Vapotherm

Clinical Stabilization of Hypercapnia NIPPV v HVNI

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Vapotherm, Inc

Hypercapnia Stabilization RCT NIPPV v HVNI

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Protocol Title:	**Hypercapnia Clinical Efficacy by NIPPV v HVNI: A Randomized Control Trial in the Stabilization of Acute Hypercarbic Respiratory Failure (HYPERACT)**
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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 "Hypercapnia Clinical Efficacy by NIPPV v HVNI: A Randomized Control Trial in the Stabilization of Acute Hypercarbic Respiratory Failure" (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: _____

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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): HVNI exists as a refined form of HFNC, 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.

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 patient 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), an accepted and well-published form of measuring breathlessness, is determined by patients and clinicians to using specific descriptors, on a scale of 0 (no dyspnea) to 10 (unbearable dyspnea).

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(s). 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. CRFs may be digitally compiled. The CRFs are the property of Vapotherm.

I. Background and Significance

Patients with Chronic Obstructive Pulmonary Disease experience a complex physiologic derangement marked by various levels of chronic increased mucus production and chronic alveolar destruction. Ultimately, this leads to impaired ventilation and difficulties with gas exchange, producing hypercapnia, and in some cases leading to hypoxia. While the chronic disease typically progresses gradually over many years, patients experience several intermittent rapid decompensations per year, in the form of acute exacerbations. The etiology of these acute exacerbations is multi-factorial, but they are often hallmarked by increased work of breathing, discomfort/shortness of breath, and the more severe exacerbations progress to hypercapnic respiratory acidosis, hypoxia, and ultimately respiratory failure.[1]

Treatment of acute exacerbations of COPD is multimodal; these modalities often include bronchodilators, steroids, and antibiotics. Respiratory support and treatment of acute hypercapnic respiratory failure (AHRF) secondary to an Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) is most commonly provided through non-invasive positive pressure ventilation (NIPPV), or in some cases mechanical ventilation (MV). A recent Cochrane meta-analysis by Osadnik et al 2017 compared the efficacy of NIPPV when applied in conjunction with usual care practices versus usual care without MV in adults with AHRF secondary to AECOPD.[2] Data from 17 randomized controlled trials containing 1264 patients, this Cochrane meta-analysis demonstrated that NIPPV decreased the risk of mortality by 46% and decreased risk of requiring intubation by 65%, which resulted in an associated reduction in hospital LOS, reduced incidence of complications, and improvement in pH & PaO_2 within 1-hour. The improvement in $PaCO_2$ was shown to trend but was not found to be statistically significant. Further *post hoc* analysis showed a positive statistical result. The authors concluded that NIPPV is "beneficial as a first-line intervention in conjunction with usual care for reducing the likelihood of mortality and intubation in patients admitted with AHRF secondary to AECOPD," and the benefits "appear similar for patients with mild acidosis (pH 7.30 to 7.35) versus a more severe nature (pH < 7.30), and when NIV is applied within the intensive care unit (ICU) or ward setting."

Ventilatory therapy has historically been delivered via various devices that provide positive pressure (MV, NIPPV, and continuous positive airway pressure [CPAP]). The goal of using these devices is to have an effect on the volume component of the alveolar ventilation equation: Alveolar ventilation = (Volume-Dead Space) X Respiratory Rate. Flow-based therapy, particularly High-Velocity Nasal Insufflation [HVNI], supports oxygenation and ventilation by flushing the dead space component of the alveolar ventilation equation.[3,4] Furthermore, it has been demonstrated that NIPPV & HVNI provide comparable therapeutic support. [5-7] Two separate mechanisms of action are available which influence alveolar ventilation. HVNI has been shown to be a therapeutic alternative to NIPPV.[5]

Vapotherm HVNI therapy, is premised on the technical ability to create ideally conditioned medical grade vapor, which is delivered nasally with an intent to support spontaneous ventilation. [3,8] Vapotherm technology is unique in its ability to provide this optimally conditioned gas through a small-prong nasal cannula resulting in a high velocity, physiologically warmed humidified gas without the well-known adverse effects related to drying and cooling of the nasal mucosa that occurs with simple oxygen therapy. [9] In addition and uniquely, 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.[3] 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. This mechanism operates similarly to that of oxygen conservation masks (re-breathers). These masks create an

artificial reservoir through bags to reduce the bulk flow requirements from the oxygen source to achieve the same oxygenation effect. [3,10] HVNI uses the anatomic dead space as a natural reservoir for oxygen to support patients who require oxygenation when needed as well as utilize anatomic dead space to flush CO_2 from the respiratory stack.[4] Based on mathematical modeling of standard anatomy, 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 of CO_2 in the window of time between breaths. [4,11-13]

Vapotherm's humidification system is specifically designed to tolerate a high back pressure in the humidification cartridge that is generated by passing these high flow rates through small bore cannulae that result in the appropriate flow velocities (turbulent energy). [10] 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. [3,9,10,14,15] A multi-center 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. [5] The current study is an extension of the prior published studies' outcomes. The goal of this randomized control trial is to evaluate, the relative efficacy of HVNI or NIPPV to clinically stabilize & relieve the patient's moderate-to-severe hypercapnic respiratory distress, through oxygenation and ventilation, upon presentation.

II. Overall Study Objective

The **overall objective** of this randomized study is to evaluate the efficacy of HVNI, in comparison to NIPPV, to clinically stabilize and provide respiratory therapy to patients who have COPD with moderate-to-severe hypercapnic respiratory distress upon presentation.

The **hypothesis**: HVNI is comparable to NIPPV in the stabilization and relief of moderate-to-severe hypercapnic respiratory distress upon presentation, by relieving the patient's dyspnea (breathlessness) within 4 hours to a comparable degree to NIPPV.

Ho: $\mu_T <= \mu_C - 1$
Ha: $\mu_T > \mu_C - 1$,
where μ_T and μ_C are the improvement in modified BORG at 4 hours for treatment (Vapotherm) and control (NIPPV), respectively, and the non-inferiority margin is 1.

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

Aim #1: Primary Outcome. The primary endpoint is to evaluate the patient's relief of dyspnea, as measured by the modified Borg, rated perceived dyspnea [RPD 0-10], during the 4-hour post-therapy initiation interval. These measurements will be compiled over the time course of the study – baseline, 30min, 1h, and 4h.

Aim #2: Secondary Outcomes. The secondary endpoints evaluate treatment failure (need for intubation), indices of Work of Breathing (patient vitals [HR, RR, SpO_2]), patient's clinical stability during hypercapnic respiratory distress, as measured by an index of patient communication capability [Patient Stability Index: 0-10], venous blood gases (pH, PCO_2, PO_2, bicarbonate, base excess), basic metabolic panel* (lactate, Na^+, K^+, Cl^-, glucose), and patient disposition (length of stay [LOS]). These measurements will be compiled over the time course of the study – baseline*, 30min, 1h, and 4h. The Patient Stability Index is described in the protocol.

***Basic metabolic panel (BMP) will be collected at baseline only.**
Aim #3: Tertiary Outcomes. The tertiary endpoints evaluate patient and clinician assessment of therapy. For the patient perception/satisfaction these include: (1) relief of symptoms, and (2) comfort/tolerance. For the clinician perceptions these include: (1) expected/perceived patient outcomes, (2) patient comfort & tolerance, and (3) ease of use.

These **endpoints** will establish comparability of HVNI to NIPPV in Acute Hypercapnic Respiratory Distress.

III. Subject Selection

Patients will be identified and recruited by study investigators or research staff trained on this particular trial. The study will initiate in an Emergency Department setting, or from an inpatient setting, and transfer to an acute-care unit that is sufficiently staffed and skilled in NIPPV and HVNI to support patients presenting with moderate to severe hypercapnic respiratory acidosis. Testing during this study will be performed in the presence of health care individuals who will provide appropriate supervision and staff training to maintain patient safety. The test will evaluate the patient's relief of dyspnea, clinical stability, WOB indices (vitals, RPD, ventilation, oxygenation), patient disposition, and patient and physician perceptions for each study arm before and during therapy for hypercapnic respiratory distress. Initial patient contact will be made by study investigators or research staff trained on this particular trial. Participants may or may not decide to enroll after being consented. Consent in this ED/acute-care-setting-based study will be obtained by a verbal consent prior to participation/randomization followed by written consent (when patient is medically stable), or a written consent prior to participation/randomization. The verbal consent will be obtained and documented in the patient chart along with a witnessed attestation. The written consent will be obtained once patient is able to participate in a consent discussion, when their respiratory symptoms are manageable.

Inclusion Criteria – *Selection of Inclusion*

1. Adults, 18 years or older with a known or suspected diagnosis of COPD
    a. Suspected diagnosis of COPD defined as a history of smoking or significant second-hand smoke, plus clinical history of wheezing, chronic cough, bronchospasm, or exacerbations, and/or exposure with hypercapnia
2. Presentation with acute hypercapnic respiratory failure defined as:
    a. Moderate to Severe patient baseline hypercarbia/hypercapnia, defined as a baseline PCO_2 of 60 mmHg or higher (as measured by venous blood gas)
3. Venous pH of 7.0 – 7.35

Exclusion Criteria

1. Severe metabolic derangements, e.g. suspected drug overdose, mixed acid/base disorder (bicarbonate at normal or above to be eligible)
2. Need for airway protection, e.g. neurologic disorder(s)
3. Primary condition of Congestive Heart Failure, e.g. Acute Severe Decompensated Heart Failure
4. Need for emergent intubation
5. Pneumonia diagnosis with significant infiltrate on chest x-ray that is clinically correlated with pneumonia
6. Inability to provide informed consent
7. Pregnancy
8. Known contraindication to perform procedures listed, or therapies described in the protocol
9. Respiratory arrest or significant respiratory depression on presentation
10. Significant nasal occlusion either unilateral or bilateral
11. Absence of spontaneous respiration or known contraindication to HVNI
12. Extreme agitation or uncooperativeness that would hinder either arm of randomized therapy
13. Determined by the clinician to be sufficiently unstable or unsuitable for this study

IV. Study Design

This will be performed as a prospective, unblinded (by definition), multicenter, 1:1 randomized non-inferiority design clinical trial to evaluate the efficacy of HVNI compared to NIPPV (two approved interventions for the management of acute respiratory distress) in the clinical stabilization and relief of moderate-to-severe respiratory distress requiring ventilatory support upon presentation. Patients deemed to fit the criteria for inclusion will perform the study procedures for one of the study arms of the randomized study design. Patient completion of either of the study arms will provide an evaluation of the efficacy of HVNI or NIPPV in stabilization and relief of respiratory acidosis and will record patient ventilatory/WOB indices, treatment failure, disposition, and physiologic parameters during a 4-hour therapy-response window. Additionally, tertiary outcomes will provide an evaluation of patient comfort, and therapeutic response, per the study aims. Patients are expected to complete the study in one session, per the noted parameter sampling intervals (baseline, 30min, 1hr, 4hr). After the patient completes the randomized study arm (HVNI or NIPPV), the clinicians and patients will complete perception score assessments. The clinical management will otherwise remain unchanged, based on individual study site standard of care and practice.

This study will utilize two arms. Patients presenting with acute hypercapnic respiratory failure (per Inclusion criteria, in need of clinical stabilization and relief of moderate-to-severe respiratory distress) who are escalated to treatment with a non-invasive respiratory support modality will be randomized to one of the following:

- Vapotherm high flow nasal cannula therapy (HVNI) administered as defined below (HVNI arm)
- Non-invasive positive pressure ventilation (NIPPV) delivered via single-limb circuit with a full face mask using a pressure support mechanical ventilator system (e.g., Respironics Vision, V60) administered as defined below (NIPPV arm)

The study design will focus on six distinct phases for each study arm, which will be identical except for the therapy randomization (HVNI or NIPPV): (1) Study Start, (2) Baseline Characterization, (3) Therapy Evaluation Interval 1, (4) Therapy Evaluation Interval 2, (5) Therapy Evaluation Interval 3, and (6) Study End. Primary, secondary, and tertiary outcomes will be completed upon the completion of all study phases.

The Study Start Phase will follow screening and consent, and will confirm randomization to either study arm, and gather the patient background, history, health, demographics, and current respiratory therapies. For Phase 2, Baseline Characterization will provide the initial clinical evaluation along with the baseline physiologic parameters, ventilation parameters, Patient Stability Index, and blood gases. For Phase 3, the Therapy Interval 1 will provide the current patient status at 30minutes post randomized therapy interval and will include this interval's physiologic parameters, ventilation parameters, Patient Stability Index, and venous blood gases. For Phase 4, the Therapy Interval 2 will provide the current patient status at 1hour post randomized therapy interval and will include this interval's physiologic parameters, ventilation parameters, Patient Stability Index, and venous blood gases. For Phase 5, the Therapy Interval 3 will provide the current patient status at 4-hour post randomized therapy interval and will include this interval's physiologic parameters, ventilation parameters, Patient Stability Index, and venous blood gases. Following the 3rd Therapy Evaluation Interval at 4hours, Phase 6 will be implemented, which concludes with Study End. Phase 6 will include Visual Analog Scale (VAS) for both patient and clinician assessment scores. The clinician and the patient will complete VAS perception scores for their randomized study arm (HVNI or NIPPV) at designated intervals.

This study will be conducted in an Emergency Department or Inpatient Critical Care setting, if applicable, where patient care and testing can be performed with appropriate supervision and staff training to maintain patient safety. In this acute-care setting study, participants may or may not decide to enroll after being consented. Patients may be excluded after randomization, as this study takes place in the ED or inpatient critical care unit and patients may need to be randomized and treated immediately to maintain patient safety. All respiratory interventions will be tracked during the study window for each patient.

V. Subject Enrollment

Subjects will be solicited by investigators and consented as described above (Section III), due to the emergent need for treatment at time of initial presentation. Should subjects provide initial verbal or written consent, only then will data be compiled and used as part of the subject participation in this study (Aims 1-3). Once enrolled, and randomized 1:1 to study arms, the participants and investigators will complete data collection in all Aims during the course of the trial timeline.

Sample Size:

This trial will randomize subjects 1:1 to Vapotherm:NIPPV. A total sample size of 64 subjects (~32 per arm) randomized with endpoint data, and a one-sided alpha of 0.025 will provide at least 80% power to demonstrate non-inferiority. This sample size assumes a difference of 0.9 between treatment and control with standard deviation of 2.4 and 2.9 for treatment and control, respectively, and a non-inferiority margin of 1.0.

Allowing for up to 20% attrition, approximately 80 subjects (40 per arm) will be enrolled in order to achieve 64 subjects with an endpoint.

From Doshi et al, comparable moderate-to-severe hypercapnic respiratory distress patient data was analyzed, which informed this sample size calculation's assumed difference and standard deviations in treatment (HVNI) and control (NIPPV) for the modified Borg score.[5]

Change in modified Borg over 4 hours	**Mean**	**Standard Deviation**
NIPPV arm (Control)	-3.208	2.431
HVNI arm (Treatment)	-4.143	2.931

The minimal clinically important difference (MCID) for modified Borg was informed from literature, as a difference value of 1.0.[16]

NOTE: As this is an Emergency Department or inpatient acute care study, and treatment is often immediate due to need for maintaining patient safety, there is an expected patient dropout (i.e. incomplete or unusable subject number) of randomized & enrolled patients into this study. After presenting to the ED or inpatient acute care setting, should the patients be transferred to another area of the hospital, the study procedures will continue until complete.

VI. Study Procedures

This head-to-head non-inferiority randomized control trial is non-blinded by necessity, as the devices are different in size, apparatus, and appearance, when viewed by both patients and clinicians. Patients may prefer HVNI over NIPPV or NIPPV over HVNI; however, this will not play a role in patient randomization. The study is a 1:1 randomized control design trial that will measure & compare the physiologic effect of the tested devices, specifically the effect on relieving patient dyspnea, and the stabilization and improvement of patient pH and PCO_2 (venous blood gas). In addition, patient physiologic outcomes (e.g. HR, RR, BP, SpO_2), patient disposition (LOS), patient venous blood gases (pH, PCO_2, PO_2, bicarbonate, base excess ,) and patient & clinician assessment scores will be assessed and documented. Figure 1 illustrates a flowchart of overall study procedures. Except for the randomized study arm (HVNI or NIPPV device), the study procedures are identical.

Screening, Enrollment, & Management

Upon screening and fitting subject selection criteria, known at time of presentation to the ED or Acute Care unit for treatment, subjects may or may not be able to be asked to be randomized and enrolled into this study. In ED or Acute Care settings, there is a need to treat immediately to maintain patient safety. As such, consent in this study will take place through verbal consent prior to participation/randomization followed by written consent (when respiratory symptoms are manageable), or written consent prior to participation/randomization. Patients will be reassured that their medical care will not be impacted in any way and their medical providers will not change. All patients randomized, but not included in the final study population, will be accounted for in a CONSORT diagram, noting the dropout criteria (i.e. refused consent, met exclusion criteria, incomplete dataset, etc.). All study procedures will be explained to the subject.

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/care at the trial site, relying on the judgment of qualified medical professionals on staff.

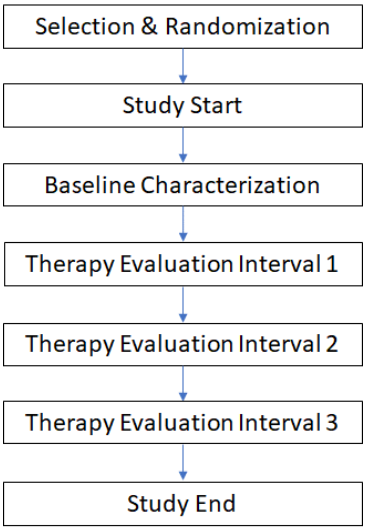

Figure 1. Framework of the clinical study procedures discussed within this protocol for the two study arms: HVNI and NIPPV.

Phase 1 – Study Start/Setup & Patient Background
Upon enrollment and randomization, the Study Start Phase will confirm inclusion criteria, record randomization to either study arm (HVNI or NIPPV), and will collect/record appropriate patient background, history, health, demographics, anthropometrics, and current respiratory therapies and respiratory status.

Appropriate Patient Background data will be collected (see below under Data Collection), including patient demographics (e.g. age, gender, ethnicity, race), anthropometrics (e.g. weight, height, BMI), COVID-19 status, 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). Patient medication data will be recorded and tracked for this study. Patient data necessary for calculating the severity index score of BAP-65 will be recorded at this time.

Phase 2 – Baseline Characterization
The baseline characterization will provide the initial clinical evaluation. Upon enrollment, randomization, and patient background collection, an venous blood gas sample will be drawn to establish the patient baseline at the time just prior to placing the patient on either of the study arm therapies (HVNI or NIPPV). Patient baseline for physiologic parameters (RR, HR, SpO2, BP, RPD) and venous blood gas parameters (PCO_2, PO_2, pH, bicarbonate, base excess,) will be collected at this time, prior to the initiation of the assigned/randomized therapy. A basic metabolic panel (BUN, CO_2, Creatinine, Glucose, Chloride, Potassium, Sodium, Calcium) will also be collected at this time. For the RPD, the clinician will record patient scores. Patient Stability Index evaluation will be evaluated by clinicians and recorded at this time, described as follows: to assess patient clinical stability using a continuous VAS score on a scale from unable to speak, due to severe respiratory distress, up to speaks in full sentences without severe respiratory distress.

At baseline, only patient perception scores will take place. During the noted study phases, the clinician and the patient will complete VAS perception scores (annotated on 100mm line with an "X") for their randomized study arm (HVNI or NIPPV). Patient & Clinician Perception Assessment will be performed by the clinician or therapist performing or participating in the testing procedures. The Perception Assessments will be completed for each of the three endpoints for clinician assessment and the two endpoints for the patient assessment. For the patient perception/satisfaction these include: (1) relief of symptoms, and (2) comfort/tolerance. For the clinician perceptions these include: (1) expected/perceived patient outcomes, (2) patient comfort & tolerance, and (3) ease of use.

The assigned therapy per randomization will be implemented per the initial settings identified below, after which settings will be titrated per standard practice for optimal effect. Patients will be managed by routine care while study data is captured as per the timeline given in Table 1. Note: All decision making for intubation, treatment regimen, discharge, and disposition will be made per standard practice at each center using the judgment of the PI, Sub-I or their designee.

Initial Settings for Comparative Therapies – HVNI and NIPPV
The initial settings in the two arms are designed as a standardization of usual medical treatment for the respective therapies and were devised to provide critical intervention and rapid abatement of both dyspnea and increased work of breathing. Once the patient has been placed upon the initial settings, the medical staff may, and should, manipulate and titrate the settings to optimize effectiveness and subject's tolerance. Overall

target should be to lower respiratory rate by 20% or below 24 br/min, while subsequently clinically stabilizing and reliving moderate-to-severe hypercapnic respiratory distress.

HVNI will be initiated *per the settings identified here*, after which settings will be titrated per standard practice for optimal effect. Patients will be fitted with a Vapotherm nasal cannula that will be applied by a respiratory therapist or other clinician skilled in management of HVNI (not to exceed 50% occlusion of the nares). When appropriate cannula are placed, the HVNI initial settings will be the following: FiO_2 = 0.50 (unless the patient is receiving supplemental O_2, and then FiO_2 will reflect amount of O_2 patient is receiving provided that the SpO_2 monitor reflects sufficient oxygenation), Flow = 30 L/min, and Temperature = 37°C. The flowrate can be decreased/increased as rapidly as necessary to optimize patient response and comfort, after a 5min acclimatization. Starting temperature will be 37°C; if patients find the gas temperature to be uncomfortable (warm), 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 (if any) to initially to assure adequate oxygenation, but this should be adjusted (range 0.21 to 1.0) to maintain an SpO_2 88-94%, per normal clinical management. If possible, FiO_2 should be weaned to 0.30 or lower while maintaining SpO_2 88-94%. NOTE: The flow rate is expected to be increased to the maximum rate of 40 L/min before a patient is removed from HVNI therapy.

NIPPV will be initiated *per the initial settings identified here*, after which settings will be titrated per standard practice for optimal effect. When patients are placed, the NIPPV initial settings will be the following: 12 cmH_2O / 6 cmH_2O (IPAP/EPAP), such that IPAP is 6 cmH_2O above EPAP, with Backup Ventilation Rate = 0-4 breathes/min (lowest), and applied at the site's standard of care (SOC) for humidification (settings to be recorded). Patients will be fit with an oronasal mask using a fitting gauge that will be applied by a respiratory therapist or other clinician skilled in management of NIPPV. Initial pressures will be at low end of suggested range but can be increased as rapidly as necessary to alleviate respiratory distress. Targeted tidal volumes of 6-8 ml/kg ideal body weight will be the volume goal. If patients find pressures uncomfortably high/low, they can be adjusted as necessary by 1 to 2 cmH_2O decrements to enhance tolerance. EPAP (PEEP) can also be adjusted upward as needed to reduce triggering effort (by counterbalancing auto-PEEP) or to improve oxygenation. FiO_2 will be 0.50 initially to assure adequate oxygenation (unless the patient is receiving supplemental O_2, and then FiO_2 will reflect amount of O_2 patient is receiving provided that the SpO_2 monitor reflects sufficient oxygenation), but should be adjusted promptly to maintain an SpO_2 88-94%, per normal clinical management. If possible, FiO_2 should be weaned to 0.30 or lower while maintaining SpO_2 88-94%.

Treatment failure *will be defined as:*

1. Failure to tolerate device if the patient is unable to tolerate the mask, nasal prongs, air flow or pressure, has persisting asynchrony and is unable to cooperate with the therapy.
2. Failure to oxygenate if the modality is unable to sustain an SpO_2 sat > 88 - 92% or PaO_2 > 60 – 65 mmHg despite maximal treatment with FiO_2=100% and optimal manipulations of flow rate and/or airway pressures, in spite of maximal settings per institutional standard.
3. Failure to ventilate if patients remain acutely hypercapnic and acidemic with lack of reduction in PCO_2 or improvement in pH, in spite of maximal settings per institutional standard.
4. Deteriorating medical status correlating to worsening venous blood gases related to respiratory distress, manifested by worsening mental status or hemodynamics, manifested by hypotension

(systolic BP < 90 mmHg), unremitting tachycardia (>140 or increase by >20% during therapy) or other conditions interpreted by the patient's clinicians as constituting evidence of deterioration.

Intubation Criteria will be at the discretion of the treating physician. Researchers will not interfere with clinical management decision. Researchers will attempt to ascertain the physician's rationale for intubation and categorize as one of the following: (may include multiple reasons, or other):

1. Intubation will be undertaken for unremitting respiratory failure despite maximal use of initial and/or crossover therapy as manifested by failure to maintain > 88% despite FIO_2 1.0 and optimization of flow and/or PEEP settings.
2. Progressive increase > 10 mmHg in PCO_2 and concomitant drop in pH despite maximal attempts to enhance ventilation.
3. Inability to cooperate with therapy in the face of persisting evidence of respiratory failure.
4. Unremitting agitation interfering with ability to cooperate and with persisting evidence of respiratory failure.
5. Deteriorating mental status despite maximal therapy with HVNI and/or NIPPV.
6. Worsening hemodynamic status (systemic SBP <90 mmHg or MAP < 60 mmHg despite fluid resuscitation and use of low dose pressors), unremitting life-threatening arrhythmias, cardiac or respiratory arrest or any other condition which, in the judgment of the clinical care team, warrants intubation.

Phase 3 – Therapy Evaluation Interval #1
The Therapy Evaluation Interval 1 at 30-minutes will be used to perform a VBG draw for all patients to determine if patients need emergent intubation or if Flow/FiO_2 or IPAP/EPAP/FiO_2 settings should be adjusted.

At the 30-minutes post-initiation of randomized therapy (HVNI or NIPPV), the patient will be evaluated. Patient Stability Index evaluation will be evaluated by clinicians and recorded at this time. At 30-minutes post initiation of randomized therapy, a venous blood gas sample will be drawn to establish the patient status. Patient status for physiologic parameters (RR, HR, SpO_2, BP, RPD) and venous blood gas parameters (PO_2, PCO_2, pH, bicarbonate, base excess) will also be collected at this time. For the RPD, the clinician will record patient scores. For VAS, at this time, only patient assessment scores will take place.

Any changes in the assigned therapy settings will be recorded at this interval. Record any relevant treatment intolerance and failure, need for endotracheal intubation, time spent under positive-pressure ventilation , patient mortality, elevation of patient status, and transfer to other inpatient ward/units. Should the patient be placed on intubation prior to this therapy evaluation interval, the physiologic parameters and venous blood gas parameters will be subsequently collected at intubation time. Should the patient be designated by attending clinician for discharge from the ED prior to this therapy evaluation interval, the physiologic parameters, venous blood gas parameters, and final assessment scores (per Phase 6) will be subsequently collected at this time.

Phase 4 – Therapy Evaluation Interval #2
At the 1-hour post-initiation of randomized therapy (HVNI or NIPPV), the patient will be evaluated. Patient Stability Index evaluation will be evaluated by clinicians and recorded at this time. At 1-hour post initiation of randomized therapy, a venous blood gas sample will be drawn to establish the patient status. Patient status for physiologic parameters (RR, HR, SpO_2, BP, RPD) and venous blood gas parameters (PO_2, PCO_2, pH,

bicarbonate, base excess) will also be collected at this time. For the RPD, the clinician will record patient scores. For VAS, at this time, only patient assessment scores will take place.

Any changes in the assigned therapy settings will be recorded at this interval. Record any relevant treatment intolerance and failure, need for endotracheal intubation, time spent under positive-pressure ventilation, patient mortality, elevation of patient status, and transfer to other inpatient ward/units. Should the patient be placed on intubation prior to this therapy evaluation interval, the physiologic parameters and venous blood gas parameters will be subsequently collected at intubation time. Should the patient be designated by attending clinician for discharge from the ED prior to this therapy evaluation interval, the physiologic parameters, venous blood gas parameters, and final assessment scores (per Phase 6) will be subsequently collected at this time.

Phase 5 – Therapy Evaluation Interval #3
At the 4-hour post-initiation of randomized therapy (HVNI or NIPPV), the patient will be evaluated. Patient Stability Index evaluation will be evaluated by clinicians and recorded at this time. At 4-hour post initiation of randomized therapy, a venous blood gas sample will be drawn to establish the patient status. Patient status for physiologic parameters (RR, HR, SpO_2, BP, RPD) and venous blood gas parameters (PO_2, PCO_2, pH, bicarbonate, base excess) will also be collected at this time. For the RPD, the clinician will record patient scores. For VAS, at this time, patient assessment scores will take place. Clinician VAS scores may take place either at this Phase, or at Study End (Phase 6).

Any changes in the assigned therapy settings will be recorded at this interval. Record any relevant treatment intolerance and failure, need for endotracheal intubation, time spent under positive-pressure ventilation, patient mortality, elevation of patient status, and transfer to other inpatient ward/units. Should the patient be placed on intubation prior to this therapy evaluation interval, the physiologic parameters and venous blood gas parameters will be subsequently collected at intubation time. Should the patient be designated by attending clinician for discharge from the ED prior to this therapy evaluation interval, the physiologic parameters, venous blood gas parameters, and final assessment scores (per Phase 6) will be subsequently collected at this time.

Phase 6 – Study End & Assessment Scores
Following the Therapy Evaluation Interval at 4 hours, Phase 6 will be implemented, which concludes with Study End. Patients will be actively screened for adverse events. Any information regarding patient intubation and rationale, if it pertains, will be recorded, if not previously recorded. The therapy settings at time of study end will be recorded. Any patient disposition information during the time course of these study procedures will be recorded, in addition to the patient transfer/discharge information (e.g. home, outpatient, hospital ward, etc.). A patient severity assessment score, BAP-65, will be calculated (or data needed for the calculation will be collected) before the study is completed.

At the end of the study, Phase 6 will include VAS for patient assessment score, and clinician assessment score (if not completed during Phase 5).

Upon completion of this last Phase, the study testing procedures will be deemed completed, and any final study data will be completed at this time.

Other Medical Care

All other medical treatment will remain the purview of the attending physician and will be administered per institution standards. This head-to-head randomized control trial, performed as a prospective, unblinded, multicenter, 1:1 randomized trial is designed to evaluate the efficacy of HVNI compared to NIPPV in the stabilization and relief of moderate-to-severe hypercapnic respiratory distress upon presentation. 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 for each Phase of the Study.

	Study Start	Baseline Characterization	Therapy @ 30 minutes	Therapy @ 1hr	Therapy @ 4hr	@ Study End
Patient History & Health Profile	X					X
Treatment: Flow & O2	X	X	X	X	X	X
Patient Stability Index		X	X	X	X	
Physiologic Parameters	X	X	X	X	X	
Blood Gas Parameters		X	X	X	X	
Clinician Perception Scores		X			X	X
Patient Perception Scores		X	X	X	X	X

Patient enrollment data collection will include patient history, health, demographics, and current respiratory therapies. Patient data will also include COVID-19 status. Only Phase 1, study start, will record the patient history and background information. All data collection will be noted with date/time as possible by the clinicians and per the SOC or available medical records. Blood samples (VBG) will be drawn within +15/-15 min of the indicated time from therapy initiation. Vital signs and indices will be recorded within +5/-5 of the indicated time from therapy initiation. Vital signs, including heart rate (HR), respiratory rate (RR) and blood oxygen saturation by pulse oximetry (SpO_2), will be reported from the patient monitoring systems in use. If patient is intubated this date and time, blood gases, and physiologic parameters will be recorded in addition to the reason for intubation, as deemed by the clinician(s).

For each phase, the following data will be recorded for comparison:

Physiologic Parameters

- Rated Perceived Dyspnea (RPD), SpO_2, HR, RR, BP

Blood Gas Parameters

- Venous PCO_2, PO_2, pH, bicarbonate, base excess Patient Stability Index
  - continuous VAS score on a scale from unable to speak, due to severe respiratory distress, up to speaks in full sentences without severe respiratory distress.

Primary Endpoint

- Primary Parameter – Change in modified Borg (RPD) over 4-hours

Secondary Endpoints

- Physiologic parameters –SpO_2, HR, RR, BP,
- Secondary Blood Gas parameters – Changes in venous PCO_2, venous PO_2, venous pH, venous bicarbonate, venous base excess
- Patient Stability Index – continuous VAS score on a scale from unable to speak, due to severe respiratory distress, up to speaks in full sentences without severe respiratory distress.

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.
    - "How satisfied were you with the degree of respiratory support that this patient received since presenting and enrolling in the study?"
  - Clinician assessment of patient comfort and tolerance of therapy, ranging from Insufficient to Excellent as continuous VAS.
    - "How satisfied were you with the degree of comfort and tolerance exhibited by this patient on the received therapy since presenting and enrolling in the study?"
  - Clinician assessment of simplicity of set-up and use, ranging from Complex to Simple, as continuous VAS.
    - "During the study procedures, what degree of challenge did you find in setting up and using/adjusting the device providing therapy for this patient?"

VIII. Statistical Analysis

The data analysis will be "per protocol," and per the "intention-to-treat" model. Baseline patient demographics and characteristics will be summarized, compared, and appropriate statistical testing will be performed for the continuous and categorical variables. Primary outcomes will be analyzed for statistical significance to test the null hypothesis. Assuming a non-normal data distribution for this 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 used if the measurements present a normal distribution. Otherwise, for the categorical variables, the Fisher's Exact test will be performed and shown by category. Data for patient parameters will be compared across treatment arms and time-period using Repeated Measures analysis ANOVAs to assess dependence on treatment and interactions with time. Data will be compared and graphed accordingly for a visual comparison with accompanied statistical notations. Significance will be accepted where $p < 0.05$. Analyses will be performed using SAS version 9.2 or higher or comparable statistical software.

IX. Risks and Discomforts

Vapotherm HVNI therapy has been deemed non-inferior to NIPPV.[5] This study in this patient population of acute hypercapnic respiratory failure does not present significant risk to patients, as supplemental oxygen and flushing of anatomic dead space is routinely provided to patients as a standard/routine practice in the study hospitals. [3,4,17,18] 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, which is well below any known threshold for injury. [19,20] 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. [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 approximately seventeen years. During either study arm, 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. The trial may result in knowledge that leads to improvements in the quality of care, patient experience and the effect HVNI therapy can have on patient dyspnea relief, in addition to providing valuable information on other effective modalities shown to provide comparable therapeutic effect to NIPPV.

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. Audit of the study CRF's will be regularly conducted by the Sponsor. The clinical trial site will follow all IRB regulations.

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 either of the randomized 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 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. The CRFs will have a list of predetermined adverse events to be used actively to screen during the study procedures.

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

a. 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.

b. 2. Osadnik CR, Tee VS, Carson-Chahhoud KV, Picot J, Wedzicha JA, Smith BJ. Non-invasive ventilation for the management of acute hypercapnic respiratory failure due to exacerbation of chronic obstructive pulmonary disease. *The Cochrane database of systematic reviews.* 2017;7:CD004104.

c. 3. Dysart K, Miller TL, Wolfson MR, Shaffer TH. Research in high flow therapy: mechanisms of action. *Respiratory medicine.* 2009;103(10):1400-1405.

d. 4. 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.

e. 5. 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.

f. 6. Hernández G, Roca O, Colinas L. High-flow nasal cannula support therapy: new insights and. *Critical care.* 2017;21(1):1-11.

g. 7. 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.

h. 8. Waugh JB, Granger WM. An evaluation of 2 new devices for nasal high-flow gas therapy. *Respiratory care.* 2004;49(8):902-906.

i. 9. 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.

j. 10. 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.

k. 11. 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.

l. 12. 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.

m. 13. Yoder BA, Manley B, Collins CL, et al. Consensus approach to nasal high-flow therapy in neonates. *Journal of Perinatology.* 2017;Advanced Online Publication.

n. 14. 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.

o. 15. Shepard JW, Jr., Burger CD. Nasal and oral flow-volume loops in normal subjects and patients with obstructive sleep apnea. *The American review of respiratory disease.* 1990;142(6 Pt 1):1288-1293.

p. 16. Ries AL. Minimally clinically important difference for the UCSD Shortness of Breath Questionnaire, Borg Scale, and Visual Analog Scale. *Copd.* 2005;2(1):105-110.

q. 17. Spoletini G, Alotaibi M, Blasi F, Hill NS. Heated Humidified High-Flow Nasal Oxygen in Adults: Mechanisms of Action and Clinical Implications. *Chest.* 2015;148(1):253-261.

r. 18. Laboratories ATSCoPSfCPF. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med.* 2002;166(1):111-117.

s. 19. 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.

t. 20. 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.

u. 21. 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.

v. 22. 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.