CLINICAL EFFICACY IN RELIEF OF DYSPNEA BY HVNI: EVALUATION OF NEW CANNULAE DESIGNS

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Vapotherm, Inc

HVNI Cannula Efficacy in Relieving Dyspnea

Confidential

Protocol Title:	**Clinical Efficacy in Relief of Dyspnea by HVNI: Evaluation of New Cannulae Designs**
Protocol Number:	RP-VTPF2019001Sci
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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): 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.

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 ($breaths \cdot min^{-1}$).

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 (TcPCO2): 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 $L \cdot min^{-1}$ through Vapotherm's neonatal cannulae, or 25 to 40 $L \cdot min^{-1}$ through Vapotherm's adult cannulae, would purge the anatomical reservoir of the upper airway in the window of time between breaths. [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] As Vapotherm leads the innovation of new cannulae for the purpose of HVNI, we seek to evaluate the ability of these cannulae to impact ventilatory work effort on dyspneic patients. The goals of the current study are to: (1) evaluate if next generation dual prong (Prosoft) cannulae provide comparable dyspneic relief among hypercapnic adults with accompanying dyspnea compared to current legacy (control) cannula design, and (2) assess if next generation Solo (Unicorn) cannulas at lower flows provide comparable dyspneic relief among hypercapnic adults with accompanying dyspnea compared to current legacy to Dual-prong cannula (Prosoft) design.

II. Overall Study Objective

The **overall objective** of this study is to evaluate the ability of HVNI next generation Prosoft nasal cannula designs to effect ventilation and related physiological responses relative to the conventional legacy cannula design, with which there are published clinical outcomes data.

The **hypothesis**: The next generation nasal cannula designs (Prosoft and Unicorn) will be comparable at relieving patient dyspnea while on HVNI, when compared to the conventional legacy cannula.

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 scale (rated perceived dyspnea [RPD]) for each cannula 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 arterial CO2 as measured by a transcutaneous CO2 device (TcPCO2). These measurements will be compiled for each cannula design tested.

Aim #3: Tertiary Outcomes. The tertiary endpoints evaluate both patient and clinician perception assessment scores. 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.

These **endpoints** will establish equivalence of outcomes between the legacy cannula and the new cannula designs (both Unicorn and Prosoft) in terms of the ability to relieve dyspnea in adult hypercapnic patients experiencing dyspnea.

III. Subject Selection

Subjects will be identified and recruited by study investigators. The study will take place in an inpatient setting sufficient to support patients presenting with hypercapnic respiratory failure. Testing during this study will be performed in the presence of health care professionals who will provide appropriate supervision and staff training to maintain patient safety. The test will evaluate patient dyspnea, vital signs, ventilation, and oxygenation for each cannula design tested. Initial patient contact will be made by study investigators. Participants may or may not decide to enroll in the study after being consented.

Inclusion Criteria

1. Adults, 18 years or older
2. The cannula prong(s) (Unicorn and Prosoft) will fit the nostril(s) so that the cannula prongs will not occlude more than 50% of the available nostril aperture of any single nostril accommodating a cannula prong.
3. Demonstrated dyspnea at baseline, established by patient OR clinician assessment (see below)
    a. Borg Rated Perceived Dyspnea (scale 0-10) of 3 or higher
4. Severe patient baseline hypercarbia/hypercapnia of 50 mmHg or higher as measured by TcPCo2 or arterial or venous blood gas

Exclusion Criteria

1. Patient has unstable cardiovascular condition
2. Significant unilateral or bilateral nasal occlusion
3. Vigorous physical activity should not be performed within 2 hours of testing
4. Inability to provide informed consent
5. Pregnancy
6. Known contraindication to perform steps of the protocol
7. Absence of spontaneous respiration or known contraindication to HVNI
8. Inability to use nasal cannula and HVNI therapy
9. Agitation or uncooperativeness
10. Determined by the clinician to be sufficiently unstable or unsuitable for this study

IV. Study Design

This will be an efficacy study, performed as a prospective, order-randomized crossover design trial to evaluate the ability of next generation HVNI nasal cannula designs (Unicorn and Prosoft) to effect ventilation and related physiological responses relative to the conventional legacy cannula design. Patients deemed to fit the criteria for inclusion will perform the study procedures for both arms of the crossover design. Completing both arms will compare the next generation cannula designs to the commonly used legacy design for comfort, comparative therapeutic response, and outcomes per the study aims. Patients are expected to complete the study in one session, with appropriate pauses between each nasal cannula design testing procedures. After each of the study arms, the clinicians will complete perception score assessments. The clinical management will otherwise remain unchanged based on site standard of care practice.

Each phase of the study will correspond to a different cannula design. Patients will be enrolled and initially entered into the control/baseline phase with the conventional legacy cannula (control), then will be order randomized to either of the next generation cannula designs (Test: Unicorn, or Prosoft).

- Phase 1 – Conventional Legacy cannula design (Control)

- Phase 2 – Next generation cannula design (Test#1) (order randomized)
- Phase 3 –Next generation cannula design (Test#2) (order randomized)

This study design will focus on four distinct segments for each phase: (1) baseline characterization, (2) therapy acclimatization, (3) therapeutic characterization, and (4) VAS for both patient and clinician assessment scores. The baseline characterization for Phase 1 will provide patient background, history, and initial clinical evaluation. For Phases 2 and 3, baseline characterization will only include the initial clinical evaluation, as no further initial evaluation is warranted. The acclimatization period will provide patients time to become accustomed to the HVNI therapy and both designs of nasal cannula design. Titration of therapy (Flow/FiO2) is only expected during Phase 1 (or in the event the patient decompensates and needs adjustment), the legacy cannula, as this study is a comparison of cannula efficacy. For the therapeutic characterization, final patient data for the cannula design will be recorded. Following this, the clinician and the patient will complete the cannula design's VAS perception scores. Primary and secondary outcomes will be completed upon the conclusion of all study phases. Tertiary outcomes will be completed at the end of each individual phase.

This study will be conducted in an inpatient 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 during the study window for each patient.

V. Subject Enrollment

Subjects will be recruited by investigators and 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 course of the cannula trial period.

Sample Size:

To provide a sufficiently powered sample dataset, we will enroll up to 32 subjects to complete this study on nasal cannula 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.[15-17] Estimated minimal clinical important difference of dyspnea was determined to be a difference value of 2 in modified Borg for dyspnea.[15] 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 study is non-blinded by necessity, since the difference in cannulas can be perceived by both the clinician and patient. Patients may not know the difference between legacy and next generation cannulae, except in case of the Unicorn cannula design (as it employs a single-nasal prong). The next generation cannulae will be order-randomized after the conventional legacy cannula is used during the control evaluation. The study is a crossover design trial that will measure the ventilatory and comfort performance of nasal cannula design, specifically the effect on relief of dyspnea as demonstrated by RPD assessment, and measurement by TcPCO2 device. In addition, patient physiologic outcomes (e.g. HR, RR, BP, SpO2), and patient & clinician assessment scores will be assessed and documented. Figure 1 illustrates a flowchart of overall study procedures.

Screening, Enrollment, & Management

Upon screening, subjects will be asked to participate in this study, and if so, they will provide informed consent prior to enrollment. During screening, patient will be evaluated for nostril aperture areas, which will accommodate the various cannula designs without occluding greater than 50% of the aperture area of a nostril by any cannula design (per inclusion criteria #2). Subjects are instructed that if at any time during the study that they wish to discontinue 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 (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 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 participation will be made per standard practice at the trial site, relying on the judgment of the medical staff. Using cards coded to trial patient number, the two next generation test cannulae will be order-randomized and that randomization will be determined by the clinician or study staff opening sequential numbered opaque envelopes directing such randomization. Time required from screening to the end of the study, is estimated to be two hours and fifteen minutes.

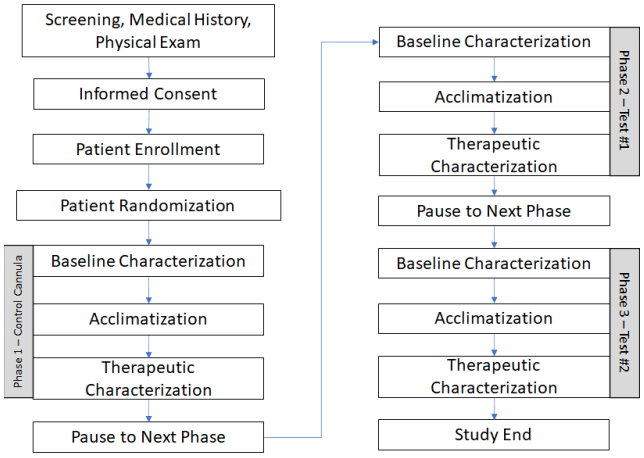

Figure 1. Framework of the clinical study procedures discussed within this protocol. Each Phase is designated by a different cannula design, with 'Test' symbolizing the order-randomized new cannula designs (i.e. Unicorn and Prosoft).

Phase 1 – Conventional Legacy cannula design (Control)
This test session is represented by Phase 1 in Figure 1, where the patient is placed on HVNI therapy with an appropriately fitted conventional legacy cannula design. Phase 1 will follow four distinct segments: (1) baseline characterization, (2) therapy acclimatization, (3) therapeutic characterization, (4) patient and clinician assessment scores. After Phase 1 is completed the next generation cannula test #1 will be able to start, as deemed appropriate by the clinician.

Baseline Characterization will be performed just prior to the therapy acclimatization segment of this Phase. If there is a reason the clinician does not deem the patient appropriate for the study, per inclusion/exclusion criteria, they may stop procedures during baseline characterization. The inpatient may be sitting or lying down in a comfortable environment. The patient will be set up and prepared for the cannula 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 time. 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 appropriately sized nasal cannula from the conventional legacy design (not to exceed 50% occlusion of the nares). Patients will be notified of best practice for the therapy, and clinicians will record whether patients prefer 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 recorded.

> 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, 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 SpO_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 Assessments will be performed by the clinician or therapist performing this phase's testing procedures. Immediately following the completion of this phase, as soon as possible, the continuous Visual Acuity Scale (VAS) will be completed for each of the five endpoints for clinician assessment and the two endpoints for patient assessment. The patient perception/satisfaction assessments include: (1) relief of symptoms, and (2) comfort/tolerance. The clinician perception assessments 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 this phase, the testing will pause for 15 minutes, until patient has returned to baseline dyspnea, prior to proceeding with the next nasal cannula design test. During this pause the patient will not perform known to worsen dyspnea. During the pause the patient will resume on their current oxygen therapy.

Phase 2 – Test #1 (randomized)
This test session is represented by Phase 2 in Figure 1, where the patient is placed on HVNI therapy with the order-randomized next generation cannula designs. Phase 2 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 there is a 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 cannula testing with appropriate data recording devices. The patient will be ON current/home oxygen therapy at this time. 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.

Therapy acclimatization (5 – 10 minutes) will be performed after the baseline characterization segment is complete, and in accordance to site SOC to maintain patient safety. The patient will be fitted with appropriately sized nasal cannula (not to exceed 50% occlusion of the nares).

- IF order-randomized to the Unicorn cannula, then use the FiO2 & one-half the Flow settings from Phase 1 as a reference for the Therapeutic Settings.
    - For nostril selection of Unicorn cannula: Ask the patient to state which nostril is easiest to breathe through. Use that nostril to place the Solo/Unicorn cannula.
- IF order-randomized to the Prosoft cannula, then use the FiO2 & the Flow settings from Phase 1 as a reference for the Therapeutic Settings.

After the designated 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. Patient perception assessment will also be evaluated at this time.

- **NOTE:** Should the patient or clinician deem that the therapy is not providing a comparable relief of dyspnea, then after recording the data stated above, proceed to increase titration of the flow until relief of symptoms, with attention to TcPCO2. At this time, the therapy acclimatization segment should be repeated, and data will be appropriately recorded to account for this 'settings' adjustment. This is to understand any difference in cannula efficacy between legacy design and next generation cannula , designs.

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, as soon as possible, the continuous Visual Acuity Scale (VAS) will be completed for each of the five endpoints for clinician assessment and the two endpoints for the patient assessment. For the patient perception these include: (1) relief of symptoms, and (2) comfort/tolerance. For the clinician perception 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.

Upon completion of this phase, the testing will pause for 15 minutes, until patient has returned to baseline dyspnea, prior to continuing with the next nasal cannula design test. During this pause the patient will not perform known to worsen dyspnea. During the pause the patient will continue with their current oxygen therapy.

Phase 3 – Test #2 (randomized)

For Phase 3, go back and repeat all procedures from Phase 2 with the difference of testing the second randomized cannula (Prosoft or Unicorn).

Upon completion of this phase, the study testing procedures will be deemed completed, and any final study data will be finished 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 in accordance with clinic standards. This study is designed to evaluate only the patients' ventilatory performance, oxygenation, and physiologic parameters while on HVNI with current and next generation cannula designs. It is assumed that the ancillary interventions will adhere to common clinical practice guidelines and conventions. All treatments given to subjects will be documented on their 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

Patient enrollment data collection will include patient history, health, demographics, and current respiratory therapies. Only Phase 1 will record the patients' history and background information. For each segment of each phase, the following data will be recorded for comparison:

Physiologic Parameters
- SpO_2, HR, RR, BP

Ventilation Parameters
- RPD, TcPCO2

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

Secondary Endpoints
- Physiologic parameter(s) – SpO_2, HR, RR, BP
- Ventilation parameter(s) –TcPCO2

Tertiary Endpoints – Patient & Clinician Assessments
- 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 assessment 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

The data analysis will be "per protocol." 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 study does not present significant risk to patients, as supplemental oxygen is routinely provided to patients as a means of standard/routine practice in the study hospitals [18]. Use of high flow nasal cannula therapy has no known risks and has been used in the clinical setting for approximately 17 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, which is well below any known threshold for injury. [19,20] Additionally, it has been demonstrated that delivery of high flows of conditioned gas from a nasal cannula has a positive effect on airway mucosal function. [21,22] The patients 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 about 17 years. During both sessions, patients will be closely monitored as part of the normal care. Patients may experience mild discomfort from a cannula coming into contact with their nose, face or around their ears; patients may also experience 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 HVNI cannula study will themselves benefit from participation in this study. The trial may result in scientific knowledge that leads to improvements in the quality of patient care, patient experience, and the effect cannula designs have on patient dyspnea relief.

XI. Monitoring and Quality Assurance

The clinical trial site will be monitored in accordance with policies at Vapotherm 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 the protocol. All investigators will be appropriately trained to ensure compliance with the 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 case report forms. These include, but are not limited to items such as the following:

- Deviation from the procedural sequencing, per the protocol
- Failure to complete the Baseline characterization
- Failure to complete all sections of the Study Phases
- Failure to capture time and place in trial 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 subjects' participation in the study, the investigator will determine whether any adverse events have occurred. For the purposes of this protocol, an adverse event is defined as 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, whether 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 subject identification and test-related information and to adhere to government regulations concerning privacy. Methods to protect the privacy of subjects and clinical information are employed and built into the trial. 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 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

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