. Then the study will pause until the next ambulation test is scheduled. The next ambulation test will be determined per standard practice and when deemed appropriate by the investigator.

**Test Session**
The Test session (with HVNI therapy) will follow three phases (see Figure 1 & Table 1): Baseline Characterization, Ambulation Test, and Recovery Interval. After these phases are complete, and all associated data is collected (per Table 1), the coordinator will collect all end-of-study data prior to study completion.

HVNI will be initiated per the initial settings identified below, after which settings will be titrated per standard practice for optimal effect. When patients are placed to the test arm, the HVNI start settings will be the following: $FiO_2$ = 1.0, Flow = 35 L/min, and Temperature = 35 -37°C.

- Patients will be fit with a Vapotherm adult nasal cannula that will be applied by a respiratory therapist or other clinician skilled in management of HVNI. Initial flow will be set to 35 L/min but can be decreased or increased as rapidly as necessary to alleviate respiratory distress and optimize patient comfort. Targets should be to lower respiratory rate to the low 20s and with an HVNI flow rate between 20 to 35 L/min. Starting temperature will be between 35 to 37°C; if patients find the gas temperature to be uncomfortable, it can be lowered as necessary down to 33 C to enhance tolerance. The $FiO_2$ will be 1.0 initially to assure adequate oxygenation, but this should be adjusted promptly to maintain an $FiO_2$ of no greater than 0.6 to maintain a $PaO_2$ > 88%.

Prior to the Test Session baseline characterization, the subjects will be placed on HVNI, titrated per above settings, and subjects will be allowed to acclimate to the supplemental oxygen (HVNI therapy). The subjects should wear comfortable clothing, appropriate walking shoes, and usual walking aids (cane, walker, etc.). No vigorous exercise should be performed 2 hours prior to the ambulation test [33]. Record the start date & time of placement on HVNI therapy.

Baseline Characterization will be performed just prior to the next scheduled ambulation test, as deemed appropriate for the patient by the investigator. Sitting down, the subject will be setup and prepared for the ambulation test with appropriate data recording devices and supplementary oxygen (only HVNI). While subject is at rest, standing up, the following data will be collected (see Table 1): RR, HR, BP, $SpO_2$, and RPD (Modified Borg scale 0-10). For the RPD & RPE, the coordinator will record patient scores. Record the $FiO_2$ and flow settings for any supplemental oxygen provided to the patient before/during/after this baseline phase.

The Ambulation Test will be performed after the baseline characterization is complete, and in accordance to the standard practice of the site and judgment of the investigator to maintain patient safety. The definition for this ambulation test will be to walk until 18 minutes has elapsed or the patient is unable to continue. A timer will keep track of the test duration, and the clinician will keep track of the distance traveled during ambulation. At test start, test end, & 1-minute intervals the subjects will be asked to rate their RPD & RPE (Modified Borg scale 0-10). The subject vitals will be monitored during this ambulation test and recorded as follows: HR, RR, $SpO_2$. The ambulation test will end if, the subject has completed 18 minutes, stops walking for more than 10 seconds, has to sit down, has any adverse events, or should the investigator deem necessary.

Recovery Interval will begin immediately following the end of the Ambulation Test. The subject will perform this recovery interval while safely seated. The time to return to the subject's resting-while-standing RPD score (Baseline) will be used as recovery time. At the end of the recovery interval, record the subject RR, HR, BP, $SpO_2$, and RPD & RPE. Any adverse events will be recorded. Any exacerbations from ambulation walk test will be recorded during the recovery interval. Record the recovery end time and date.

After the Recovery Interval is complete, all associated data will be collected (per Table 1). This includes all end-of-study data prior to study completion including perception/satisfaction scores.

**Other Medical Care**
All other pharmaceutical and medical treatment will remain the purview of the attending physician and will be administered per the current standards. This study is designed to evaluate only intervention of HVNI in conjunction with standard (TAU) ambulatory practice, and it is assumed that the ancillary interventions will

follow common clinical practice guidelines and conventions. All treatments given to the subjects will be noted on their CRFs.

## VII. Data Collection

**Table 1. Key study data and collection points.**

| | Baseline Characterization | Ambulation Test | Recovery Interval | @ Study End |
|---|---|---|---|---|
| **Patient History & Health** | X | | | X |
| **Treatment: Flow & O2** | X | X | X | X |
| **Physiologic Parameters** | X | X | X | X |
| **Performance Parameters** | | X | | |
| **Recovery Parameters** | | | X | |
| **Clinician Perception Scores** | | | X | X |
| **Disposition** | X | | | X |

Patient enrollment data collection will include patient history, health, demographics, and interventions. For each test session the following data will be recorded for comparison.

*Physiologic Parameters*
- $SpO_2$, HR, RR, BP, RPE, RPD

*Performance Parameters*
- Test duration and test distance traveled

*Recovery Parameters*
- Return time to baseline RPD, HR, RR, BP, $SpO_2$, RPD, RPE

**Primary Endpoint**
- Distance and duration of exercise during ambulation

**Secondary Endpoints**
- Physiologic parameters – $SpO_2$, HR, RR, BP, RPE, RPD
- Recovery parameters: return time to baseline Rated Perceived Dyspnea score
- Modified Borg scale scores – Rated Perceived Exertion (RPE), Rated Perceived Dyspnea (RPD)

**Tertiary Endpoints**
- Clinician perception of patient respiratory response to therapy, ranging from NO Response to Excellent Response, as continuous VAS.
- Clinician perception of frequency of rain-out, interface slippage or other technical/clinical difficulties applying therapy, ranging from Never to Frequent as continuous VAS.
- Clinician perception of patient comfort and tolerance of therapy, ranging from Very Poorly Tolerated to Very Well Tolerated as continuous VAS.

- Clinician perception of Simplicity of set-up and use, ranging from Complex to Setup and Use to Simple to Setup and Use, as continuous VAS.
- Clinician perception of Monitoring and support of therapy required (adjustments, refilling fluids, adjusting interface), ranging from Almost Constantly to Almost Never, as continuous VAS.

**VIII. Statistical Analysis**

The data analysis will be "per protocol." Baseline patient demographics and characteristics will be summarized, and appropriate statistical testing will be performed for the continuous and categorical variables. Assuming a non-normal data distribution for this crossover study design, the non-parametric Wilcoxon Signed Rank Sum test will be performed with significance interval of 0.05 on all applicable variables. Otherwise, for the categorical variables, the Fisher's Exact test will be performed. Data will be compared and graphed accordingly for a visual comparison with accompanied statistical notations.

**IX. Risks and Discomforts**

This pilot study does not present significant risk to patients, as supplemental oxygen is routinely provided to patients and the 6MWT is a standard/routine practice [33]. The Treatment-as-Usual at the study sites involves the application of simple supplemental oxygen during mobilization. Use of the high flow nasal cannula therapy has no known risks and has been used in the clinical setting for approximately seventeen years without known reports of adverse events related to the administration of high nasal flows when appropriately conditioned to near body temperature and fully humidified. The literature indicates that approximately only 4 $cmH_2O$ of distending pressure may be generated in the upper airway [34,35] which is well below any known threshold for injury. In addition, it has been demonstrated that delivery of high flows of conditioned gas from a nasal cannula has a positive effect on airway mucosal function [36,37]. The patients will be closely monitored as part of standard medical practice. Ambulation is implemented as part of the standard care practice for the patients included in this study.

For these reasons, we have determined that this study represents non-significant risk to the subjects, beyond the discomfort related to routine ambulation therapy.

**X. Potential Benefits**

Subjects may or may not receive any direct health benefit from participation. Due to the short duration of the exposure, it is not likely that the patients enrolled in the HVNI ambulation pilot study will themselves benefit from participation in this study. The trial may result in knowledge that leads to improvements in the quality of care, patient experience and ultimately cost of care associated with the care for patients with respiratory distress and/or failure. Compensation will be provided to participants for enrollment into this study.

**XI. Monitoring and Quality Assurance**

The clinical trial site will be monitored in accordance with policies at Vapotherm and those federal regulations that pertain to clinical research, namely 21 CFR Parts 50, 54, 56 and 812 and others as applicable and GCP/ICH guidelines. Monitoring will occur at regular frequency by the sponsor, such as to allow ongoing review of data collected, site qualifications and compliance with the protocol. All investigators and study staff will be appropriately trained to ensure compliance with the protocol.

## XII. Protocol Deviations

Any deviations from the Data Collection plan identified during monitoring or through other means will be documented on case report forms. These include, but are not limited to items such as the following:

- Failure to compete the Baseline characterization
- Failure to capture time and place of any device failure
- Failure to capture/record data included in the protocol
- Subject inability to complete both the control and test study arms

If the study site demonstrates a pattern of consistent and frequent deviations, the Sponsor will undertake appropriate activities (e.g. re-training) to attempt to bring the site into compliance with the protocol. A pattern of repeated serious deviations from the protocol may result in site termination from the study.

## XIII. Adverse Event Reporting

During the course of the subject's participation in the study, the investigator will determine whether any adverse events have occurred. For the purposes of this protocol, an adverse event is any undesirable clinical/medical occurrence in a subject that is or is not attributed to the device or procedure required by this protocol. If any adverse event occurs, either anticipated or unanticipated, the investigators will immediately contact the sponsor's representative (site monitor) indicated on page 1.

## XIV. Confidentiality

Rigorous procedures will be followed to maintain confidentiality of subject identification and test-related information and to adhere to government regulations concerning privacy. The privacy rules and requirements according to governing regulations will be adhered to. Methods to protect the privacy of subjects and clinical information will be used. A unique identification number designed to protect the identity of subjects will be used to identify the subject on case report forms, recruitment logs, data forms or other reports.

This unique identification number will not be linked to identifiable data; no personal or identifiable patient data will be collected. The clinical research site will maintain the linking log behind locked door. All Vapotherm representatives involved in this study will only have access to the patients' unique identification number. The linked data will be stored within the study binder at the clinical research site for two years from the end of the study.

Confidentiality will be protected and maintained to the extent allowed by law.

## XV. References

1. Ejiofor SI, Bayliss S, Gassamma A, Turner AM. Ambulatory Oxygen for Exercise-Induced Desaturation and Dyspnea in Chronic Obstructive Pulmonary Disease (COPD): Systematic Review and Meta-Analysis. *Chronic Obstr Pulm Dis.* 2016;3(1):419-434.
2. Doshi P, Whittle JS, Bublewicz M, et al. High-Velocity Nasal Insufflation in the Treatment of Respiratory Failure: A Randomized Clinical Trial. *Annals of emergency medicine.* 2018;72(1):73-83 e75.
3. Hernández G, Roca O, Colinas L. High-flow nasal cannula support therapy: new insights and. *Critical Care.* 2017;21(1):1-11.

4. Lavizzari A, Colnaghi M, Ciuffini F, et al. Heated, Humidified High-Flow Nasal Cannula vs Nasal Continuous Positive Airway Pressure for Respiratory Distress Syndrome of Prematurity: A Randomized Clinical Noninferiority Trial. *JAMA Pediatr.* 2016.
5. Dysart K, Miller TL, Wolfson MR, Shaffer TH. Research in high flow therapy: mechanisms of action. *Respir Med.* 2009;103(10):1400-1405.
6. Miller SM, Dowd SA. High-flow nasal cannula and extubation success in the premature infant: a comparison of two modalities. *Journal of perinatology : official journal of the California Perinatal Association.* 2010;30(12):805-808.
7. Ameer F, Carson KV, Usmani ZA, Smith BJ. Ambulatory oxygen for people with chronic obstructive pulmonary disease who are not hypoxaemic at rest. *Cochrane Database Syst Rev.* 2014(6):CD000238.
8. Ries AL, Bauldoff GS, Carlin BW, et al. Pulmonary Rehabilitation: Joint ACCP/AACVPR Evidence-Based Clinical Practice Guidelines. *Chest.* 2007;131(5 Suppl):4S-42S.
9. Zomorodi M, Topley D, McAnaw M. Developing a mobility protocol for early mobilization of patients in a surgical/trauma ICU. *Crit Care Res Pract.* 2012;2012:964547.
10. Andrianopoulos V, Franssen FM, Peeters JP, et al. Exercise-induced oxygen desaturation in COPD patients without resting hypoxemia. *Respir Physiol Neurobiol.* 2014;190:40-46.
11. Casanova C, Cote C, Marin JM, et al. Distance and oxygen desaturation during the 6-min walk test as predictors of long-term mortality in patients with COPD. *Chest.* 2008;134(4):746-752.
12. Jolley SE, Moss M, Needham DM, et al. Point Prevalence Study of Mobilization Practices for Acute Respiratory Failure Patients in the United States. *Crit Care Med.* 2017;45(2):205-215.
13. Vainshelboim B, Kramer MR, Izhakian S, Lima RM, Oliveira J. Physical Activity and Exertional Desaturation Are Associated with Mortality in Idiopathic Pulmonary Fibrosis. *J Clin Med.* 2016;5(8).
14. Walker ML, Austin AG, Banke GM, et al. Reference group data for the functional gait assessment. *Phys Ther.* 2007;87(11):1468-1477.
15. Suntharalingam J, Hippolyte S, Knowles V, Freeman D, Patel I, Hardinge M. When should I be considering home oxygen for my patients? *NPJ Prim Care Respir Med.* 2016;26:15074.
16. Jolly EC, Di Boscio V, Aguirre L, Luna CM, Berensztein S, Gene RJ. Effects of supplemental oxygen during activity in patients with advanced COPD without severe resting hypoxemia. *Chest.* 2001;120(2):437-443.
17. Long-Term Oxygen Treatment Trial Research G, Albert RK, Au DH, et al. A Randomized Trial of Long-Term Oxygen for COPD with Moderate Desaturation. *N Engl J Med.* 2016;375(17):1617-1627.
18. Sandland CJ, Morgan MD, Singh SJ. Detecting oxygen desaturation in patients with COPD: incremental versus endurance shuttle walking. *Respir Med.* 2008;102(8):1148-1152.
19. Combes A, Costa MA, Trouillet JL, et al. Morbidity, mortality, and quality-of-life outcomes of patients requiring >or=14 days of mechanical ventilation. *Crit Care Med.* 2003;31(5):1373-1381.
20. Nishiyama O, Miyajima H, Fukai Y, et al. Effect of ambulatory oxygen on exertional dyspnea in IPF patients without resting hypoxemia. *Respir Med.* 2013;107(8):1241-1246.
21. Burns JR. Early Ambulation of Patients Requiring Ventilatory Assistance. *Chest.* 1975;68(4):608.
22. Dyer F, Flude L, Bazari F, et al. Non-invasive ventilation (NIV) as an aid to rehabilitation in acute respiratory disease. *BMC Pulm Med.* 2011;11:58.
23. Menadue C, Alison JA, Piper AJ, Flunt D, Ellis ER. Bilevel ventilation during exercise in acute on chronic respiratory failure: a preliminary study. *Respir Med.* 2010;104(2):219-227.
24. Jolley SE, Dale CR, Hough CL. Hospital-level factors associated with report of physical activity in patients on mechanical ventilation across Washington State. *Ann Am Thorac Soc.* 2015;12(2):209-215.
25. Hodgson CL, Stiller K, Needham DM, et al. Expert consensus and recommendations on safety criteria for active mobilization of mechanically ventilated critically ill adults. *Crit Care.* 2014;18(6):658.
26. Spruit MA, Watkins ML, Edwards LD, et al. Determinants of poor 6-min walking distance in patients with COPD: the ECLIPSE cohort. *Respir Med.* 2010;104(6):849-857.
27. Waugh JB, Granger WM. An evaluation of 2 new devices for nasal high-flow gas therapy. *Respiratory care.* 2004;49(8):902-906.

28. Woodhead DD, Lambert DK, Clark JM, Christensen RD. Comparing two methods of delivering high-flow gas therapy by nasal cannula following endotracheal extubation: a prospective, randomized, masked, crossover trial. *Journal of perinatology : official journal of the California Perinatal Association.* 2006;26(8):481-485.
29. Frizzola M, Miller TL, Rodriguez ME, et al. High-flow nasal cannula: impact on oxygenation and ventilation in an acute lung injury model. *Pediatric pulmonology.* 2011;46(1):67-74.
30. Greenspan JS, Wolfson MR, Shaffer TH. Airway responsiveness to low inspired gas temperature in preterm neonates. *The Journal of pediatrics.* 1991;118(3):443-445.
31. Shepard JW, Jr., Burger CD. Nasal and oral flow-volume loops in normal subjects and patients with obstructive sleep apnea. *Am Rev Respir Dis.* 1990;142(6 Pt 1):1288-1293.
32. McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2015(2):CD003793.
33. Laboratories ATSCoPSfCPF. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med.* 2002;166(1):111-117.
34. McGinley BM, Patil SP, Kirkness JP, Smith PL, Schwartz AR, Schneider H. A nasal cannula can be used to treat obstructive sleep apnea. *Am J Respir Crit Care Med.* 2007;176(2):194-200.
35. Parke R, McGuinness S, Eccleston M. Nasal high-flow therapy delivers low level positive airway pressure. *British journal of anaesthesia.* 2009;103(6):886-890.
36. Hasani A, Chapman TH, McCool D, Smith RE, Dilworth JP, Agnew JE. Domiciliary humidification improves lung mucociliary clearance in patients with bronchiectasis. *Chron Respir Dis.* 2008;5(2):81-86.
37. Williams R, Rankin N, Smith T, Galler D, Seakins P. Relationship between the humidity and temperature of inspired gas and the function of the airway mucosa. *Crit Care Med.* 1996;24(11):1920-1929.