Vapotherm, Inc.

Maintaining Optimal Delivery using Automatic Titration of Oxygen in Preterm Infants receiving High Velocity Nasal Insufflation Therapy: MODERATION Neo

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Vapotherm, Inc

MODERATION Neo – Maintaining **O**ptimal **DE**live**R**y Using **A**utomatic **TI**tration of **O**xyge**N** Neonatal

Confidential

Protocol Title:	**Maintaining Optimal Delivery using Automatic Titration of Oxygen in Preterm Infants receiving High Velocity Nasal Insufflation Therapy: MODERATION Neo**
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Study site should keep protocol, all contents and related information confidential.

Vapotherm, Inc

MODERATION Neo – Maintaining **O**ptimal **DE**live**R**y Using **A**utomatic **TI**tration of **O**xyge**N** Neonatal

Confidential

Protocol Approval

Investigator Statement

As Investigator of the study titled "Maintaining Optimal Delivery using Automatic Titration of Oxygen in Preterm Infants receiving High Velocity Nasal Insufflation Therapy : MODERATION Neo (the "Study"), I agree to:

(i) conduct the Study in accordance with: this Investigator Agreement; the Study's Protocol as approved by the ethics committee (the "Protocol"); all applicable laws and regulations; and any ethics committee or regulatory 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 as supplied to me by Vapotherm, Inc. (the "Sponsor"), without first obtaining the written approval of the Sponsor;
(v) provide the Sponsor with accurate financial information as required by appropriate regulations;
(vi) supervise all testing of investigational devices that involves any Study subject;
(vii) maintain Study documentation for the period of time as required by appropriate regulations; and
(viii) supply to the Sponsor, as part of this Investigator Agreement, my curriculum vitae.

INVESTIGATOR

Signature: _____

Printed Name: _____

Date: _____

Glossary of Definitions and Terms

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.

Oxygen Assist Module (OAM): this module utilizes a closed loop control algorithm, used in conjunction with the HVNI therapy provided by Vapotherm Precision Flow, that maintains patient oxygen saturation in an optimally controlled range (90-95%). In the Reynolds study this was labeled as the IntellO_2 module.

Pulse oxygen saturation (SpO_2; %): Arterial blood oxygen saturation as measured by pulse oximetry.

Fraction of inspired oxygen (FiO_2): The fractional proportion (generally presented as a fraction but may be spoken of as percentage) of the delivered respiratory gas mixture that is oxygen.

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 key will be maintained by the site principal investigator at each center. The CRFs are the property of Vapotherm.

I. Background and Significance

The current study is designed to provide a technical validation for the Oxygen Assist Module (OAM; Vapotherm, Exeter, NH, USA) used in conjunction with the Vapotherm Precision Flow for titrating oxygen to neonates requiring non-invasive respiratory support. The Vapotherm OAM product integrates proven pulse oximetry and gas delivery technology with an innovative and proprietary algorithm that increases or decreases the FiO_2 setting to assist the clinical staff in maintaining the patient in a target SpO_2 range. The Vapotherm OAM product is a module for the Precision Flow device, which communicates with the Precision Flow through the serial interface connecting the two products: the device to the module. The Precision Flow is a Class II device and was FDA cleared (K072845) on July 17, 2008. The current Product Code under which the Precision Flow Hi-VNI is marketed is QAV. The initial Vapotherm OAM Gen0 design was used in a clinical trial in the UK (2016-2017, REC London-Chelsea 16/LO/1272, NCT02074774).[1] The Vapotherm OAM, a module to the Precision Flow device, is designed to assist the caregiver in optimizing the patients' oxygen saturation levels, but is not life sustaining as it will not replace the standard of care provided to the infant; i.e., standard SpO_2 alarms are in place and caregivers are instructed to make manual adjustments per standard care procedures.

Risk of both hyperoxia and hypoxia in preterm infants have been well described. The NeoProm Collaboration Meta-analysis confirmed that a lower SpO_2 range was associated with a higher risk of death and necrotizing enterocolitis.[2] Poets, et al., studied SpO_2 values in 1019 infants born with a mean gestational age of 25.8 weeks, and birthweight of 855g who had hypoxemic episodes of less than 80% SpO_2 for longer than 1 minute had a significantly greater odds ratio (OR, 95%CI) for late-death or disability (3.4, 1.95-5.83), cognitive/language delay (2.88, 1.65-5.02), motor impairment (5.20, 2.48-10.92), and severe ROP (2.95, 1,47-5.90) versus episode length equal to or less than 50 seconds[3]. As a result, many neonatal units target a higher range of SpO_2, for example, 90%–95%. For staff, maintaining SpO_2 targets presents a compliance challenge.[4] Avoiding both hypoxia and hyperoxia is an important goal.[5] While additional training improves compliance[6] manual maintenance of the target range 90%–95% may only be achieved less than 50% of the time.[7]

Based on prior studies, it is anticipated that the Vapotherm OAM will allow patients to spend more time in the target SpO_2 range, with the potential for other benefits. [1-7] In practice, the clinician sets the target SpO_2, and the OAM uses a validated algorithm that combines analysis of real-time measurements and trending to choose the appropriate O_2 delivery. The use of smart averaging and hysteresis algorithms protects the system from artifact causing too-rapid cycling of O_2 delivery. The system alerts the health care provider if it is unable to maintain the target within the healthcare provider's set FiO_2 limits or if maintaining the target requires a significant percentage change in the O_2 percentage delivered. In the case of system detection of inadequate SpO_2 signal, the module will alarm and revert to a clinician-set FiO_2 setting. The Vapotherm OAM maintains trend data for both SpO_2 readings and FiO_2 settings that is captured every second.

Closed loop control of inspired oxygen concentration has been in use since at least 1979 using indwelling PaO_2 electrodes and since at least 1992 using pulse oximetry (SpO_2).[8] Claure and Bancalari discuss the use of algorithms and trend data in closed loop FiO_2 control systems for keeping SpO_2 at "the target level or range set by the clinician" and summarize that "available data indicate the feasibility of automated closed loop control of FiO_2 in this population [premature infants] and suggest potential benefits by achieving a better oxygenation control while limiting oxygen exposure." [9]

In a paper from 2009, Claure and colleagues conducted a pilot clinical trial to evaluate a system for automated control of FiO_2 in maintaining SpO_2 within an intended range in preterm infants with erratic fluctuations in SpO_2.[10] The study involved sixteen infants with frequent hypoxia episodes and compared maintenance of SpO_2 within the intended range during one 4-hour period of manual adjustment and one 4-hour period of automatic adjustment. This randomized study was conducted using the Avea ventilator with a built-in automated FiO_2 adjustment function. The authors conclude that this system of automated FiO_2 adjustment improved maintenance of SpO_2 with reduced exposure to supplemental O_2, but that studies of longer duration and with standard clinical conditions are warranted.

Claure and colleagues later conducted a larger randomized trial as documented in "Multicenter Crossover Study of Automated Control of Inspired Oxygen in Ventilated Preterm Infants."[11] This study involved thirty-two infants studied during two consecutive 24 hr periods in random sequence; manual FiO_2 adjustment by clinical staff and automated adjustment. This study was, again, conducted using the Avea ventilator and SpO_2 measured with a neonatal pulse oximeter (Radical, Masimo, Irvine, CA). This study showed that automatic FiO_2 adjustment improved maintenance of an intended SpO_2 range, but increased time spent with SpO_2 between 80% and 86%. Moreover, automatic FiO_2 adjustments led to reduced exposure to high SpO_2 values, overall lower inspired oxygen concentration and reduced staff effort compared with manual adjustment.

The module examined during the aforementioned clinical studies is a currently CE-marked product (Avea-$CLiO_2$ (Vyaire [previously 'Care-Fusion'], Mettawa, IL, USA). Maria Wilinska MD, PhD and Anna Wasco, MD documented their routine use of the CliO2 for approximately a year and reported the module to be very effective in a broad range of patients.[12] The Vapotherm OAM product has the same intended function as the Avea $CliO_2$ module, namely to maintain the patient in the target SpO_2 range, but instead of building the automated FiO_2 into a ventilator, the control algorithm and pulse oximetry is incorporated into a separate system that communicates with Vapotherm's Precision Flow Hi-VNI unit. Similar to the $CliO_2$, the Vapotherm OAM is using Masimo's pulse oximetry technology to monitor SpO_2.

The Vapotherm OAM product initially featured the control loop algorithm developed by John Taube (Columbia Life Systems, Chapel Hill, NC, USA), and it has since been improved. The foundation for the algorithm has been licensed by Vapotherm, Inc. The original algorithm was validated in animal studies, before use in human infants.[13] In 1992, Dr. Bhutani and colleagues published a study using the Taube algorithm to manage oxygen delivery for infants using an oxygen hood system.[14] In this study, the patients' SpO_2 was maintained within a steady target range for a much greater percentage of time with the

automated system (81%; $p < 0.01$) compared to routine management (54%) or intense manual control with adjustments every 2 to 5 min (69%). This original algorithm was used in a clinical study conducted at Cooper University Hospital in conjunction with Vapotherm's 2000i device (the predicate to the Precision Flow) interacting with a 'Smart Blender'. In the report of the Cooper study, Drs. Saslow and Pyon demonstrated in 14 subjects studied, using each patient as their own control, that patients spent 80% of the time within their predetermined saturation range versus 60% during the manual mode ($p < 0.001$). Furthermore, the authors reported no adverse events associated with the use of the SmartBlender in either mode.[15]

The Vapotherm OAM initial version (named IntellO_2 at the time) was evaluated in a prospective order-randomized crossover clinical trial of 30 infants demonstrating at least moderate FiO_2 requirement lability.[1] The trial was conducted in the UK (John Radcliffe Hospital, Oxford University, Oxford, and St. Peter's Hospital, Chertsey) under the direction of Drs. Peter Reynolds and Kevin Ives, respectively. This study consisted of identification of preterm infants requiring HVNI therapy for ventilatory support. Patients' parents were approached for consent, and the study was performed under ethical approval and monitored by an independent Data Safety Monitoring Committee. Each baby was randomized to receive 24 hours of therapy during which the OAM (or IntellO_2 at the time) was set to either Automatic or Manual Mode. For both modes, the nursing staff were instructed to continue standard monitoring of the baby and make all necessary FiO_2 adjustments necessary to maintain SpO_2 within the range of 90 to 95%. At 24 hours, the baby was crossed over to the alternative mode of OAM (or IntellO_2 at the time) control for an additional 24 hours of data collection under the same instructions. The primary outcome was proportion of time spent within the target SpO_2 range. Similar to the Saslow experience, Reynolds, et al. found the median proportion of time spent in target range was 49% (IQR 40-57%) under manual control versus automated control time in range of 80% (IQR 70-87%), $p<0.0001$.[1] No adverse events were noted in either arm of the study. This was the longest duration data collection of any automated controller using an open (cannula) system.

In this proposed study, the algorithm is incorporated into latest generation hardware (OAM) working in conjunction with the latest generation Vapotherm HVNI system, which incorporates a precision blender (Precision Flow Hi-VNI). The updated hardware employs improved user interface characteristics but uses a similar algorithm as with the UK Reynolds study, and imparts no new risk in administration.

II. Objectives

The overall objective of this study is to demonstrate that the Vapotherm OAM, when coupled with the Precision Flow device, provides safe and efficacious automated control of fraction of inspired oxygen (FiO_2) adjustments in spontaneously breathing infants with fluctuating arterial blood oxygen saturation levels in the routine clinical environment.

Primary Safety Objective
To demonstrate that safety is not worse than standard practice. Specifically, to demonstrate that the Vapotherm OAM, used in conjunction with the Vapotherm Precision Flow Hi-VNI to treat infants with heated, humidified high velocity nasal insufflation (HVNI), is not inferior to standard practice for time that infants' arterial blood oxygen saturation exceed or drop below a target range, thus minimizing the proportion of time the subject is exposed to elevated or reduced levels of oxygen in the inspired gas.

Primary Performance Objective
To demonstrate that percent time oxygen saturation is maintained in a target range is higher than standard practice. More specifically, to demonstrate that Vapotherm OAM used in conjunction with Vapotherm Precision Flow Hi-VNI is superior to standard practice for maintaining infants' arterial blood oxygen saturation in a target range, thus minimizing the proportion of time the subject is exposed to elevated or reduced levels of oxygen in the inspired gas.

Secondary Performance Objective 1
To demonstrate that the percent time oxygen saturation is maintained in a target range is higher than standard practice for both weight categories (1000g-2500g, 2501g-3500g).

Secondary Performance Objective 2
To demonstrate that the percent time SpO_2 is maintained in a target range is higher than standard practice for subjects with both light and dark skin pigmentation.

Additional Objectives
To quantify and compare OAM to standard practice performance with additional measures including:

- Proportion of Time, Number of Episodes, and Average Duration of Episodes in both high and low SpO_2 ranges (with or without FiO_2 at or above 21%)
    - SpO_2 below target range
    - SpO_2 below 80% for episodes ≥60s
    - SpO_2 below 80%
    - SpO_2 above target range at FiO_2>0.21 (not at air)
    - SpO_2 below 70%
    - SpO_2 in 80% to 86% range
    - SpO_2 in target range at FiO_2=0.21
    - SpO_2 above 98% at FiO_2>0.21 (not at air)

  - SpO_2 below target range at FiO_2=0.21
- Number of manual adjustments to FiO_2 in manual mode compared to automated control (manual override).
- Proportion of Time at or below FiO_2 ranges compared between study arms
  - FiO_2 at 0.21 (air)
  - FiO_2 below 0.25
- SpO_2 fluctuations auto compared to manual control
  - Coefficient of variance for SpO_2 for the study arm
  - Standard deviation of SpO_2 for the study arm
- FiO_2 fluctuations Auto compared to manual control
  - Coefficient of variance for FiO_2 for the study arm
  - Standard deviation of FiO_2 for the study arm
- Index of overshoot (an elevated SpO_2 resulting from the FiO_2 titration response to a low SpO_2) and characterization of such excursions.
  - The proportion of time, number of episodes, and average duration per episode of Overshoot, defined as SpO_2 > range following SpO_2 < range for ≥10 seconds duration.
  - The proportion of time, number of episodes, and average duration per episode of Overshoot, defined as SpO_2 > range for 70s following SpO_2 < range.
- Number of Episodes of hypoxia (below range) within 60-180s after a return to FiO_2=0.21 compared between arms.
- Number of Episodes of hypoxia (below range) within 60-180s after a return to FiO_2=0.21 followed by hyperoxia (above range) within 60-180s after a return to FiO_2=0.21 compared between arms.
- The mean FiO_2 of the study arms
- Number of overall adjustments (or adjustments/hour) to FiO_2 in manual mode compared to automated control.
- The care ratio (i.e., Nurse:Baby) will be recorded, patients will be separated to care ratio, and each care ratio group will be compared between study arms for the proportion of time, number of episodes, and average duration of episodes
  - SpO_2 in target range
  - SpO_2 below target range
  - SpO_2 below 80% for episodes ≥60s
  - SpO_2 below 80%
  - SpO_2 below 70%
  - SpO_2 in 80% to 86% range
  - SpO_2 above target range at FiO_2>0.21 (not at air)
  - SpO_2 in target range at FiO_2=0.21
  - SpO_2 above 98% at FiO_2>0.21
  - SpO_2 below target range at FiO_2=0.21
- Comparison between Day versus Evening/Overnight of the Proportion of Time, Number of Episodes, and Average Duration of Episodes in target, high, and low SpO_2 ranges (with or without FiO_2 at or above 21%) by study arm

  - SpO_2 in target range
  - SpO_2 below target range
  - SpO_2 below 80% for episodes ≥60s
  - SpO_2 below 80%
  - SpO_2 below 70%
  - SpO_2 in 80% to 86% range
  - SpO_2 above target range at FiO_2>0.21 (not at air)
  - SpO_2 in target range at FiO_2=0.21
  - SpO_2 above 98% at FiO_2>0.21
  - SpO_2 below target range at FiO_2=0.21
- CONSORT Diagram will be used to articulate the patient numbers
- For each arm of the study will aggregate the proportion of time for SpO2 for data bins from <80% to 100%, and displayed using a histogram.
- For each arm of the study will aggregate the proportion of time for FiO2 for data bins 0.21 to 1.0, and displayed using a histogram.
- Adverse events as reported on the CRFs (Summarized by seriousness and relatedness to therapy)
  - Specific Serious Adverse Event
    - Death
    - Necrotizing enterocolitis or focal intestinal perforation
    - Microbiologically-confirmed or clinically suspected late-onset invasive infection
    - Intracranial abnormality (hemorrhage or focal white matter damage) on cranial ultrasound scan or other imaging
    - Pulmonary hemorrhage
  - Specific Adverse Event Related to Therapy
    - Adverse Event from SpO2 Probe
    - Related to the oxygen delivery mode, either automated or manual

III. Subject Selection

The **subjects** in this study are infants in neonatal intensive care units, born prematurely and requiring respiratory support via HVNI. The inclusion criteria are designed to identify infants who require supplemental oxygen and who therefore present an oxygen titration challenge by demonstration of spontaneous fluctuations in SpO_2 requiring adjustment of FiO_2.

As part of the interim analyses done by the data safety monitoring committee (defined below under Safety Monitoring), a review of data after every ten patients will confirm subject inclusion/exclusion criteria.

Inclusion Criteria

1. Infants delivered at a gestational age of less than or equal to 35 6/7 weeks (Preterm) being treated with high velocity nasal insufflation therapy for the management of respiratory distress syndrome

2. Patients that clinically require SpO_2 maintenance within the target range of 90-95%
3. A need for supplemental oxygen as demonstrated by a required $FiO_2 > 0.25$ at enrollment
4. Requiring a flow rate of greater than 2 $L \bullet min^{-1}$ such that the assumed inspired oxygen fraction matched delivered oxygen fraction (definition of HVNI).
5. A minimum of 6 manual FiO2 adjustments in the 24hr period prior to trial enrollment.
6. Willing/Able to complete informed consent.

Exclusion Criteria

1. Current patient weight of <1000g or >3500g at time of study
2. Major congenital abnormalities
3. Hemodynamic instability, defined as being outside of a normotensive range based on an infant's individual characteristics by clinician
4. Persistent unresolved apnea defined as: requiring 6 stimulations or more per 6 hours
5. Seizures
6. Ongoing sepsis
7. Meningitis
8. Clinician's concern regarding stability of the infant

Infants who meet the inclusion criteria and none of the exclusion criteria will be considered. Informed consent will be obtained from the infant's Parent or guardian prior to enrollment in the study, following which appropriate profile and baseline data will be recorded on the subject's Case Report Form (CRF).

IV. Study Design

This study will be a prospective, multi-center, randomized, crossover trial of automated oxygen titration versus manual titration (conventional method). Patients enrolled will have their FiO_2 managed by two mechanisms of titration (study arms) for two consecutive 24-hour periods in random order.

- Automated control (OAM), where the FiO_2 is adjusted by the OAM system with clinical staff ability to override FiO_2 when required, and instructed to do so – regardless of the mode
- Manual control (Manual), where FiO_2 is only adjusted by the clinical staff

In both arms, the infants will be receiving high velocity nasal insufflation treatment using the Vapotherm Precision Flow Hi-VNI.

The study model does not change the nature of care that is provided by the clinical staff, and the clinical staff will be largely naive to the function of the OAM mode. Therefore, if the clinical staff see fit to change FiO_2 during the Automated arm of the study they may override the module by changing the setting on the Precision Flow (without interacting with the OAM). Any manual override, and the justification for the override, will be noted on the subject's Case Report Form (CRF). SpO_2 will continue to be monitored on the ICU patient monitors per standard of care.

In both study arms, data for FiO_2, nasal cannula HVNI flowrate, gas temperature, SpO_2 and pulse rate will be logged every 1 sec by the OAM, as well as being displayed / logged by the usual patient monitoring systems in each unit. Note that the OAM can log any manual adjustments during auto mode (overrides) as well as all data while in manual mode (Auto mode off). Offline computerized analysis will reduce the recorded data for both periods to assess time spent in the specified SpO_2 range, time spent above and below the specified SpO_2 range as well as other benchmark SpO_2 values (see Data Collection and Statistical Analysis). Time spent below benchmark FiO_2 values will be assessed (e.g., FiO_2 at 21%, <25%). OAM data will be analyzed based on a modified intention-to-treat, whereby for any time the automated system is manually overridden in the 24-hour window, these outcomes data will be included into the analysis as well as the number of occurrences where manual manipulation is needed.

This study will be conducted at multiple sites, consisting of Academic Level III and IV Neonatal Intensive Care Units with proven record of experience in management of Preterm Infants requiring HVNI therapy delivered using the Precision Flow Hi-VNI technology. Each arm of the study will be assessed for 24 hours under routine clinical conditions. All staff members will be trained on the OAM operation and will have the ability to discontinue the study should the clinical condition of the patient require it.

V. Statistical Methods and Data Analyses

Descriptive statistics will be used to summarize data including mean, standard deviation, median, range and interquartile range for continuous data, and counts and percent for categorical data. Hierarchical

testing will be used to test the secondary objective(s). If both primary safety non-inferiority endpoints are passed and the primary performance endpoint is passed, we will test the secondary endpoint(s) for potential labeling claims. Analyses will be performed using SAS version 9.2 or higher, or comparable statistical software. Data from technically compromised data collection shall not be included in the analysis but will be described in detail if there are any instances.

Technical Definition of Analyzed Target Range – To be in line with common practice, for all data analyses the term 'target range' is defined as an SpO_2=90%–95% or an SpO_2=90%–100% if FiO_2=0.21. The analyzed targeted oximetric blood oxygen saturation range denoted as 'target range' in the safety performance, primary performance, secondary performance, and additional objectives/analyses is defined here, to include those babies who are not hypoxic (<90% SpO_2) whilst on room air (FiO_2=0.21). Thus, at FiO_2=0.21, an SpO_2=90%-100% is deemed within target range. These are not clinically deemed 'out of target range' when FiO2=0.21 (at air, Eupoxia), even when the SpO_2 is greater than 95%. This definition of the analyzed target range does not change the clinical practice, as clinicians still target babies to a target range of SpO_2=90%–95% by adjusting FiO_2 accordingly.

Analysis Cohorts:

Full Analysis Set (FAS) – Subjects that are randomized and receive any period of time on at least one treatment will be included in the adverse event summary.

Modified Intent to Treat (mITT) – Subjects that are randomized and receive any period of time on both treatments will be included in the primary safety and performance endpoints.

Per Protocol (PP) – Subjects that are randomized, receive both the treatments as randomized (in the correct order) and without any major deviations (e.g., inclusion/exclusion violations, informed consent not obtained) will be included in the primary safety and performance endpoints as a supplemental analysis.

Challenge Population – Subjects in the PP with at least 6 FiO2 adjustments in the manual arm will be identified as sufficiently labile subjects and will be included in supplemental analysis for safety and performance endpoints.

Missing Data

The impact of missing data due to loss to follow-up prior to completing both arms will be assessed by sensitivity analyses using several methods of imputation including multiple imputations for the primary performance and primary safety endpoints. Details will be specified in a separate statistical analysis plan.

Poolability

A poolability analysis will be performed to assess the poolability of sites with respect to the primary performance endpoint measure in the mITT subjects. A Student's t-test will be used to test for a difference in performance across sites. A significance level of 0.15 will be used to determine whether the sites are poolable. If a significant difference is found between sites, additional analyses will be done to identify factors that may be associated with this difference. Additionally, if a significant difference is observed, a random site adjusted estimate of the performance endpoint, along with 95% CI, will be provided.

Although enrollment will be monitored in an effort to strive for even allocation between sites, for purposes of the poolability analysis those sites with less than five (5) evaluable patients enrolled will be combined into a pseudo-site for purposes of analysis.

Primary Safety Objective

Objective: To demonstrate that safety is not worse than standard practice. Specifically to demonstrate that the Vapotherm OAM, used in conjunction with the Vapotherm Precision Flow Hi-VNI to treat infants with heated, humidified high velocity nasal insufflation (HVNI), is not inferior to standard practice for time that infants' arterial blood oxygen saturation exceed or drop below a target range, thus minimizing the proportion of time the subject is exposed to elevated or reduced levels of oxygen in the inspired gas.

Endpoint: There are two safety endpoints: the proportion of time spent above the target SpO2 range and the proportion of time spent below. The proportion of time expressed as a percentage will be measured by pulse oximetry (SpO_2), abstracting and analyzing recorded data over two contiguous 24-hour study periods; one 24-hour period with automated control (OAM) and one 24-hour period with manual control.

Subjects to Analyze: Subjects in the mITT cohort will be the primary analysis. Additional supplemental analyses will repeat this analysis using the FAS, the PP and Challenge cohorts. This will be used to provide an Adverse Event(s) summary.

Hypotheses:
Non-inferiority, proportion of time above range:
Ho: $D \geq \delta$
Ha: $D < \delta$,
where D = difference in proportion of time above range (OAM – standard practice) and δ is the non-inferiority margin of 5.
Non-inferiority, proportion of time below range:
Ho: $D \geq \delta$
Ha: $D < \delta$,
where D = difference in proportion of time below range (OAM – standard practice) and δ is the non-inferiority margin of 5.

If both of the non-inferiority tests below reject the null and conclude non-inferiority is achieved, we will test for superiority.

Superiority, proportion of time above range:
Ho: $D \geq 0$
Ha: $D < 0$,
where D = difference in proportion of time above range (OAM – standard practice)

Superiority, proportion of time below range:
Ho: $D \geq 0$
Ha: $D < 0$,
where D = difference in proportion of time below range (OAM – standard practice)

Analysis Method: The difference (OAM – standard practice) of the proportion of time in range will be tested using a paired t-test using a one-sided alpha of 0.025 to test non-inferiority. If both are passed, testing for superiority will be performed again using a one-sided alpha of 0.025. Both superiority tests must be passed in order to claim superiority.

Primary Performance Objective

Objective: To demonstrate that percent time oxygen saturation is maintained in a target range is higher than standard practice. More specifically, to demonstrate that Vapotherm OAM used in conjunction with Vapotherm Precision Flow Hi-VNI is superior to standard practice for maintaining infants' arterial blood oxygen saturation in a target range, thus minimizing the proportion of time the subject is exposed to elevated or reduced levels of oxygen in the inspired gas.

Endpoint: The proportion of time (expressed as a percentage) spent in the targeted arterial blood oxygen saturation range. The percentage will be measured by pulse oximetry (SpO_2), to determine the ability of the OAM to effectively titrate FiO_2 to the needs of the infant. This value will be assessed by abstracting and analyzing recorded data over two contiguous randomized 24-hour study periods; one period with automated control (OAM) and one 24-hour period with manual control.

Subjects to Analyze: Subjects in the mITT cohort will be the primary analysis. Additional supplemental analyses will repeat this analysis using the FAS, the PP and Challenge cohorts. This will be used to provide an Adverse Event(s) summary.

Hypothesis:
Ho: $D \leq 0$
Ha: $D > 0$,
Where D = difference in proportion of time in range (OAM – standard practice)

Analysis Method: The difference (OAM – standard practice) of the proportion of time in range will be tested using a paired t-test using a one-sided alpha of 0.025.

Secondary Performance Objective 1

Objective: To demonstrate that the percent time SpO_2 is maintained in a target range is higher than standard practice for subjects in each of the weight category subgroups (1000g-2500g, 2501g-3500g).

Endpoint: The proportion of time (expressed as a percentage) spent in the targeted arterial blood oxygen saturation range. The percentage will be measured by pulse oximetry (SpO_2), to determine the ability of the OAM to effectively titrate FiO_2 to the needs of the infant. This value will be assessed by abstracting and analyzing recorded data over two contiguous randomized 24-hour study periods; one period with automated control (OAM) and one 24-hour period with manual control.

Subjects to Analyze: Subjects in the mITT cohort will be the primary analysis. Additional supplemental analyses will repeat this analysis using the FAS, the PP and Challenge cohorts. This will be used to provide an Adverse Event(s) summary.

Hypothesis:
Ho: $D \leq 0$
Ha: $D > 0$,
Where D = difference in proportion of time in range (OAM – standard practice)

Analysis Method: The difference (OAM – standard practice) of the proportion of time in range will be tested using a paired t-test using a one-sided alpha of 0.025 for subjects in each category using a Hochberg adjustment to control alpha.

Secondary Performance Objective 2

Objective: To demonstrate that the percent time SpO_2 is maintained in a target range is higher than standard practice for subjects with both light and dark skin pigmentation.

Endpoint: The proportion of time (expressed as a percentage) spent in the targeted arterial blood oxygen saturation range. The percentage will be measured by pulse oximetry (SpO_2), to determine the ability of the OAM to effectively titrate FiO_2 to the needs of the infant. This value will be assessed by abstracting and analyzing recorded data over two contiguous randomized 24-hour study periods; one period with automated control (OAM) and one 24-hour period with manual control.

Subjects to Analyze: Subjects in the mITT cohort will be the primary analysis. Additional supplemental analyses will repeat this analysis using the FAS, the PP and Challenge cohorts. This will be used to provide an Adverse Event(s) summary.

Hypothesis:
Ho: $D \leq 0$
Ha: $D > 0$,
Where D = difference in proportion of time in range (OAM – standard practice)

Analysis Method: The difference (OAM – standard practice) of the proportion of time in range will be tested using a paired t-test using a one-sided alpha of 0.025 for subjects in each skin pigmentation (light or dark) category using a Hochberg adjustment to control alpha. Skin pigmentation classification will be based upon assessing the subject's skin tone as specified in Section XIII. Additionally, summaries by individual classification of skin pigmentation will be provided by each level using descriptive statistics along with a 95% confidence interval.

Additional Analyses

These exploratory analyses will use descriptive statistics to quantify values in each arm and the difference (OAM – standard practice). These analyses will use the mITT and PP populations except for adverse event summaries

To quantify and compare OAM automatic mode to standard manual practice performance with additional measures including:

- Proportion of Time, Number of Episodes, and Average Duration of Episodes in both high and low SpO_2 ranges (with or without FiO_2 at or above 21%)
  - SpO_2 below target range
  - SpO_2 below 80% for episodes ≥60s
  - SpO_2 below 80%
  - SpO_2 above target range at FiO_2>0.21 (not at air)
  - SpO_2 below 70%
  - SpO_2 in 80% to 86% range
  - SpO_2 in target range at FiO_2=0.21
  - SpO_2 above 98% at FiO_2>0.21 (not at air)
  - SpO_2 below target range at FiO_2=0.21
- Number of manual adjustments to FiO_2 in manual mode compared to automated control (manual override).
- Proportion of Time at or below FiO_2 ranges compared between study arms
  - FiO_2 at 0.21 (air)
  - FiO_2 below 0.25
- SpO_2 fluctuations compared to manual control
  - Coefficient of variance for SpO_2 for the study arm
  - Standard deviation of SpO_2 for the study arm

- FiO_2 fluctuations compared to manual control
  - Coefficient of variance for FiO_2 for the study arm
  - Standard deviation of FiO_2 for the study arm
- Index of overshoot (an elevated SpO_2 resulting from the FiO_2 titration response to a low SpO_2) and characterization of such excursions.
  - The proportion of time, number of episodes, and average duration per episode of Overshoot, defined as SpO_2 > range following SpO_2 < range for ≥10 seconds duration.
  - The proportion of time, number of episodes, and average duration per episode of Overshoot, defined as SpO_2 > range for 70s following SpO_2 < range.
- Number of Episodes of hypoxia (below range) within 60-180s after a return to FiO_2=0.21.
- Number of Episodes of hypoxia (below range) within 60-180s after a return to FiO_2=0.21 followed by hyperoxia (above range) within 60-180s after a return to FiO_2=0.21.
- The mean FiO_2 of the study arms
- Number of overall adjustments (or adjustments/hour) to FiO_2 in manual mode compared to automated control.
- The care ratio (i.e., Nurse:Baby) will be recorded, patients will be separated to care ratio, and each care ratio group will be compared between study arms for the proportion of time, number of episodes, and average duration of episodes
  - SpO_2 in target range
  - SpO_2 below target range
  - SpO_2 below 80% for episodes ≥60s
  - SpO_2 below 80%
  - SpO_2 below 70%
  - SpO_2 in 80% to 86% range
  - SpO_2 above target range at FiO_2>0.21 (not at air)
  - SpO_2 in target range at FiO_2=0.21
  - SpO_2 above 98% at FiO_2>0.21
  - SpO_2 below target range at FiO_2=0.21
- Comparison between Day versus Evening/Overnight of the Proportion of Time, Number of Episodes, and Average Duration of Episodes in target, high, and low SpO_2 ranges (with or without FiO_2 at or above 21%)
  - SpO_2 in target range
  - SpO_2 below target range
  - SpO_2 below 80% for episodes ≥60s
  - SpO_2 below 80%
  - SpO_2 below 70%
  - SpO_2 in 80% to 86% range
  - SpO_2 above target range at FiO_2>0.21 (not at air)
  - SpO_2 in target range at FiO_2=0.21
  - SpO_2 above 98% at FiO_2>0.21
  - SpO_2 below target range at FiO_2=0.21

- CONSORT Diagram will be used to articulate the patient numbers
- For each arm of the study will aggregate the proportion of time for SpO2 for data bins from <80% to 100%.
- For each arm of the study will aggregate the proportion of time for FiO2 for data bins 0.21 to 1.0.
- Adverse events as reported on the CRFs (Summarized by seriousness and relatedness to therapy) – See Appendix B for the list of adverse events and classification criteria.

Sample Size Calculations

The sample size was initially based upon data from the Reynolds trial looking at a subset of subjects expected to be enrolled in this trial (enrollment weight initially 1000g-2500g, now 1000g – 3500g). These data are presented in Tables 1 and 2 below. While we are requesting with this IDE Study to now enroll larger babies, the Study sample size will not be changing.

Table 1. Summary of unpublished Reynolds data for infants with enrollment weight 1000g or greater.

		Auto (OAM)			Manual (Standard Practice)			Difference		
SpO2 % time	**N**	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**
In range	18	76.0	12.3	79.1	47.6	14.0	50.4	28.4	10.8	27.1
Above	18	13.5	5.7	12.4	28.5	17.5	23.4	-15.0	16.2	-10.0
Below	18	14.4	7.1	12.6	27.0	8.9	27.4	-12.6	10.8	-11.5

Table 2. Summary of unpublished Reynolds data for infants by weight category.

			Auto (OAM)			Manual (Standard Practice)			Difference		
Weight	**SpO2 % time**	**N**	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**
1000-1500g	**In range**	11	74.4	11.3	77.0	47.4	11.9	50.2	26.9	6.5	26.4
	Above	11	14.2	5.4	13.6	26.8	15.1	23.3	-12.6	12.6	-10.2
	Below	11	15.3	6.6	13.9	28.7	9.5	29.4	-13.4	11.3	-14.5
1500g-2500g	**In range**	7	78.5	14.1	83.2	47.8	17.8	52.1	30.7	15.8	27.1
	Above	7	12.3	6.5	9.5	31.2	21.6	29.0	-18.9	21.3	-8.9
	Below	7	13.1	8.1	10.5	24.4	7.8	22.4	-11.3	10.8	-10.0

For sample size calculations comparing the difference of values in the same subject, the sample size is driven by the standard deviation. We will identify what difference the trial is powered to detect with the specified sample size and standard deviation.

Safety co-Endpoints – Time Above Target Range and Below Target Range:
The safety co-endpoints will be powered to detect superiority even though we will first test for non-inferiority. The change in proportion of time SpO2 was above and below range was

-15.0% ± 16.2% and -12.6% ± 10.8%, respectively. Using the largest standard deviation of 16%, again using PASS 14, a sample size of 38 will be adequate with at least 95% power for each test with a one-sided alpha of 0.025 to detect a difference as small as 10%. Both safety endpoints are powered at 95% ensure overall power is at least 90%.

Primary Performance Endpoint – Time in Target Range:
The change in proportion time SpO_2 was in target range is 28.4% ± 10.8%. Rounding the standard deviation up to 11, using PASS 14 test for paired means with a nonparametric adjustment, a two-sided alpha of 0.05, with at least 90% power, a sample size of 40 will detect a difference from zero with a mean change as small as 6%. Our expected difference far exceeds this amount.

Secondary Performance Endpoint 1 – Time in Target Range by weight subgroup:
For the secondary performance endpoint (weight stratification subgroups of primary performance endpoint), using the maximum standard deviation from the Reynolds data, a standard deviation of 15.8% will be rounded to 16% for sample size calculations. Using PASS 14, with a two-sided alpha of 0.05 and at least 90% power, a standard deviation of 16, the sample size of 17 subjects per weight stratification will be adequate to detect differences as small as 14% for time in range with adequate power.

Secondary Performance Endpoint 2 – Time in Target Range by skin pigmentation:
For the secondary performance endpoint (stratification subgroups of primary performance endpoint by skin pigmentation [light or dark]) pilot data are unavailable by skin pigmentation, but we will assume the performance is similar to the maximum standard deviation from the Reynolds data, a standard deviation of 15.8% will be rounded to 16% for sample size calculations. Using PASS 14, with a two-sided alpha of 0.05 and at least 90% power, a standard deviation of 16, the sample size of 17 subjects per skin pigmentation stratification (light or dark) will be adequate to detect differences as small as 14% for time in range with adequate power.

Overall sample size will be driven by goal of at least 17 subjects per weight group and an overall sample size of at least 40 subjects per the primary performance endpoint. Allowing up to 15% attrition, expected enrollment will be 47 subjects.

VI. Study Procedures

Necessary staff at each center will be trained on the study objectives, including the target SpO_2 ranges, alarm limits and operation of the OAM. Care of the infants is not altered, and clinical staff have the option of overriding the OAM to make manual adjustment to FiO_2 as needed throughout the study. During the Manual arm of the study, staff will be instructed to adjust FiO_2 as per normal protocol and to respond to SpO_2 alarms (titrating FiO_2 up or down) in a typical manner. Sites will be selected which are already familiar with clinical use of the HVNI therapy.

After informed consent is received and the infant is enrolled, the descriptive data will be completed on the CRF and the order of providing FiO_2 control will be randomly assigned (i.e. OAM in Automated mode followed by manual mode, or vice versa). The baby will remain instrumented to provide standard clinical monitoring (including SpO_2). A second pulse oximetry probe will be put in place to send an SpO_2 signal to the OAM without interrupting the SpO_2 signal used for the standard patient monitoring, and the placement of the OAM SpO_2 probe will be confirmed to be in the right hand (for pre-ductal values) and that the signal is valid.

The patient file will be created in the OAM and the OAM configured in recording mode; the start time will be noted in the CRF. For the manual arm, the OAM will be set to record but the automatic control setting will be left in the OFF configuration. For the automated arm, again the module will be set to record, but the automatic control setting will be selected to the AUTO mode. When the nurses conduct their routine hourly charting of SpO_2 and FiO_2, they are to confirm that the SpO_2 reading on the OAM matches that on the standard patient monitor and that the FiO_2 reading on the OAM matches that displayed on the Precision Flow.

During the study, these hourly records of SpO_2 and FiO_2 are to also be recorded on the CRF. The alarm limits and any adjustments to the alarm limits will be recorded with date/time on the CRF. The time that the study switches modality-arm will be recorded on the CRF (i.e., after the first 24-hours), and the OAM configured to preserve the prior recorded data and allow for a new recording period. During the Auto-arm of the study, any manual overrides will be recorded on the CRF along with the justification for the override. The time when the study has ended will be recorded on the CRF and the recording of data by the OAM halted. The recorded data files will be exported from the OAM onto a specified USB memory drive and delivered to the site principal investigator along with the CRF.

All FiO_2 adjustments (both manual and automatic) as well as SpO_2 parameters (including SpO_2 value and quality index) will be recorded by the OAM in the data file. Following data collection, recorded data will be downloaded to a spreadsheet for subsequent analysis. Clinical staff are instructed to perform FiO_2 adjustments as required, regardless of the study arm.

At 7-days post enrollment or at discharge from the hospital or death (if occur earlier), the infants will be checked and evaluated for specific or non-specific untoward events, as deemed by the clinical judgement of the clinician(s). This will be recorded on the CRF.

Target SpO_2 Range

For this study, the target SpO_2 range on the OAM will be 90% to 95% in all infants. The usual site's monitor's low and high alarm limits will be set to 90% and 95%, respectively.

Safety Monitoring

Care for the infants will be unchanged from normal standard of care during the conduct of this study. During the Automated arm, clinical staff has the option of making a manual adjustment to FiO_2 if deemed necessary per normal clinical decision making. These manual adjustments, SpO_2 and rationale for the change will be recorded on the CRF.

The OAM used in the study will be equipped with the following features and alerts:

- Automatic FiO_2 control: selectable ON/OFF
- User settings for upper and lower SpO_2 targets,
    - Alert for Failsafe mode (see below)
    - NOTE: The ALARMS on the standard patient monitoring collected concurrently will be set consistent with the target SpO_2 range.
- Percent Oxygen (FiO2) Alarm Limit: The clinician will set a $\%O_2$ alarm limit where, if the delivered $\%O_2$ is equal to or above the clinician-set $\%O_2$ alarm limit for 30 seconds continuous, the device provides a silent alert message. If the delivered $\%O_2$ is above the alarm limit for 1 minute continuous, it will audibly alarm.
    - NOTE: This FiO2 clinician-set alarm limit value is recorded on CRF 4 at study start and date/time when changed during study period. A significant increase in $\%O_2$ as commanded by the OAM may mask patient deterioration. Set the $\%O_2$ alarm limit appropriate for the patient to provide further notification of automatic $\%O_2$ increases.

Failsafe Mode

The OAM used in the study will be configured with a failsafe mode that defaults to a clinically-selected default FiO_2 if the SpO_2 signal becomes unreliable. The OAM will default to a failsafe FiO_2 if:

- >2 min continuous without a SpO_2 signal

Failsafe FiO_2 will be the highest of following values:

- Backup FiO_2: 21% to 100% FiO_2 set by user (for this study, the backup FiO_2 value will be left at 21%)

- Baseline FiO_2: FiO_2 setting calculated to keep the patient in the allowable target SpO_2 range during the period the Automatic FiO_2 algorithm was running
- Median FiO_2 of the last 15 seconds Automatic FiO_2 control was active

Data Safety Monitoring Committee

An independent data and safety monitoring committee will review the data set after every 10 infants enrolled and recommend termination of the study if study related adverse events indicated risk to the infants or the primary outcomes are significantly worse for the Automated arm than for the Manual arm. During this review, the independent reviewer(s) will identify for the investigators any patients that do not meet the subject inclusion/exclusion criteria.

Other Medical Care
All other pharmaceutical and medical treatment will remain the purview of the medical staff and be administered per the current standards of care in each institution. This study is designed to evaluate only the impact of automated oxygen titration via the OAM and it is assumed that the ancillary interventions will follow common clinical practice guidelines and convention.

VII. Data collection

Manually Entered Data

At the point of enrollment, baseline data will be recorded on the CRF, which includes:

- Weight at birth (grams)
- Weight at time of the study (grams)
- Gestational Age at birth (Weeks Days/7)
- Age at the time of the study (Days)
- Gender
- Race / Ethnicity, and Skin Pigmentation Classification
- Current FiO_2
- Current HVNI flow settings ($L \cdot min^{-1}$)
- Diagnoses (Primary and Secondary)
- Medications
- Acuity Score
- Confirm site of SpO_2 probe placement (right hand)
- Caregiver : Patient ratio

During the study, the clinical staff will record on the CRF the following:

- Time the study was started and confirm the initial arm (Automatic / manual)
- Time the study switched arms, and confirm the second arm (Automatic / manual)
- Hourly SpO_2 and FiO_2 readings

- Any overrides during the Automatic arm and the rationale for the override
- The time and description of any procedures done on the infant that could affect breathing or performance of pulse oximetry
- Medications listing

Automated data collection

Data logged by the data collection module(s) will be abstracted to produce total counts of events per recording period, normalized and presented per-hour, the 24-hour average, as well as hourly median/mean/stdev/min/max SpO_2 and FiO_2 values for trending.

Data logged by the data collection module(s) will be abstracted and analyzed for the following parameters:

Index	Mean ± SD	Proportion of total time spent	Episodes of occurrence	Duration of Episodes
SpO_2 within range		X		
SpO_2 coefficient of variance	X			
SpO_2 within range (any FiO_2) and between 90-100% whilst FiO_2 at 0.21		X	X	X
SpO_2 > range		X	X	X
SpO_2 > range w/ FiO_2 > 0.21		X	X	X
SpO_2 > 98%		X	X	X
SpO_2 > 98% w/ FiO_2 > 0.21		X	X	X
SpO_2 < range		X	X	X
SpO_2 in 80% to 86% range		X	X	X
SpO_2 < 80%		X	X	X
SpO2 <80% for ≥ 60 sec		X	X	X
SpO_2 < 70%		X	X	X
Overshoot: SpO_2 > range following SpO_2 < range ≥10 seconds duration		X	X	X
Overshoot: SpO_2 > range for 70 sec following SpO_2 < range		X	X	X
Time with FiO_2 at 0.21		X		
Time with FiO_2 < 0.25		X		
FiO_2 adjustments: Manual & Auto	X			
Night/Day: SpO2 within range		X	X	X

To support patient safety and to serve as an index of adequate oxygenations, pulse rate data will be logged from the SpO_2 signal and analyzed for stability within a normal range and for the occurrence of excursions outside of the normal range. The determination of normal range will be relative to each infant's clinical status. An episode, considered to be a clinically meaningful excursion, is defined with a minimum duration of 5 seconds (or, ≥5 sec) into the specified 'range of interest,' unless otherwise noted.

The designated study arm duration of 24 hours each, for a total of 48 hours was determined to reflect a normal clinical practice 'unit of time,' wherein this would allow for sufficient time to assess manual mode oxygen control behavior in at least two care giver's (e.g. clinicians – MD, RN, and RRT) shifts as well as take into account any other diurnal variation in either the patient or the NICU, to allow a reliable comparison between both study arms. Furthermore, recent publications have similarly utilized 24-hour study arms to compare manual and automated control in neonatal closed loop control algorithms: Claure 2011, Hallenberger 2014, Waitz 2015, Reynolds 2018, van del Heuvel 2018, and Gajdos 2018. Patient data which includes any study arm of less than 12 hours duration will be deemed a major protocol violation. Patient data which includes any study arm of between 12 hours and 18 hours duration will be deemed a minor study violation. Patient data collection which includes study arm data of greater than 18 hours will be deemed satisfactory and without protocol deviation.

IX. Risks and Discomforts

This study does not present any significant risk to the infants because infant monitoring during each arm of the study will be per normal standard clinical care. Clinical staff will be instructed to disregard the actions of the investigational module in their own clinical decision making and will be able to manually adjust FiO_2 if required.

Because this Study includes Physiologic Closed Loop Control technology and involves neonate patients, FDA has concluded this to be a significant risk study.

During this study any inherent risk of using adaptive control loops to manage FiO_2 is mitigated by the fact that the adaptive control algorithm that drives the OAM has been previously tested in clinical trials, and by the user configurable alarm features built into the OAM. Moreover, the study protocol calls for all medical staff to override the auto-control feature if out-of-range SpO_2 values are not corrected, or if manual adjustment to FiO_2 is clinically indicated. Lastly, a data safety monitoring committee will be able to assess unforeseen patient risk at periodic interim points in the study.

There is no foreseen discomfort associated with the study. The infants enrolled will not undergo a change in their respiratory support modality and adjustments in FiO_2 do not affect the comfort of the patient.

X. Potential Benefits

The trial may result in acceptance of a technology that leads to improvements in the ability for clinicians to provide high-quality care. Such improvement in providing clinician support may subsequently result in improved patient outcomes and the cost of care associated with management of infants' oxygen delivery needs. However, due to the short duration of the exposure, it is not likely that the patients enrolled in the study will themselves benefit from participation in this study, nor is the study intended to provide sufficient support for improvement in any specific pathophysiologic outcome.

XI. Monitoring and Quality Assurance

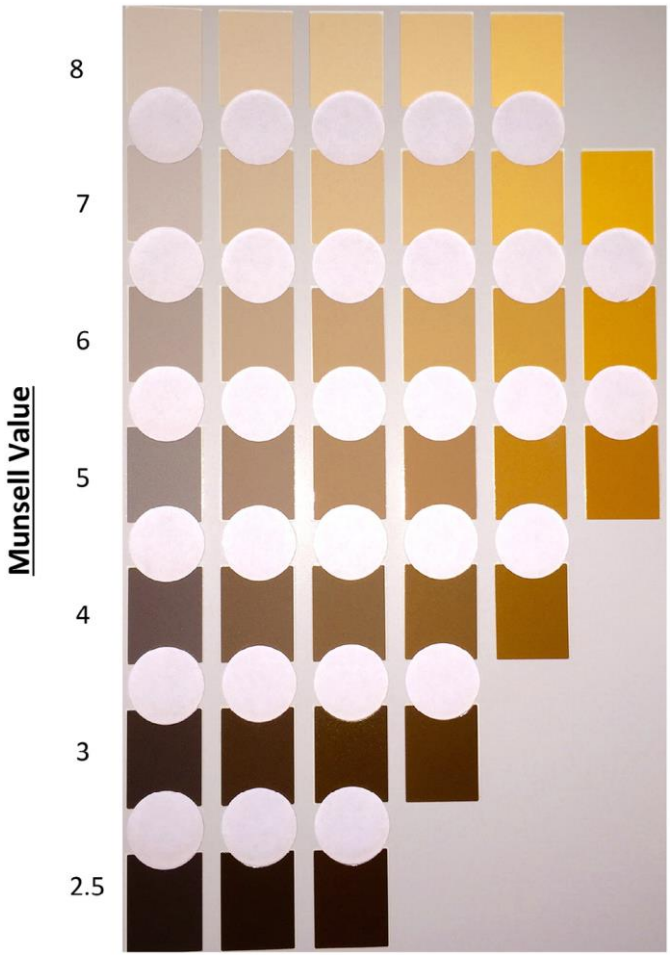
The clinical trial site will be monitored in accordance with policies at Vapotherm and those federal regulations that pertain to good clinical practice in clinical research; namely ISO 14155 and others as applicable or as directed by the human research ethics committee. Monitoring will occur at a regular frequency, such as to allow ongoing review of data collected, site qualifications and compliance with the protocol. All monitors will be appropriately trained to ensure compliance with the protocol.

XII. Confidentiality

Rigorous procedures will be followed to maintain confidentiality of subject identification and test-related information and to adhere to government regulations concerning privacy. A unique identification number designed to protect the identity of subjects will be used to identify the subject being monitored on case report forms, recruitment logs, data forms, and any or other reports containing information or referring to a device/module assigned to a particular patient.

This unique identification number will not be linked to identifiable data; no personal or identifiable patient data will be collected. The Vapotherm employee assigned to manage 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.

XIII. Skin Pigmentation Color Scale



To provide a plausible and applicable skin pigmentation scale to this study, the Munsell System Soil Color Chart (2009 Revision, Munsell Color, Grand Rapids, Michigan), Hue 7.5YR will be utilized to describe skin pigmentation. This color scale for skin pigmentation has been previously implemented clinically, and most recently in the Foglia 2017 clinical study that evaluated pulse oximetry bias of skin pigmentation in infants with hypoxemia.[16] Similar to Foglia 2017, and multiple pediatric/adult studies, skin pigment stratification will be classified and defined as Light or Dark skin pigment.

Specific to the Munsell Scale: Light skin pigment will be designated as values 7 and 8, Dark skin pigment will be designated as 2.5, 3, 4, and 5, and a value of 6 will be considered intermediate and not classified as either light or dark pigment.[16]

XIV. References

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APPENDIX A: Case Report Form (CRF)

APPENDIX B: ADVERSE EVENTS and SERIOUS ADVERSE EVENTS