Tool Revision History:

Version Number	Version Date	Summary of Revisions Made
1	30 March 2020	Original version
1	30 March 2020	IRB Clarification Request Edits
2	30 March 2020	Corrected version date
3	31 March 2020	IRB Requested Revisions
4	31 March 2020	Updated Section 14.2 Costs to the Participant
5	15 April 2020	Changed study to multi-center

OPEN-LABEL MULTI-CENTER STUDY OF EMERGENCY HYPERBARIC OXYGEN FOR RESPIRATORY DISTRESS IN PATIENTS WITH COVID-19

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Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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List of Abbreviations

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
CSOC	Clinical Study Oversight Committee
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
FFR	Federal Financial Report
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ISM	Independent Safety Monitor
MOP	Manual of Procedures
N	Number (typically refers to participants)
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
US	United States
HBOT	Hyperbaric Oxygen Therapy
COVID-19	2019 Novel Coronavirus

Protocol Summary

Title	Open Label Multi-Center Study of Emergency Hyperbaric Oxygen for Respiratory Distress in Patients with COVID-19
Short Title	Hyperbaric Oxygen for COVID-19 Patients
Brief Summary	This is a multi center prospective pilot cohort study to evaluate the safety and preliminary efficacy of hyperbaric oxygen therapy (HBOT) as an emergency investigational device for treating patients with respiratory distress due to a novel coronavirus disease, COVID-19. HBOT is a therapy that has been FDA approved for the treatment of decompression sickness, gas gangrene, late effects of radiation and others. HBOT is a medical intervention using a rigid chamber and compressed oxygen to treat hypoxia and modulate negative inflammatory responses. It has demonstrated a good safety profile and has been shown to blunt the damaging immune responses in animal models. The mechanism of respiratory failure in COVID-19 is unknown but lung pathology demonstrates “edema, proteinaceous exudate, focal reactive hyperplasia of pneumocytes with patchy inflammatory cellular infiltration and multi nucleated giant cells. Fibroplastic plugs were also noted in airspaces.”[1] One potential mechanism is thought to be due to a cytokine storm from an over whelming viral load. Hyperbaric Oxygen therapy has been shown to modulate the immune system in the laboratory rat model and is used to modulate the inflammatory response in reperfusion injury. We hypothesize that hyperbaric oxygen may be useful to modulate the immune response in COVID-19 infected patients and increase oxygenation. A recently non-peer reviewed study of hyperbaric oxygenation in Wuhan, China demonstrated that it was well-tolerated, safe with clinical improvement of oxygenation for all five patients that were enrolled. In summary, HBOT treatment will be provided to patients as an adjunct to standard therapy for a cohort of 40 COVID19-positive patients with respiratory distress at NYU Winthrop Hospital. All patients prior to the clinical application of HBOT will be evaluated by the primary care team and hyperbaric physician. During the interim analysis of the first 10 patients and after the intervention portion of this study, a chart review will be performed to compare the outcomes of intervention patients versus age and gender matched control patients who received standard of care.
Phase	Emergency Investigational Device
Objectives	Determine Safety and Efficacy of Hyperbaric Oxygen as an adjunctive treatment for COVID 19 hospitalized patients
Methodology	This is a prospective interventional cohort study that will evaluate the risks and benefits of HBOT utilization for COVID-19 confirmed patients in the hospital setting.
Endpoint	Primary endpoint: Death Secondary endpoints: Need for invasive mechanical ventilation, reduction in days on a ventilator Safety endpoints: Incidence of adverse events (AE) and severe adverse events (SAE)
Study Duration	Approximately two months, but subject to change given the nature of the ongoing pandemic.
Participant Duration	Duration of inpatient hospitalization.
Intervention	Up to 5 hyperbaric oxygen treatments at 2.0 ATA for 90 minutes dependent on the ability of the patient to participate
Population	Patients greater than 18 years of age diagnosed with COVID19 and under respiratory distress.

Eligibility Criteria	Inclusion criteria: 1. Laboratory confirmed COVID-19 positive or a clear clinical diagnosis of COVID-19 2. SpO2 <93% after trial of non-rebreather with no less than 85% SpO2 3. At least 18 years of age 4. No absolute contraindication for Hyperbaric Oxygen Exclusion criteria: 1. Pregnancy 2. Untreated Pneumothorax
Study Sites	NYU Winthrop Hospital NYU Langone School of Medicine Northwell Hospital Cleveland Clinic Loma Linda Jacobi/Einstein University of Kentucky Hospital Westchester Medical Center Geisinger Commonwealth School of Medicine Spectrum Health Hospital University of Illinois at Urbana-Champaign
Number of participants	40 patients in severe respiratory distress (SpO2 < 93% on RA, but oxygen responsive)
Description of Study Agent/Procedure	Hyperbaric oxygen therapy involves placing patients in an enclosed chamber with 100% inhaled oxygen at an increased atmospheric pressure. HBOT chambers have shown efficacy and been cleared by the FDA for 13 conditions: • Air or gas embolism • Carbon monoxide poisoning • Clostridal myositis and myonecrosis (gas gangrene) • Crush injury, compartment syndrome, and other acute traumatic ischemias • Decompression sickness • Enhancement of healing in conditions including: o Diabetically derived illness, such as diabetic foot, diabetic retinopathy, diabetic nephropathy o Exceptional blood loss (anemia) o Intracranial abscess o Necrotizing soft tissue infections (necrotizing fasciitis) o Osteomyelitis (refractory) o Delayed radiation injury (soft tissue and bony necrosis) o Skin grafts and flaps (compromised) o Thermal burns
Reference Therapy	Standard of care matched cohort of patients that did not receive HBOT based on age and gender and if possible underlying medical comorbidities and initial disease severity.
Key Procedures	• Hyperbaric Oxygen Treatment • Review of standard of care pre and post treatment blood draws to evaluate the blood oximetry along with markers of inflammation (e.g., D-dimer, Lymphocytes, IL-6, Ferritin, LDH, CRP, ESR, Fibrinogen, and troponin) • Chart review
Statistical Analysis	For binary primary and secondary endpoints, chi-squared analysis of proportions between the two matched groups with multivariate logistic regression if we find identifiable differences in the two study arms. T-test and linear regression for secondary endpoints that are continuous variables.

Schematic of Study Design

Intervention arm:

Cohort A	Treatment arm	40	HBO

Chart review:

Cohort A	Treatment arm	40	HBO
Cohort B	SOC	120	SOC

1 Key Roles

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2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

A novel coronavirus, similar to the one that caused severe acute respiratory syndrome (SARS) that began in Wuhan, China, is now a pandemic.[2–4] With first cases confirmed in the United States nearly 4-6 weeks ago, we anticipate this spread will continue to increase before it plateaus or even decreases. It is highly contagious and is quickly evolving. The first cases were originally linked to animal-human transmission but has since then been transmitted from human-to-human at an exponential rate. Aerosol transmission through respiratory droplets from coughing or sneezing is another primary mechanism.

However, those individuals that are affected have presented in variable clinical presentations from asymptomatic to mild disease to extensive systemic immune reactions requiring mechanical ventilatory assistance. The pathogenic mechanism is still under research but seems complex. The viral infection amounts an excessive immune reaction within the host, activating leukocytes and interleukins that maintain a pro-inflammatory disease state.[5]

Hospital staff, beds, and supplies are limited. The growing number of patients requiring supplemental oxygen and mechanical ventilation is increasing. There is an urgent need to capture this subset of COVID-19 patients prior to clinical respiratory deterioration.

Hyperbaric oxygen therapy (HBOT) presently has been trialed in Wuhan and Italy and has shown feasibility and safety. Hyperbaric oxygen provides patients with 100% inhaled oxygen at an increased atmospheric pressure and has been used as adjuvant therapy to decrease inflammatory states.[6–8] It has been used in supportive therapy for refractory hypoxia, however, the efficacy of HBOT in treating severe hypoxia in patients with COVID-19 has not been evaluated. Due to the severity of this illness further treatment and studies are needed to begin as soon as possible.

2.2 Name and Description of the Investigational Agent

An ETC/Baromedical Monoplace Chamber will be used to deliver hyperbaric oxygen at 2.0 ATA for 90 minutes daily for up to 5 treatments.

2.2.1 Preclinical Data

It is hypothesized that in addition to treating hypoxia, HBOT may also improve negative inflammatory responses due to COVID-19 infection. Preclinical studies have found HBOT can reduce inflammatory markers and improve healing and survival outcomes in human cells[6–8] several animal models, including models of multiple organ dysfunction syndrome (MODS).[9–15]

With regard to COVID-19, there are no preclinical studies to our knowledge that have explored HBOT specifically to treat COVID-19-related complications.

2.2.2 Clinical Data to Date

HBOT is and FDA cleared treatment that has been used as the primary treatment for Decompression Sickness and Carbon monoxide poisoning and adjunctive treatment for a multitude of disease states. Its mechanism of action is to reverse local tissue hypoxia, promote angiogenesis, increase circulating

stem cells, reduce edema and blunt the inflammatory immune response. It has been used for over 50 years and has an excellent safety profile. There is no contraindication for treating patients with viral pneumonia and the only absolute contraindication would be an untreated pneumothorax. The rationale for using HBOT to treat COVID-19 respiratory distress is based on the pure hypoxia with an increase in inflammatory markers including D-dimer, Lymphocytes, IL-6, Ferritin, LDH, and CRP. To our knowledge, the only cases that have been performed thus far are preliminary cases in Wuhan, Italy and potentially South Korea in patients with severe respiratory distress. These patients have shown clinical objective improvement in symptoms and on re-examination of imaging. At this time, it is available as non-peer reviewed data (see attachment).

2.2.3 Dose Rationale (if applicable)

The dose of 2.0ATA for 90 minutes was chosen as this is the most common treatment protocol for hyperbaric oxygen for a wide variety of disease states. If air breaks are needed, they will be added by the treating physician.

2.3 Rationale

Covid-19 is a novel respiratory pathogen with alarming rates of transmission and morbidity and mortality. The predominant presentation is URI symptoms that may present as hypoxic respiratory failure without hypercarbia and tachypnea. Patients are then noted to develop acute pulmonary edema requiring ventilatory support. It is thought that an inflammatory cascade leads to increased capillary permeability.[5] Hyperbaric oxygen may have a role if delivered before patients develop respiratory failure thus decreasing the need for ventilators

2.4 Potential Risks & Benefits

2.4.1 Known Potential Risks

Risks Associated with Hyperbaric Therapy:

The risks of hyperbaric oxygen are well reported. Hyperbaric oxygenation typically requires constant care and may be difficult for individuals experiencing nausea or vomiting, claustrophobia, or altered mental status from lack of oxygen. The most common side effects that you may feel, because of the high pressure and small space, include fatigue, lightheadedness, anxiety or claustrophobia, and ear discomfort which can be a pain and a “popping” feeling. More severe side effects include fluid buildup of the middle ear, sinus damage, trauma from the increased air pressure (baurotrauma), change in vision, oxygen toxicity seizures, and development of collapsed lungs (pneumothorax). Development of a pneumothorax may result in cardiopulmonary collapse, and ultimately death. However, patients will be instructed on how to prevent these side effects and the oxygen dose given to participants will be determined specifically by healthcare providers who will take into consideration participants' overall health and age to reduce complications.

There also exists the risk of recurrence of symptoms after exiting from the chamber. Furthermore, there exists the risk of cross contamination/exposure of other strains of COVID-19, however all the chambers will be set up specifically for COVID-19 positive patients and will be thoroughly cleaned after used in order to reduce risk of cross-contamination. Due to the oxygen rich environment there is an increased inherent fire risk. Due to the novelty of COVID-19, the risks of hyperbaric oxygen specifically for COVID-19 patients are currently unknown.

2.5 Known Potential Benefits

Hyperbaric Oxygen has the benefit of improving local and systemic tissue hypoxia, reducing edema and may blunt the inflammatory response.

3 Objectives and Purpose

Due to the rapidity and unpredictability of patient decompensation any therapeutic modality that can decrease the need for ventilatory support and mortality should be considered. The purpose of this trial is to assess the role of hyperbaric oxygen in the COVID-19 patient both for safety and efficacy.

3.1 Primary Objective

Evaluate whether HBOT can reduce mortality rate in patients under respiratory distress due to COVID-19 compared to standard of care.

3.2 Secondary Objectives (if applicable)

Evaluate whether HBOT can reduce need for mechanical ventilation or duration of ventilation in patients under respiratory distress due to COVID-19 compared to standard of care.

4 Study Design and Endpoints

4.1 Description of Study Design

This is a multi-center prospective pilot cohort study to evaluate the safety and efficacy of hyperbaric oxygen therapy (HBOT) as an emergency investigational device for treating patients with a novel coronavirus, disease, COVID-19. Patients that meet inclusion criteria will be consented by the hyperbaric physician. They will then be transported from the ED or other unit to the hyperbaric unit maintaining airborne precautions based on the most current hospital protocol. All study personnel will have proper PPE at all times. The patient will then be placed into the monoplace chamber and when the chamber door is closed the patient will remove any respiratory filter/mask that was placed. The patient will receive 90 minutes of hyperbaric oxygen at 2.0 ATA with or without airbreaks per the hyperbaric physician. Upon completion of the treatment the patient will then return to the medical unit and continue all standard of care. Additional treatments (up to 5 total) can be given if warranted and agreed upon by the patient and all members of the team caring for the patient. An interim analysis after the 1st 10 patients will be conducted for all endpoints. During the interim analysis of the first 10 patients and after the intervention portion of this study, a chart review will be performed to compare the outcomes of intervention patients versus age and gender matched control patients who received standard of care.

4.2 Study Endpoints

4.2.1 Primary Study Endpoints

The primary endpoint will be patient mortality.

4.2.2 Secondary Study Endpoints

The secondary endpoints will be whether a patient needed invasive mechanical ventilation and the number of days on a ventilator for those who did receive ventilation. The rate of patients who needed mechanical ventilation among those who received hyperbaric oxygen will be compared to the rate in a matched cohort of patients that received standard of care and did not get hyperbaric oxygen.

4.2.3 Safety Endpoints

We will collect all adverse events (AE), including severe adverse events (SAEs) for the study. For AEs potentially related to HBOT we will consider otic barotrauma, myopia, oxygen toxicity seizures and acute pulmonary edema. For each patient we will count the total number of AEs and SAEs during hospitalization.

5 Study Enrollment and Withdrawal

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Male or female, age > 18 years
2. Positive COVID 19 test or clear clinical diagnosis of COVID-19. Positive COVID-19 test will be confirmed based on a result or patient reported history. Clear clinical diagnosis of COVID-19 will be a combination of respiratory symptoms and clinical findings based on laboratory values and radiographs.
3. Respiratory compromise defined by SpO2 <93% on room air
4. No untreated pneumothorax. The study team will check for untreated pneumothorax by checking the results of a clinically indicated X-ray.

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Pregnancy
2. Untreated Pneumothorax
3. Intubated patients
4. Patients on IV drips

Other conditions are all relative contraindications that need to be discussed with the treating physician and the hyperbaric medicine physician.

5.3 Vulnerable Subjects

Vulnerable subjects will not be included.

5.4 Strategies for Recruitment and Retention

This study will be targeting patients that have tested positive for the novel coronavirus, disease, COVID-19 in the emergency department or other in-patient unit. Patients that meet inclusion criteria will be consented by the hyperbaric physician prior to the first treatment. Study subjects will be transported from the ED or other unit to the hyperbaric unit maintaining airborne precautions based on the most current hospital protocol.

5.5 Use of DataCore/Epic Information for Recruitment Purposes

This study will utilize internal physician referral of patients that have tested positive for COVID-19 and are thought to benefit from HBOT and study enrollment. EPIC will be used to determine if subjects meet study eligibility criteria. Any recruitment information sent by email will utilize Send Safe email.

Once contact is made, approved recruitment language will be used to communicate the reason they are being contacted and subjects will be asked if they are interested in participating in this specific study. Should the potential subjects agree, the study team will provide the subjects with information regarding the next steps for participation.

If a subject requests information regarding opting out of further recruitment for all research, subjects will be directed to contact research-contact-optout@nyumc.org or 1-855-777-7858.

Epic will also be utilized to access deidentified data on patients who received standard treatment.

5.6 Duration of Study Participation

Study participation for all subjects will be for the total duration of inpatient hospitalization.

5.7 Total Number of Participants and Sites

There are a total number of 11 sites. All sites will submit their own individual IRB proposal to be approved by their respective institution's IRB. NYU is the lead site and the Co-Principal Investigators, Dr. Gorenstein and Dr. Lee, will be the lead coordinators of this study.

Recruitment will end when approximately 40 participants are enrolled in the HBOT group.

We will create a comparison cohort from chart review of 120 patients who received standard treatment and were matched with 40 HBOT patients in 3:1 ratio, such that the comparison group will consist of 120 standard of care patients. For this retrospective comparison group, we will be requesting a waiver of consent and authorization for this cohort.

5.8 Participant Withdrawal or Termination

Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- The patient does not tolerate increased pressure in the HBOT chamber
- Study early termination

5.9 Handling of Participant Withdrawals or Termination

Investigators will have the right to discontinue a subject from the trial at any time during the study. Furthermore, subjects will have the right to withdraw from study at any time. Consultation with the study doctor must be encouraged before early discontinuation from the trial. Discontinuation reason (for example, subject withdrawal, investigator decision due to clinical worsening or subject incompliance) must be recorded in the subject study records and electronic case report form. Subjects who choose to withdraw consent at the time of early discontinuation must have a vital status documented at the day of study discontinuation. Study team will continue to follow-up of withdrawn or terminated participants or participants who discontinue study treatment but remain in the study for follow-up, especially for safety and efficacy study endpoints including protocol-specified safety follow-up procedures to capture alternate treatments, AEs, serious adverse events (SAEs), and unanticipated problems (UPs).

5.10 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.
Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility
- If the study team deems that transport or treatment of patients in the hyperbaric unit significantly increases the risk of respiratory failure
- If any patient experiences a death which is likely to be attributable to the use of HOBT.

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the IRB.

6 Study Agent (Study drug, device, biologic, vaccine etc.) and/or Procedural Intervention

6.1 Study Agent(s) and Control Description

NYU's Manager of Research Regulatory Affairs determined that this study using HBOT chambers is considered a non-significant risk (NSR) device based on the following:

1. The device is not intended as an implant
2. The device is purported or represented to be for a use in supporting or sustaining human life ("to rescue 20 patients with respiratory failure caused by COVID-19"), but it does *not* present a potential for serious risk to the health, safety, or welfare of a subject
3. The device is for a use of substantial importance in mitigating disease ("to rescue patients with 30 respiratory distress caused by COVID-19"), but does *not* present a potential for serious risk to the health, safety, or welfare of a subject
4. The device otherwise does not present a potential for serious risk to the health, safety, or welfare of a subject

Therefore, an Investigational Device Exemption application did not need to be submitted to the U.S Food and Drug Administration (FDA).

6.1.1 Acquisition

The hyperbaric oxygen chambers already exist in the Wound Healing and Hyperbaric Medicine Program at NYU Winthrop where the patients will be treated.

6.1.2 Formulation, Appearance, Packaging, and Labeling

N/A

6.1.3 Product Storage and Stability

N/A

6.1.4 Preparation

N/A

6.1.5 Dosing and Administration

Up to 5 hyperbaric oxygen treatments at 2.0 ATA for 90 minutes dependent on the ability of the patient to participate. The dose of 2.0ATA for 90 minutes was chosen as this is the most common treatment protocol for hyperbaric oxygen for a wide variety of disease states.

6.1.6 Route of Administration

Participants will be inhaling pure oxygen within the hyperbaric oxygen chambers.

6.1.7 Starting Dose and Dose Escalation Schedule

The starting dose is 2.0 ATA for 90 minutes and will not be escalated.

6.1.8 Dose Adjustments/Modifications/Delays

N/A

6.1.9 Duration of Therapy

Each hyperbaric oxygen treatment will last for up to 90 minutes dependent on the ability of the patient to participate.

6.1.10 Tracking of Dose

N/A

6.1.11 Device Specific Considerations

ETC Baromedical Monoplace Hyperbaric Chamber. Chamber compression/decompression rates will be collected. The unit will be considered COVID contaminated. Transport and sanitizing will be according to hospital protocol per infection control specialist. These are monoplace chambers with high flow oxygen that vents to the roof of the building in accordance with UHMS specifications. Chambers will be sanitized between patient use.

6.2 Study Agent Accountability Procedures

N/A

6.3 Study Behavioral or Social Intervention(s)

6.3.1 Administration of Intervention

N/A

6.3.2 Procedures for Training Interventionalists and Monitoring Intervention Fidelity

N/A

6.3.3 Assessment of Subject Compliance with Study Intervention

N/A

6.4 Study Procedural Intervention(s) Description

N/A

6.4.1 Administration of Procedural Intervention

N/A

6.4.2 Procedures for Training of Clinicians on Procedural Intervention

N/A

6.4.3 Assessment of Clinician and/or Participant Compliance with Study Procedural Intervention

N/A

7 Study Procedures and Schedule

7.1 Study Procedures/Evaluations

7.1.1 Study Specific Procedures

- Hyperbaric oxygen therapy (HBOT)

7.1.2 Standard of Care Study Procedures

- Blood oximetry test
- Blood test to determine markers of inflammation (D-dimer, Lymphocytes, IL-6, Ferritin, LDH, CRP, ESR, Fibrinogen, and troponin)
- Pregnancy test

- The following will be collected from medical records if was done as part of standard of care:
    - Medical history will be obtained from medical records
    - Medication history: complete and/or currently taken
    - Physical examination including vital signs, height, weight, and organ systems
    - Biological specimens, laboratory procedures and laboratory evaluations
    - Imaging and diagnostic testing during the hospitalization

7.2 Laboratory Procedures/Evaluations

No laboratory procedures will be administered for this study. However, we will review the results of standard of care pre and post treatment blood draws to evaluate the blood oximetry along with markers of inflammation (D-dimer, Lymphocytes, IL-6, Ferritin, LDH, CRP, ESR, Fibrinogen, and troponin)

7.2.1 Clinical Laboratory Evaluations

- Blood oximetry
- Markers of inflammation (D-dimer, Lymphocytes, IL-6, Ferritin, LDH, CRP, ESR, Fibrinogen, and troponin)

7.2.2 Other Assays or Procedures

N/A

7.2.3 Specimen Preparation, Handling, and Storage

N/A

7.2.4 Specimen Shipment

N/A

7.3 Study Schedule

7.3.1 Screening

Screening/Enrollment Visit (Day 1)

- Obtain informed consent of potential participant verified by signature on written informed consent for screening form.
- Review medical history to determine eligibility based on inclusion/exclusion criteria.
- Review medications history to determine eligibility based on inclusion/exclusion criteria.
- Review standard of care test results (e.g. blood oximetry) to determine eligibility based on inclusion/exclusion criteria.
- Schedule hyperbaric oxygen treatment for participants who are eligible and available for the duration of the study.
- Women of childbearing potential age must have a negative serum or urine pregnancy test prior to initial HBO treatment.

7.3.2 Final Study Visit

Final Study Visit (Hospital Discharge)

- *Record adverse events as reported by participant or observed by investigator.*
- *Record results of blood oximetry test and inflammatory markers* (D-dimer, Lymphocytes, IL-6, Ferritin, LDH, CRP, ESR, Fibrinogen, and troponin).
- *Record participant's adherence to treatment regimen.*
- *If participant has diabetes, administer a glucometer test to confirm participant is not hypoglycemic*

- *All ongoing AE/SAEs will be followed up by study team until resolution or back to baseline for 30 days* after the last day of study *participation.*

7.3.3 Withdrawal/Early Termination Visit

If the patient withdraws from the study early, we will perform the same procedures listed above for the final study visit provided patient's approval

- *Record adverse events as reported by participant or observed by investigator.*
- *Record results of blood oximetry test and inflammatory markers* (D-dimer, Lymphocytes, IL-6, Ferritin, LDH, CRP, ESR, Fibrinogen, and troponin).
- *Record participant's adherence to treatment regimen.*
- *If participant has diabetes, administer a glucometer test to confirm participant is not hypoglycemic*
- *Standard of care treatments, tests, procedures and medications will be collected throughout the length on in-patient hospitalization, unless patients withdraw consent.*

7.3.4 Unscheduled Visit

N/A

7.4 Concomitant Medications, Treatments, and Procedures

All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and non-prescription medications.

7.5 Justification for Sensitive Procedures

N/A

7.6 Precautionary Medications, Treatments, and Procedures

N/A

7.7 Prohibited Medications, Treatments, and Procedures

There are no absolute medications that might be contraindicated, only relative ones which will be determined by the hyperbaric oxygen physician. Treatment with hyperbaric oxygen will not be permitted unless discussed with and approved by the hyperbaric oxygen physician.

7.8 Prophylactic Medications, Treatments, and Procedures

N/A

7.9 Rescue Medications, Treatments, and Procedures

While in the chamber the patient will be attended to by an an attending physician certified in hyperbaric medicine. Participants in this study are in respiratory distress and at risk for respiratory failure. If the patient develops respiratory failure, rescue therapy would be mechanical ventilation. In the event of a "code" the code team will be called and assume care of the patient upon arrival. Patients will be monitored by direct observation and cardiac monitor if indicated. Patients can be rapidly decompressed and removed from the chamber within 90 seconds if needed.

7.10 Participant Access to Study Agent at Study Closure

Study team will not continue to provide the HBOT to participants once they are discharged from the hospital and completed study participation.

8 Assessment of Safety

8.1 Specification of Safety Parameters

We will record all adverse events for the study as described below. To assess adverse events (AEs) potentially related to HBOT, we will consider otic barotrauma, myopia, oxygen toxicity seizures and acute pulmonary edema.

8.2 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

8.3 Definition of Serious Adverse Events (SAE)

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

8.4 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets <u>all</u> of the following criteria:

- <u>Unexpected in nature, severity, or frequency</u> (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- <u>Related or possibly related to participation in the research</u> (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- <u>Suggests that the research places subjects or others at greater risk of harm</u> (including physical, psychological, economic, or social harm).

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the

investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

8.5 Classification of an Adverse Event

8.5.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.5.2 Relationship to Study Agent

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- ***Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.*
- ***Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.*
- ***Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.*
- ***Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).*
- ***Not Related** – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.*

8.5.3 Expectedness

Dr. Scott Gorenstein will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.6 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate RF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

8.7 Reporting Procedures – Notifying the IRB

Adverse Event Reporting:
Adverse Events will be documented on the appropriate Case Report Form (CRF) as the Investigator learns of the event. The Investigator will follow all AEs until adequate resolution is achieved. The IRB should be notified of all AEs according to their notification policies.

Serious Adverse Event Reporting
In the case of a SAE, the Investigator must notify IRB according to their notification policies. All SAEs will be followed until satisfactory resolution or until the site Investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the IRB should be provided as soon as possible.

Unanticipated Adverse Device Effect Reporting
An Investigator shall submit to the reviewing IRB a report of any UADE occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect [21 CFR 812.150(a)(1)].

Investigators must report possible Unanticipated Problems to the IRB promptly. If the event requires immediate intervention to prevent serious harm to subjects or others, the investigator may act accordingly to prevent harm and then must report the event within five (5) days.

Investigators must report all other possible Unanticipated Problems occurring at the local research site and non-local research sites to the IRB as soon as possible but no later than ten (10) business days from the date of the event or from the date the investigator is notified of the event.

8.7.1 Adverse Event Reporting

The research coordinator on the study team will record all reportable adverse events with start dates occurring any time after informed consent is obtained. The investigator will inquire about the occurrence of adverse events or serious adverse events. In addition, all study participants will receive the telephone number to contact the research coordinator directly, who will inform the Principal Investigator of any events that may be related to the HBOT immediately. As the Principal Investigator specializes in hyperbaric medicine, he will contact the study participant directly to obtain additional information about the event and what medical attention the study participant should seek if needed. Events will be followed for outcome information until resolution or stabilization. All adverse events and serious adverse events will be reported to Institutional Review Board (IRB) according to the local IRB reporting guidelines.

8.7.2 Serious Adverse Event Reporting

The research coordinator on the study team will record all reportable serious adverse events with start dates occurring any time after informed consent is obtained. The investigator will inquire about the occurrence of adverse events or serious adverse events. In addition, all study participants will receive the telephone number to contact the research coordinator directly, who will inform the Principal Investigator of any events immediately. As the Principal Investigator specializes in hyperbaric medicine, he will contact the study participant directly to obtain additional information about the event and what medical attention the study participant should seek if needed. Events will be followed for outcome information until resolution or stabilization. All adverse events and serious adverse events will be reported to Institutional Review Board (IRB) according to the local IRB reporting guidelines. We plan on addressing these events expediently and making sure that other study participants are aware of any new risks identified during the course of the study intervention.

8.7.3 Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB within 48 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB in accordance with the local IRB reporting guidelines
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within 5 days of the IR's receipt of the report of the problem from the investigator.

8.7.4 Reporting of Pregnancy

Pregnant patients will not be enrolled.

8.8 Reporting Procedures – Notifying the Study Sponsor

N/A

8.9 Reporting Procedures – Notifying the FDA

NYU's Manager of Research Regulatory Affairs determined that your study using HBOT chambers is considered a non-significant risk (NSR) device based on the following:

1. The device is not intended as an implant
2. The device is purported or represented to be for a use in supporting or sustaining human life ("to rescue 20 patients with respiratory failure caused by COVID-19"), but it does not present a potential for serious risk to the health, safety, or welfare of a subject
3. The device is for a use of substantial importance in mitigating disease ("to rescue patients with 30 respiratory distress caused by COVID-19"), but does not present a potential for serious risk to the health, safety, or welfare of a subject
4. The device otherwise does not present a potential for serious risk to the health, safety, or welfare of a subject

Therefore, an Investigational Device Exemption application does not need to be submitted to the U.S Food and Drug Administration (FDA).

8.10 Reporting Procedures – Participating Investigators

N/A

8.11 Study Halting Rules

Administration of study device will be halted in the event of the following:

- If the study team deems that transport or treatment of patients in the hyperbaric unit significantly increases the risk of respiratory failure
- If any patient experiences a death which is likely to be attributable to the use of HOBT.

8.12 Safety Oversight

It is the responsibility of the co-Principal Investigators to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

Data Safety Monitoring Plan (DSMP)
Safety oversight will be under the direction of the co-Principal Investigators and co-Investigators at each site independently with statistical assistance as needed from our site by sending deidentified data. After the first 10 patients complete the protocol, a pause in enrollment will be initiated and the data will be reviewed to ensure all adverse events were reviewed.

The investigators will meet after 10, 20, and 40 patients complete the protocol to assess safety and efficacy data on each arm of the study. Events that will be monitored are 1. need for mechanical ventilation 2. upgrade in level of care 3. seizure activity and 4. death.

Investigators from all sites will report SAE and AE to the co-Principal Investigators in addition to conducting their own reviews, and the co-Principal Investigators will meet every three weeks to review data with weekly meetings as needed.

Clinical Monitoring
Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by co-investigators and study coordinators.
- Initial assessment of data quality and safety will be conducted after first enrollment.
- Further monitoring be conducted throughout the study of targeted data verification of endpoint, safety and other key data variables.
- Monitoring will occur on a weekly basis once patients are enrolled with emphasis on the predefined stopping points. Reviews will be disseminated at the weekly research meeting.

9 Statistical Considerations

9.1 Statistical and Analytical Plans (SAP)

A formal SAP will be prepared at the end of the study, the study is non-blinded.

9.2 Statistical Hypotheses

For primary endpoint: we hypothesize that the proportion of patients who died in the HBOT group will be lower than that in the SOC group. We will test the hypothesis against the null of no difference in proportions of incident mortality.

For secondary end points:

1. We hypothesize that the proportion of patient who need mechanical ventilation in the HBOT group will be lower than that in the SOC group. We will test the hypothesis against the null of no difference in proportions between the two groups.
2. We further hypothesize that the patients in the HBOT group will spend on average fewer number of days on a ventilator compared to those in the SOC group. We will test the hypothesis against the null that there is no difference in means between the two groups.

Safety analysis: We hypothesize that the rate of any severe adverse effects will be smaller in the HBOT group compared to the SOC group. We will test the hypothesis against the null of no difference.

9.3 Analysis Datasets

We will compare study endpoints and safety outcomes between the 40 patients who received HBOT treatment with a matched comparison group of 120 patients who received standard treatment. Matching will be based on age, gender, comorbidity, and disease severity. The eligibility criteria for the SOC group will be consistent with that of the HBOT group.

9.4 Description of Statistical Methods

9.4.1 General Approach

We will summarize the continuous variables using mean, median, standard deviation and ranges, and the categorical variables using frequency and proportions. Variables will also be summarized graphically. Baseline characteristics of the participants who received HBOT will be compared with that of control patients receiving SOC. If we find any significant difference in the baseline variables between the two matched groups, we will adjust for them as covariates in outcome analysis. T-test or ANOVA will be used for continuous variables whereas chi-squared test will be used for comparison of proportions. All tests will be two tailed at significance level of 0.05. Appropriate transformations (such as log transformation) will be considered for any continuous variable that indicates non-normality. Statistical software R and SAS will be used for the analysis.

9.4.2 Analysis of the Primary Efficacy Endpoint(s)

The primary endpoint will be patient mortality, a binary outcome variable indicating whether a patient died during hospitalization for COVID treatment. We will compute proportion of patients who died in each

matched group. Chi-squared test will be utilized to compare rates of incident mortality in each group. We will also report estimates of difference in proportions along with an estimate of uncertainty using 95% confidence interval.

As a follow-up analysis, we will use a multivariable logistic regression, adjusting for any baseline covariates determined to be confounder, to estimate odds-ratio of probability of mortality between HBOT group and SOC group. We will also report 95% confidence interval of the odds-ratio.

Sample size consideration: Using a sample of 160 patients, 40 in HBOT arm and 120 in SOC arm (post matching) we can detect a reduction of 22.5% with 80% power at significance level of 0.05, assuming that the proportion of mechanical ventilation needed in SOC arm is about 80%.

9.4.3 Analysis of the Secondary Endpoint(s)

The first secondary endpoint is a binary outcome indicating whether a patient needed a mechanical ventilation. We will compute the proportion of patients who needed mechanical ventilation during their treatment for each matched group. The proportion in HBOT arm will be compared with that in matched SOC using chi-square test for proportions. Estimate of difference in proportion along with 95% confidence interval will be reported. Similar to the primary analysis, we will adjust for any potential confounders, deemed important in the baseline analysis, by using multivariable logistic regression. Estimate of odds-ratio and 95% confidence interval will be reported.

To compare the average number of days spent in ventilator between the two groups, we will use linear regression analysis. The distribution of outcome, the number of days in ventilator, will be assessed graphically and by conducting test for normality. If we find the evidence of deviation from normal distribution the outcome will be log transformed before proceeding with analysis. We will also adjust for any potential confounders, deemed important in the baseline analysis. Slope coefficient along with 95% confidence interval will be reported as an estimate of difference between HBOT and SOC groups.

9.4.4 Safety Analyses

To assess severe adverse events (SAEs), we will consider otic barotrauma, myopia, oxygen toxicity seizures and acute pulmonary edema. For each patient we will count the total number of SAEs during hospitalization.

SAEs will be summarized by computing mean and standard deviation for each comparison group. We will further compare mean number of SAEs between HBOT and SOC groups using linear regression. The outcome will be log transformed to account for the potential violation of normality. We will report difference in mean along with 95% confidence interval around the mean.

9.4.5 Adherence and Retention Analyses

N/A

9.4.6 Baseline Descriptive Statistics

Addressed in general approach.

9.4.7 Planned Interim Analysis

An interim analysis of all endpoints will be performed after the first 10 patients treated with HBOT complete the study compared to matched cohort of 30 patients form case review.

9.4.7.1 Safety Review

Administration of study device will be halted in the event of the following:

- If the study team deems that transport or treatment of patients in the hyperbaric unit significantly increases the risk of respiratory failure
- If any patient experiences a death which is likely to be attributable to the use of HOBT.

It is the responsibility of the co-Principal Investigators to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

Safety oversight will be under the direction of the co-Principal Investigators and co-Investigators. After the first 10 patients complete the protocol, a pause in enrollment will be initiated and the data will be reviewed to ensure all adverse events were reviewed.
The investigators will meet after 10, 20, and 40 patients complete the protocol to assess safety and efficacy data on each arm of the study. Events that will be monitored are 1. need for mechanical ventilation 2. upgrade in level of care 3. seizure activity and 4. death.

9.4.7.2 Efficacy Review

In the interim analysis, we will also compute proportion of overall mortality along with proportion that needed ventilation. The statistician conducting the analysis will be blinded from the treatment assignment to ensure that the type 1 error of our power calculation for final analysis is preserved.

9.4.8 Additional Sub-Group Analyses

We will also compare our primary and secondary endpoints stratified by age groups and sex. However, because of small sample size these analyses will be exploratory and hypothesis generating rather than formal hypothesis testing. We will report effect estimates and their standard errors.

9.4.9 Multiple Comparison/Multiplicity

N/A

9.4.10 Tabulation of Individual Response Data

Individual participant data will be listed by measure and time point.

9.4.11 Exploratory Analyses

Please see additional subgroup analysis.

9.5 Sample Size

Using a sample of 160 patients, 40 in HBOT arm and 120 in SOC arm (post matching) we can detect a reduction of 22.5% or higher, against the null of no difference, with 80% power at significance level of 0.05, assuming that the mortality rate in SOC arm is about 80%.

For the secondary analysis, our proposed sample of 160 patients will similarly allow us to detect a difference of 22.5% in need for ventilation between HBOT group and SOC group with 80% power. For comparing the continuous outcome of number of days in ventilation, we have 80% power to detect effect size (cohen's d) of 0.51 with 160 patients.

9.6 Measures to Minimize Bias

9.6.1 Enrollment/Randomization/Masking Procedures

There will be no randomization in this study. Considering the urgency of the current pandemic, it does not seem appropriate to consent a patient and then not offer them the intervention. We are also only collecting SOC data and there is a very high volume of patients, so large numbers of patients meeting criteria will be

available for chart review for the comparison group. Any patients who might be randomized to SOC would not have any study-related activity other than collection of SOC data in the EMR.

9.6.2 Evaluation of Success of Blinding

N/A

9.6.3 Breaking the Study Blind/Participant Code

N/A

10 Source Documents and Access to Source Data/Documents

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Quality Assurance and Quality Control

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Study coordinators will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose inspection by local and regulatory authorities.

12 Ethics/Protection of Human Subjects

12.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

12.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form

will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

12.3 Informed Consent Process

12.3.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study device, study procedures, and risks are given to the participant or the participant's legally authorized representative and written documentation of informed consent is required prior to starting intervention/administering study product. A consent form is submitted with this protocol.

12.4 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Informed consent will be obtained by a member of the research team. Patients in the emergency room or other inpatient unit who have tested positive for COVID-19 or have a clear clinical diagnosis of COVID-19 and who are in respiratory distress will be approached for consent. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant or their legally authorized representative will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate.

In order to confirm that the participant is capable of providing informed consent, the hyperbaric oxygen physician will ask the patient to reiterate the information given to them.
The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g. use of a translator, consent from a legally authorized representative, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

EPIC will be used to determine if subjects meet study eligibility criteria as well as to determine if they have a legally authorized representative. If the legally authorized representative is not noted in the subject's medical record, we would follow New York State's hierarchy:

- A court-appointed Legally Authorized Representative/guardian or a guardian authorized to decide about health care pursuant to Article 81 of the Mental Hygiene Law.
- An individual who is designated as a representative/agent through a health care proxy signed by both the subject and the appointed representative/agent. For a health care proxy to be effective, it must have been signed at a time when the subject had decision-making capacity. In addition, the health care proxy must not specifically prohibit research.
- The spouse, if not legally separated from the subject, or domestic partner.
- A son or daughter 18 years of age or older.
- A parent.
- A sibling 18 years of age older.

- A step-child, step-sibling, step-parent, grandparent or grandchild 18 years of age or older who has maintained such regular contact with the subject as to be familiar with the subject's activities, health or beliefs.

Subjects will be regularly assessed throughout the study to determine whether or not they have regained or lost the capacity to consent. If subjects who have the capacity to consent at the onset of the study lose capacity during the study, their legally authorized representative will be identified and consent sought for the subject's continued participation in the study. If subjects regain the capacity to consent during the study and decline to continue participation, they will be asked if previously collected data can still be used. If they decline, this data will be discarded.

12.5 Posting of Clinical Trial Consent Form

N/A

12.6 Participant and Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at NYU Langone Medical Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NYU Langone Medical Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYU Langone Medical Center.

12.7 Research Use of Stored Human Samples, Specimens, or Data

- Data will be stored using codes assigned by the investigators. Data will be stored on RedCap. Only investigators will have access to the data.
- Tracking: Data will be tracked using random review of complete set of printed source data and/or subject electronic medical records to verify consistency between electronic source data and the eCRF. The printouts will be considered as the official clinical study records and must be filed either with the subject medical records or with the subject's eCRF.

12.8 Future Use of Stored Data

Data collected for this study will be analyzed and stored at the NYU Winthrop Department of Surgery/ NYU School of Medicine. After the study is completed, the de-identified, archived data will be transmitted to and stored internally using password protected electronic database, under the supervision of the principal investigator and co-investigators for use by other researchers and biostatisticians.

13 Data Handling and Record Keeping

The subject's name will not be used in published results and data from the study will be reported in consolidated form. All personal and medical data will be considered confidential. All of the data collected will be coded by a subject number. Each subject name and other identifiers will be replaced by a unique code which will be used to refer to the subject data. The code key will be stored separately and accessible by small number of identified research team individuals. Identifiers will be retained for 3 years after publication of primary manuscript

- All listed investigators in the protocol will have access to the data collected in this study.
- Collected PHI will include names, medical record numbers and Any elements of dates (except year) for dates directly related to an individual (e.g., date of birth/death, dates of admission/discharge, etc.)
- All identifiers will be coded prior to recording for the purpose of this study.
- Study data will be electronically collected and stored on RedCap.
- Subject-coded data will be stored for up to three years post data analysis completion and manuscript preparation.
- All information obtained will be recorded through indirect identifiers. The following provisions to protect the privacy of subjects and to maintain the confidentiality of data include:
    - Maximum retention period of the information until three years post analysis
    - Information will be used only for the purpose of research analysis
    - Only de-identified data will be shared among study members
    - There will be minimal risk of harm to subjects and no compromise to patient standard of care regardless of study participation.
    - Confidentiality of all research subjects will be maintained and protected through storage on RedCap.
-
- The research data set will be cleaned and finalized after data collection is finished. Data sets used for analysis will be de-identified and coded. Only authorized study personnel will have access to the data. Final data sets will be stored on RedCap and access will be restricted.
- Only research staff will have access to the research data and the keys to the code, so as to minimize the risk of loss of confidentiality. Study team will collect the minimum number personally identifying elements necessary to complete the study tasks. Only NYU Winthrop MCIT-supported and password protected devices will used to access project data while using secure connections

13.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

13.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication, or 2 years after the last approval of a marketing application is approved for the device for the indication for which it is being investigated or 2 years after the investigation is discontinued and FDA is notified if no application is to be filed or if the application has not been approved for such indication. No records will be destroyed without the approval of the principal investigator.

13.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity.

All protocol deviations must be addressed in study source documents.

Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

13.4 Publication and Data Sharing Policy

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.
- NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

14 Study Finances

14.1 Funding Source

This study is currently not receiving financial support from any funding agency.

14.2 Costs to the Participant

The costs of the hyperbaric oxygen therapy will be paid for by the research study.

14.3 Participant Reimbursements or Payments

Subjects enrolled in this trial will not reimbursed for their participation.

15 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial.
Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable conflict of interest policies.

16 References

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17 Attachments

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.