CLINICAL EFFICACY IN RELIEF OF DYSPNEA BY HVNI: EVALUATION OF NEW DEVICE EQUIVALENCE

NCT04590014

11 JUNE 2021

Vapotherm, Inc

New HVNI Device Design Efficacy in Relieving Dyspnea

Confidential

Protocol Title:	**Clinical Efficacy in Relief of Dyspnea by HVNI: Evaluation of New Device Equivalence**
Protocol Number:	RP-VT2.02020001Sci
Revision:	Rev 1.2 – 11 June 2021
Principal Investigator:	Charles W. Atwood, Jr., MD, FCCP, FAASM
Co-Investigators:	TBD
Sponsor:	Vapotherm, Inc 100 Domain Drive Exeter, NH 03833 1 (603) 658-0011 http://www.vtherm.com
Site Monitor(s):	Amanda DeBellis, MSc, Clinical Research Associate Sohrab Mayar, MS RRT, Clinical Research Manager

Protocol Approval

Investigator Agreement

As Investigator of the study titled "Clinical Efficacy in Relief of Dyspnea by HVNI: Evaluation of New Device Equivalence" (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): a system consisting of heated and humidified gas mixtures of varying FiO_2 delivered to a patient using a small-bore nasal cannula, at generally high flow rates imparted with increased velocity as compared to other standard large-bore cannulae. The flow rates of respiratory gas generally exceed a patient's normal spontaneous inspiratory flow demand. HVNI systems must maintain adequate heating and humidification of the delivered gas to protect the nasal tissues from dryness and provide patient comfort.

Non-Invasive Positive Pressure Ventilation (NIPPV): Breathing assist where a mask is strapped tightly to a patient's face and bi-level positive airway pressure is administered at an established frequency to support patient ventilation. NIPPV may also refer to Continuous Positive Airway Pressure (CPAP).

Intubation: The placement of an endotracheal tube to facilitate respiratory support and provide airway protection.

Respiratory Failure: The inability to maintain sufficient arterial blood oxygen saturation and/or retention of carbon dioxide levels during unassisted spontaneous breathing.

Pulmonary Rehabilitation: Exercise regimen for patients with compromised cardio-pulmonary function designed to improve pulmonary parameters.

Pulse Oximetry Reading (SpO_2): Indirect measure of a patient's arterial blood oxygen saturation using pulse oximetry technology that utilizes oxygen/hemoglobin concentrations.

Resting SpO_2: SpO_2 value the patient demonstrated at rest, while sitting upright and connected to the pulse oximetry monitor prior to the start of the study session. This value will be patient specific and reflect oxygen saturation.

Desaturation SpO_2: The SpO_2 value considered to be the point of desaturation where the value drops below a specified threshold. 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 signs and symptoms of increased physical exertion, manifested through pulmonary changes leading to the use of accessory muscles for inspiration or exhalation.

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, BPM): The number of breaths a subject takes per minute (breaths·min^{-1}).

Blood Pressure (BP): as measured by systolic and diastolic pressures of the blood contained in the circulatory system, measured for this study in mmHg.

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. The rate of perceived dyspnea (RPD)is determined by patients and clinicians to using specific descriptors, on a scale of 0 (no dyspnea) to 10 (unbearable dyspnea). The modified Borg scale is additionally used for rating the subjective perceived exertion (RPE) 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.

Transcutaneous CO_2 (TcCO2): This non-invasive method of measuring circulating CO_2 transdermally, indicating trends for arterial carbon dioxide levels using a locally heated electrochemical sensor applied to the skin, can be used to assess a patient's adequate ventilation and oxygenation.

I. Background and Significance

Hypoxemia and dyspnea are hallmark characteristics of patients with chronic pulmonary disease and can be attributed to acute respiratory failure. [1] Oxygen therapy is generally a first stage in addressing dyspnea and hypoxia. Often times this therapy is delivered via various devices that provide pressure (mechanical ventilation [MV], non-invasive positive pressure ventilation [NIPPV]) and flow-based (high-velocity nasal insufflation [HVNI] and high flow nasal cannula [HFNC]) modalities to support oxygenation and ventilation, and in many cases, NIPPV & HVNI have been demonstrated to provide comparable support. [2-4] The key difference in these modalities can best be described by the alveolar ventilation equation: alveolar ventilation = (Inspired Volume – Dead Space) X Respiratory Rate. Inspired volume is achieved by adding pressure (NIPPV) and Dead Space is eliminated via HVNI; Two separate mechanism of actions that influence alveolar ventilation. HVNI is a therapeutic alternative to NIPPV.[2]

Vapotherm HVNI therapy, a refined form of HFNC, is premised on the technical ability to create ideally conditioned medical grade vapor, which is delivered nasally with an intent to support spontaneous ventilation as opposed to simple oxygen therapy. [5,6] 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. [7] The high velocity nasal flow facilitates a well described mechanism of improving ventilatory efficiency by way of eliminating carbon dioxide traditionally stacked in anatomical dead space of the upper airway. [6]

Upper airway purge is important to alveolar gas exchange as the gas that is drawn to the respiratory regions of the lungs comes from the dead space or anatomical reservoir created by the flush, in the same way that oxygen conservation masks (re-breathers) can incorporate reservoir bags to reduce the bulk flow requirements from the oxygen source to achieve the same oxygenation effect. [6,8] Based on mathematical modeling, physiologic studies and clinical observations, a flow rate of 4 to 8 L·min^{-1} through Vapotherm's neonatal cannulae, or 25 to 40 L·min^{-1} through Vapotherm's adult cannulae, would purge the anatomical reservoir of the upper airway in the window of time between breaths. [9-12]

Vapotherm's humidification system is 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). [8] 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 [6-8,13,14].[6-8,13,14] 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 to the Emergency Department. [2] To this day trials have supported HFOT at home in patients with COPD. Low Flow Oxygen Therapy (LFOT) is not enough for COPD patients to have a safe at home stay. In these patients HFOT has been shown to be a valuable option to decrease work of breathing and improve dyspnea. In a retrospective study it was found that HFOT is a capable technology in the home and post-acute rehab facilities to maintain patients with end stage hypoxemic lung disease. As Vapotherm leads the innovation of new cannulae for the purpose of HVNI, to provide increased patient comfort, we also seek to evaluate a new device equivalent to Precision Flow technology that will impact ventilatory work effort on dyspneic patients in the home. The goal of the current study is to evaluate Precision

Flow HVNI to HVT2.0 HVNI in a head to head randomized control trial of severely hypercapneic inpatients and outpatients requiring ventilation support.

II. Overall Study Objective

The **overall objective** of this study is to evaluate the ability of HVT2.0, a new HVNI device to improve ventilation, dyspnea and related physiological responses relative to the conventional Precision Flow device design.

The **hypothesis** is that the HVT2.0 device that provides HVNI will deliver comparable ventilation and relief of patient dyspnea, when compared to the Precision Flow device in an inpatient or outpatient hospital setting.

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

Aim #1: Primary Outcome. The primary endpoint is the patient's targeted relief of dyspnea, as measured by the modified Borg (rated perceived dyspnea [RPD]) for each device design tested.

Aim #2: Secondary Outcomes. The secondary endpoints evaluate the patient vital signs (heart rate [HR], respiratory rate [RR], blood pressure [BP]), arterial oxygen saturation (SpO_2), and PCO2 as measured by a transcutaneous CO2 device (TcPCO2). These measurements will be compiled and compared for each device design tested.

Aim #3: Tertiary Outcomes. The tertiary endpoints evaluate the patient and clinician assessment scores. For the patient perception/satisfaction these include: (1) relief of symptoms, and (2) comfort/tolerance. For the clinician perceptions these include: (1) technical/clinical difficulties, (2) patient comfort & tolerance, (3) ease of use, (4) monitoring & support for therapy, and (5) expected/perceived patient outcomes.

The **endpoints** described will establish equivalence of outcomes between Precision Flow HVNI and HVT2.0 HVNI device design.

III. Subject Selection

Subjects will be identified through the use of patient medical records and recruited by study investigators. The study will take place in an inpatient or outpatient setting capable of supporting patients presenting with hypercapnic respiratory failure. Device testing during this study will be performed under the direct supervision of qualified healthcare professionals and appropriately trained study staff to maintain patient safety. The ~~test~~ study will evaluate patient dyspnea, vital signs, ventilation, and oxygenation for each device design tested. Initial patient contact will be made by study investigators. Participants may decide whether to enroll after being consented; furthermore, participants may choose to withdraw their consent at any point throughout the study.

Inclusion Criteria

1. Adults, 18 years or older
2. Demonstrated dyspnea at baseline, established by clinician OR patient assessment (see below)
    a. Borg Rated Perceived Dyspnea (scale 0-10) of 3 or higher
3. Severe patient baseline hypercarbia/hypercapnia of 50mmHg or higher as measured by TcCo2 or arterial or venous blood gas

Exclusion Criteria

1. Patient has unstable cardiovascular condition
2. Significant nasal occlusion either unilateral or bilateral
3. Inability to provide informed consent
4. Pregnancy
5. Known contraindication to perform steps of the protocol
6. Absence of spontaneous respiration or known contraindication to HVNI
7. Inability to use nasal and/or HVNI therapy
8. Agitation or uncooperativeness
9. Determined by the clinician to be sufficiently unstable or unsuitable for this study

IV. Study Design

This study is an efficacy study, which will be performed as a prospective, order-randomized crossover design trial to evaluate the ability of the new HVT2.0 HVNI device design to effect ventilation and physiological responses relative to the Precision Flow HVNI device design. Patients deemed by investigators to meet inclusion criteria will undergo the study procedures for both arms of the crossover design. Patients are expected to complete the study in one session. After each of the study arms, both clinicians and patients will complete perception score assessments as measured by continuous Visual Analogue Scales (VAS). The clinical management of patients will otherwise remain unchanged based on-site standards of care~~.~~

This study has two phases. Each phase of the study will correspond to a different device design. In phase 1, the patients will be order randomized to the Precision Flow (Control) design phase, **or** to the new HVT2.0 design (Testing) phase. In phase-2 the order will change.

- Phase 1 – Precision Flow (Control) or HVT2.0 (Testing) (order randomized)
- Phase 2 – Precision Flow (Control) or HVT2.0 (Testing) (order randomized)

This study design will focus on <u>four distinct segments for each phase</u>: (1) baseline characterization, (2) therapy acclimatization, (3) therapeutic characterization, and (4) Continuous VAS for both

patient and clinician perception assessment scores. The baseline characterization for Phase 1 will provide patient background, history, and initial clinical evaluation. For Phase 2, baseline characterization will only include the initial clinical evaluation as no further initial evaluation is warranted. An acclimatization period is not necessary for Phase 2, as both devices will have been calibrated in Phase 1, requiring only a cannula change. Titration of therapy (Flow/FiO2) is only expected during Phase 1(or in the event the patient decompensates and requires adjustment), as this study is a comparison of device efficacy. For the therapeutic characterization segment of each phase, final patient data for the corresponding device design will be recorded. Following this, the clinician and the patient will complete VAS perception scores corresponding to each device design. Primary and secondary outcomes will be evaluated and recorded upon the completion of **all** study phases. Tertiary outcomes will be evaluated and recorded upon the completion of **each** study phase.

This study will be conducted in an inpatient or outpatient hospital setting where patient testing can be performed with appropriate medical supervision and staff training to maintain patient safety. All respiratory interventions will be tracked within the study window for each patient.

V. Subject Enrollment

Subjects will be recruited by investigators using patient medical records and initial patient contact. Subjects will be consented prior to participation in this study (Aims 1-3). Once consented, the participants and investigators will complete data collection in all Aims during the trial period. Subjects have the right to withdraw consent to participate in this study at any time, for any reason.

Sample Size:
To provide a sufficiently powered sample dataset, we will enroll up to 32 subjects to complete this study on designs, with a calculated sample size of N=26 plus a 20% failure/fallout rate. This will provide sufficient data to adequately inform on the study objectives.

This sample size was estimated through use of references that (1) approximated minimal clinical important difference of dyspnea (modified Borg scale) and (2) approximated expected standard deviation of prior datasets measuring dyspnea.[16-18] Estimated minimal clinical important difference of dyspnea was determined to be a difference value of 2 in modified Borg for dyspnea.[16] In reviewing publications from Roca 2010 and Schwabbauer 2014, it was estimated that a value of 2 to 3 was suitable for the standard deviation of dyspnea for the modified Borg scale. Therefore, for this study, using the paired t-test sample size calculation, with an expected difference of 2, and an expected standard deviation of 3, using a desired power of 90% with alpha=0.05, the sample size is estimated at 26 to show if the data may or may not have any difference.

VI. Study Procedures

This validation study is non-blinded to investigators and patients by necessity, as there is a distinct difference in size and appearance between the Precision Flow and HVT2.0 HVNI device designs. However, patients may not know the difference between conventional and new device design. This study is a crossover design trial that will measure, ventilation, comfort, and efficacy—specifically the effect of relief of dyspnea as demonstrated by RPD assessment and measured by TcPCO2 device. In addition, patient physiologic outcomes (e.g. HR, RR, BP, SpO2), as well as patient & clinician assessment scores will be evaluated and recorded. Figure 1 illustrates a flowchart of overall study procedures.

Screening, Enrollment, & Management

During screening, subjects will be asked to participate in this study, and if so, they will provide informed consent prior to enrollment. Subjects will be instructed that if at any time during the study that they wish to discontinue the study, they are free to stop the testing and discontinue study participation at any time. All study procedures will be explained to the subject prior to starting any procedures, and all participants will be given a copy of the informed consent form.

Upon enrollment, appropriate study data will be collected (see below under Data Collection), including patient demographics (e.g. age, gender, ethnicity, race), anthropometrics (e.g. weight, height, BMI, and applicable medical history) including a detailed focus on the patient's current respiratory status (LTOT user, positive-airway pressure therapy [NIPPV] 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 with regard to patient participation will be made in conjunction with appropriate medical professionals per standard practice at the trial site. Time required from screening to the end of the study, is estimated to be 1.65 hours in duration.

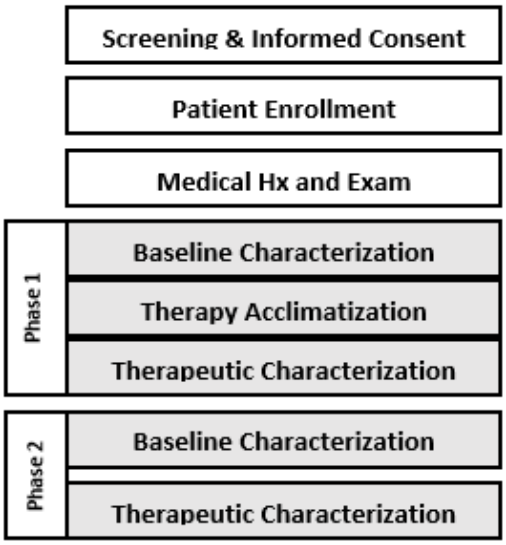

Figure 1. Framework of the clinical study procedures discussed within this protocol. Each Phase is designated by a Precision Flow or HVT2.0 design.

Phase 1 – Precision Flow (Control) or HVT2.0 (Test) design (order randomized)
This test session is represented by Phase 1 in Figure 1, where the patient is placed on HVNI device therapy with the order-randomized conventional or new device design. Phase 1 will follow four distinct segments: (1) baseline characterization, (2) therapy acclimatization, (3) therapeutic characterization, (4) patient and clinician assessment scores.

Baseline Characterization will be performed just prior to the therapy acclimatization segment of this Phase. If, for any reason, the clinician does not deem the patient appropriate for the study, per inclusion/exclusion criteria, they may stop procedures during baseline characterization. The patient may be sitting or lying down in a comfortable environment. The patient will be set up for study testing with appropriate data recording devices. While subject is at rest, the following data will be collected (see Table 1): RR, HR, BP, SpO2, TcPCO2 and RPD (Modified Borg scale 0-10). For the RPD, the clinician will record patient scores. The patient may or may not be on HVNI therapy at ~~this~~ the time the RPD is completed. The Phase 1, baseline characterization will include recording data while the patient is in an uncompromised state (e.g. ON current oxygen therapy, if applicable).

Therapy acclimatization (5 – 10 minutes) will be performed immediately after the baseline characterization segment is complete, and in accordance with site standard of care practices to maintain patient safety. The patient will be fitted with an appropriately-sized Prosoft dual-pronged nasal cannula, which is not to exceed 50% occlusion of the nares. Patient will be notified of best practice for the therapy and investigators will record whether patients choose to keep their mouths open or closed. The acclimatization segment is the interval during which HVNI is to be titrated to provide the patient the appropriate settings for effective HVNI therapy. After the final FiO2/Flow settings are implemented and the patient is acclimatized the following data will be collected (see Table 1): RR, HR, BP, SpO2, TcPCO2 and RPD (Modified Borg scale 0-10). For the RPD, the clinician will record patient scores. Effective flow ~~is~~ will be recorded. Therapy acclimatization is only necessary in Phase 1, as both devices used in this study will be operating on the same settings.

> HVNI therapy provided by either Precision Flow or HVT2.0 will be initiated per settings identified below, after which settings will be titrated per standard practice for optimal effect. When patients are placed, the HVNI initial settings will be the following: FiO_2 = level approximating the patient's prior prescription (e.g. if by nasal cannula [NC], 1LPM NC = 24%, 2LPM NC = 28%, 3LPM NC = 32%, etc.), Flow = 15 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. The flowrate can be decreased or increased as rapidly as necessary to alleviate respiratory distress and optimize patient comfort. Targets should be to provide relief of perceived dyspnea at an HVNI flow rate between 20 to 35 L/min (up to 40L/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 set initially to approximate the likely previous dosage (see above) to initially to assure adequate oxygenation, but this should be adjusted to maintain a PaO_2 > 88%.

Therapeutic Characterization will be performed 5-10 minutes after the therapy acclimatization segment is completed. This will provide the patient sufficient time to receive clinical effect of the HVNI therapy and become sufficiently comfortable with the therapy and cannula. Once the respiratory therapist or other clinician skilled in management of HVNI deems that the HVNI

settings are having a therapeutic effect, the following data will be collected (see Table 1): RR, HR, BP, SpO2, tcPCO2 and RPD (Modified Borg scale 0-10). For the RPD, the clinician will record patient scores.

Patient & Clinician Perception Assessment will be performed by the clinician or therapist performing this phase's testing procedures. Immediately following the completion of this phase, the continuous Visual Analogue Scale (VAS) will be completed for each of the five endpoints for clinician assessment and two endpoints for the patient assessment. For patient perception/satisfaction, these endpoints include: (1) relief of symptoms, and (2) comfort/tolerance. For clinician perceptions, these endpoints include: (1) technical/clinical difficulties, (2) patient comfort & tolerance, (3) ease of use, (4) monitoring & support for therapy, and (5) expected/perceived patient outcomes.

Phase 2 – Precision Flow (Control) or HVT2.0 (Test) design (order randomized) This test session is represented by Phase 2 in Figure 1, where the patient is placed on HVNI therapy with the order-randomized Precision Flow or HVT2.0 device design. Phase 2 will follow three distinct segments: (1) baseline characterization, (2) therapeutic characterization, (3) patient and clinician assessment scores. After Phase 2 is completed the patient will be placed on their original therapy. If the patient was on HVNI prior to the study period, the patient will continue, and a non-study use only Precision Flow device will be exchanged for the study Precision Flow or HVT2.0 device.

Baseline Characterization will be performed just prior to the therapy acclimatization segment of this Phase. If, for any reason, the clinician does not deem the patient appropriate for the study, per inclusion/exclusion criteria, they may stop procedures during baseline characterization. Sitting down in a comfortable environment, the patient will be setup and prepared for the testing with appropriate data recording devices. The patient will be ON current/home oxygen therapy at this time (if applicable). While the subject is at rest, the following data will be collected (see Table 1): RR, HR, BP, SpO2, tcPCO2 and RPD (Modified Borg scale 0-10). For the RPD, the clinician will record patient scores.

Therapeutic Characterization will be performed immediately after the baseline segment is completed in Phase 2 only. Once the respiratory therapist or other clinician skilled in management of HVNI deems that the HVNI settings are having a therapeutic effect, the following data will be collected (see Table 1): RR, HR, BP, SpO2, TcPCO2 and RPD (Modified Borg scale 0-10). For the RPD, the clinician will record patient scores.

Patient & Clinician Perception Assessments will be performed by the clinician or therapist performing this phase's testing procedures. Immediately following the completion of this phase, the continuous Visual Analogue Scale (VAS) will be completed for each of the five endpoints for clinician assessment and the two endpoints for patient assessment. For patient perception these endpoints include: (1) relief of symptoms, and (2) comfort/tolerance. For clinician perception these endpoints include: (1) technical/clinical difficulties, (2) patient comfort & tolerance, (3) ease of use, (4) monitoring & support for therapy, and (5) expected/perceived patient outcomes.

Upon completion of Phase 2, the study testing procedures will be deemed completed, and any final study data will be recorded at this time. At this time, the patient may resume current/home oxygen therapy.

Other Medical Care
All other medical treatment will remain the purview of the attending physician and will be administered per hospital standards. This study is designed only to evaluate patients' ventilatory performance, oxygenation, and physiologic parameters while on HVNI with current and new device designs. It is assumed that ancillary interventions will follow common clinical practice guidelines and conventions. All treatments given to the subjects will be noted on appropriate CRFs.

VII. Data Collection

Table 1. Key study data and collection points for each Phase of the Study.

	Baseline Characterization	Therapy Acclimatization	Therapeutic Characterization	@ Study End
Patient History & Health	X			
Treatment: Flow & O2	X	X	X	
Physiologic Parameters	X	X	X	
Ventilation Parameters	X	X	X	
Clinician Perception Scores			X	X
Patient Perception Scores			X	X

Data collection during enrollment will include patient history, health, demographics, and current respiratory therapies. Patients' health history and background information will be recorded in Phase 1 only. For each segment of each phase, the following data will be recorded for comparison:

Physiologic Parameters
- SpO_2, HR, RR, BP

Ventilation Parameters
- RPD, TcCO2

Primary Endpoint
- Modified Borg scale score(s) –Rated Perceived Dyspnea (RPD)

Secondary Endpoints
- Physiologic parameter(s) – SpO_2, HR, RR, BP
- Ventilation parameter(s) –TcCO2

Tertiary Endpoints – Patient & Clinician Assessment
- Patient Assessment
  - Patient assessment of respiratory response to therapy, ranging from Insufficient to Excellent Response, as continuous VAS.
  - Patient assessment of comfort and tolerance of the therapy, ranging from Insufficient to Excellent as continuous VAS.
- Clinician Assessment
  - Clinician assessment of patient respiratory response to therapy, ranging from Insufficient to Excellent Response, as continuous VAS.
  - Clinician assessment of frequency of rain-out, interface slippage or other technical/clinical difficulties applying therapy, ranging from Never to Frequent as continuous VAS.

- Clinician assessment of patient comfort and tolerance of therapy, ranging from Insufficient to Excellent as continuous VAS.
- Clinician a 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 Minimal to Frequent, as continuous VAS.

VIII. Statistical Analysis

Baseline patient demographics and characteristics will be summarized, compared, and appropriate statistical testing will be performed for the continuous and categorical variables. Assuming a non-normal data distribution for this crossover order-randomized study design, the non-parametric Wilcoxon Signed Rank Sum test will be performed with significance interval of 0.05 on all applicable variables. Parametric analytical analogues (e.g. t-test) will be use if the measurements present a normal distribution. 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 validation study does not present significant risk to patients, as supplemental oxygen is routinely provided to patients as a standard practice in hospitals [19]. Use of high flow nasal cannula (HFNC) therapy has no known risks and has been used in clinical settings for approximately 17 years. Additionally, there are no known reports of adverse events related to the administration of high nasal flows when the gas has been appropriately conditioned to near body temperature and fully humidified. Existing literature indicates that approximately only 4 cmH_2O of distending pressure may be generated in the upper airway, which is well below any known threshold for injury. [20,21] Furthermore, it has been demonstrated that delivery of high flows of conditioned gas from a nasal cannula has a positive effect on airway mucosal function. [22,23] The patients enrolled in this study will be closely monitored as part of standard medical practice.

For these reasons, we have determined that this study represents non-significant risk to the subjects. The high flow nasal cannula system used has no known risk and has been used in hospitals for approximately 17 years. During both study phases, patients will be closely monitored as part of the normal care. Patients may experience mild discomfort from a cannula in contact with their nose, face or around their ears and possibly a runny nose from the humidity contained in the gas flow.

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 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 the effect device designs can have on patient dyspnea relief.

XI. Monitoring and Quality Assurance

The clinical trial site will be monitored in accordance with Vapotherm's policies and federal regulations that pertain to clinical research, namely 21 CFR Parts 50, 54, 56 and 812 and others as applicable. Monitoring will occur at regular frequency by the PI or designee, such as to allow ongoing review of data collected, site qualifications and compliance with study protocol. All investigators will be appropriately trained to ensure compliance with study protocol. Audits of the study CRF's will be regularly conducted by the Sponsor.

XII. Protocol Deviations

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

- Deviation from procedural sequencing, per protocol
- Failure to complete Baseline characterization
- Failure to complete all sections of all Study Phases
- Failure to capture time and place in trial of any device failure
- Failure to capture/record any data included as part of the study 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 actions (e.g. re-training of site personnel) to attempt to ensure compliance with protocol. Any pattern of repeated and/or serious protocol deviations 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(s) will determine whether any adverse events have occurred. For the purposes of this protocol, an adverse event is any undesirable event experienced by 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 representative (site monitor) indicated on page 1.

XIV. Confidentiality

Rigorous procedures will be followed to maintain confidentiality of patient identification and test-related information and to adhere to government regulations concerning privacy. A unique identification number designed to protect the identity of patients will be used to identify the patient on case report forms, recruitment logs, data forms or other reports.

This unique identification number will not be linked to identifiable patient data; no personal or identifiable patient data will be reported. The Vapotherm clinical research staff member managing the study will be the only person to have knowledge pertaining to the link between the unique identifiable number and the subject. All other Vapotherm representatives involved in this study will only have access to the patients' unique identification number. The linked data will be

maintained by the site study staff and stored at the study 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. *Ann Emerg Med.* 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. Waugh JB, Granger WM. An evaluation of 2 new devices for nasal high-flow gas therapy. *Respiratory care.* 2004;49(8):902-906.
6. Dysart K, Miller TL, Wolfson MR, Shaffer TH. Research in high flow therapy: mechanisms of action. *Respiratory medicine.* 2009;103(10):1400-1405.
7. 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.
8. 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.
9. Doshi P, Whittle JS, Bublewicz M, et al. High-Velocity Nasal Insufflation in the Treatment of Respiratory Failure: A Randomized Clinical Trial. *Ann Emerg Med.* 2018.
10. Weiler T, Kamerkar A, Hotz J, Ross PA, Newth CJL, Khemani RG. The Relationship between High Flow Nasal Cannula Flow Rate and Effort of Breathing in Children. *The Journal of pediatrics.* 2017;189:66-71.
11. Yoder BA, Manley B, Collins CL, et al. Consensus approach to nasal high-flow therapy in neonates. *Journal of Perinatology.* 2017;Advanced Online Publication.
12. Miller TL, Saberi B, Saberi S. Computational Fluid Dynamics Modeling of Extrathoracic Airway Flush: Evaluation of High Flow Nasal Cannula Design Elements. *Journal of Pulmonary & Respiratory Medicine.* 2016;6(5):376.
13. 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.
14. 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.
15. Dolidon S, Dupuis J, Molano Valencia LC, et al. Characteristics and outcome of patients set up on high-flow oxygen therapy at home. *Therapeutic advances in respiratory disease.* 2019;13:1753466619879794.

16. Crisafulli E, Clini EM. Measures of dyspnea in pulmonary rehabilitation. *Multidiscip Respir Med.* 2010;5(3):202-210.
17. Schwabbauer N, Berg B, Blumenstock G, Haap M, Hetzel J, Riessen R. Nasal high-flow oxygen therapy in patients with hypoxic respiratory failure: effect on functional and subjective respiratory parameters compared to conventional oxygen therapy and non-invasive ventilation (NIV). *BMC Anesthesiol.* 2014;14:66.
18. Roca O, Riera J, Torres F, Masclans JR. High-flow oxygen therapy in acute respiratory failure. *Respiratory care.* 2010;55(4):408-413.
19. Laboratories ATSCoPSfCPF. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med.* 2002;166(1):111-117.
20. 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.
21. 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.
22. 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.
23. 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. *Critical care medicine.* 1996;24(11):1920-1929.