DRAFT PROPOSAL
The Use of Hyperbaric Oxygen Therapy to Treat Patients with COVID-19 Virus

Background / Significance:

The COVID-19 outbreak, caused by a novel coronavirus originating from Wuhan, China has now evolved into a pandemic [1-3]. Although the virus is similar to those that caused severe acute respiratory syndrome (SARS) in 2003 and Middle East respiratory syndrome (MERS) in 2012, its underlying pathologies are substantially dissimilar [31]. The new SARS-CoV2 virus is highly contagious and can lead to a variety of clinical presentations known collectively as COVID-19 disease. Although countries around the world are on different time-tables, the United States is in the dramatic acceleration phase of the pandemic. The pathogen's fecal-oral, aerosol, and personal contact mechanisms makes COVID-19 particularly dangerous [3].

Individuals affected by the disease present with a spectrum of symptoms, ranging from asymptomatic to mild disease to profound, life-threatening tissue hypoxia, respiratory, cardiac and multi-organ failure. From current research, the mechanism of disease in COVID-19 remains currently unknown, however some notable observations have been made. It has been suggested that the viral infection induces an exaggerated yet sustained immune/inflammatory response through the over-activation of various cytokines, interleukins, and other factors [5]. This uncontrolled inflammatory reaction has shown notable lung pathology including "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" [4]. Although still under research, there has also been evidence indicating diminished oxygen carrying capacity of the erythrocyte, possibly due to the effects of the coronavirus on porphyrin and the dislocation of iron [32]. Experience from treating physicians indicate that the challenge for many patients is maintenance of oxygenation and not ventilation.[F]

The rising rates of infection have rendered hospitals and the progression of severe disease in certain patients has increased the need for supplemental oxygen and mechanical ventilation. Much of the early planning for the pandemic was in securing ventilators. Once patients are placed on ventilator support they are often not able to be weaned off. [33].

It has become increasingly crucial to intervene in COVID-19 patients that have yet to develop severe clinical respiratory deterioration. If intubation could be avoided, it follows that this would result in reduced mortality and morbidity and a lowered use of limited healthcare resources. Although effective treatments targeting the virus have not yet been identified, there is an urgent need for novel therapies that ameliorate symptoms and prevent death.

No single effective targeted therapy for the ongoing COVID-19 pandemic has thus far been identified, especially in this more critical group. Aggressive, invasive therapies such as intubation and mechanical intubation or ECMO are being utilized for the most critically ill patients, but many times these patients do not improve with even these aggressive efforts. Other treatments such as anti-protease treatment and convalescent plasma therapy have shown investigative promise but are largely experimental and have not been proven to demonstrate clinical significance [34] [36]. As of April 7th, 2020, the FDA has not yet approved of any drugs to specifically treat COVID-19, limiting current treatment to traditional supportive care, a variety

of medications such as (hydroxy)chloroquine, azithromycin, antiviral therapy (e.g., remdesevir, favipiravir), and biologics such as anti-IL-6 agents (e.g., tocilizumab), and mechanical ventilatory support [32] [35]. One target area for evolving therapies for this group would be an intervention or interventions that could be utilized earlier during the onset of hypoxia that would be non-invasive but could successfully blunt and attenuate the multiple effects of this virus.

Hyperbaric oxygen therapy (HBOT) presently has been trialed in China for this indication and has demonstrated feasibility and safety.[6,7] Hyperbaric oxygen can provide patients with up to 100% inhaled oxygen at an increased atmospheric pressure. At increased atmospheric levels HBOT has long demonstrated the ability to promote oxygen delivery to tissues by the patient's plasma component. This would be beneficial as it would bypass the cellular defects SARS-CoV-2 imposes on RBCs. HBOT has also been successfully utilized as an adjuvant therapy to decrease inflammatory states.[8-10] It has been suggested that COVID-19 may be causing hypoxemia by attacking and rendering erythrocytes useless, specifically by dislodging Fe from the porphyrin in heme. [32] HBOT could increase the absorption of oxygen in the blood by increasing the partial pressure of oxygen, in accordance with Henry's law. [37] This is also shown by hyperbaric oxygen's use in supportive therapy for refractory hypoxia, however, the efficacy of HBOT in treating severe hypoxia in patients with COVID-19 has thus far only been reported in small cohort of five subjects China.[E] Due to the severity of this illness further treatment and studies are needed to begin as soon as possible.

There are few contraindications to HBOT, these include but are not necessarily limited to an unrecognized and/or untreated pneumothorax; CHF is also a contraindication for anyone with an ejection fraction <30%, due to oxygen being a vasoconstrictor; hyperthyroidism as well as poorly controlled seizure disorders are contraindications. Severe pulmonary diseases, especially obstructive disease, are a contraindication. Patients with claustrophobia may experience the confined space of a hyperbaric chamber as uncomfortable. [38]

Risks and side effects of HBOT are mostly minor and reversible, with major adverse events being rare. A progressive myopia due to pressure-induced lens deformity may occur, though this typically reverses about 6 weeks after the end of treatment. HBOT can also mature any existing cataracts at a faster rate, though it does not cause new cataract formation, nor would this be anticipated over such a short course of therapy. Mild barotrauma to the ears and sinuses is common, especially in the elderly, however most cases are reversible. Serious adverse effects may result from oxygen toxicity, which can cause seizures, CHF exacerbation, pulmonary edema, and retinal changes. [38]

Preclinical Data

It is hypothesized that in addition to treating hypoxia, HBOT may also lessen the detrimental 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[8-10] and several animal models, including models of multiple organ dysfunction syndrome (MODS)[11-17] and sepsis .[D]

Five patients were treated with HBOT. It was reported that all five patients had rapid relief of hypoxic symptoms and rapid correction of hypoxemia. All patients were treated with HBOT without complication. [E]

Clinical Data to Date

HBOT is an FDA approved treatment for a variety of medical conditions including necrotizing injuries of soft tissue, traumatic ischemia and air/gas embolism and is the primary treatment for acute carbon monoxide poisoning and decompression sickness [20-22]. The therapy involves administration of 100% Oxygen in a closed chamber and pressurized above 1 atmosphere (ATA). Its mechanism of action is to increase oxygen delivery by elevating the dissolved oxygen content of the blood which supplements hemoglobin-bound oxygen [26]. This directly inhibits localized inflammation by inducing vasoconstriction, reducing edema, and dampening the surge of inflammatory into the tissue. In addition, reversal of tissue hypoxia facilitates fibroblast proliferation and angiogenesis [24-25], contributing to wound healing. Throughout its history, HBOT has an excellent safety profile and is used in more than 190 facilities in the United States accredited by the Undersea and Hyperbaric Medical Society (UHMS) [23]. HBOT is not contraindicated for any respiratory illness resulting from viral, bacterial or fungal infections. The only absolute contraindication is untreated pneumothorax.

The motivation for using HBOT as an adjunctive treatment for COVID-19 related respiratory distress is based on observed high rates of hypoxemia with marked increases of inflammatory markers including D-Dimer, Plasmin/plasminogen, IL-6, IL-1β, TNFα, LDH, CRP, ESR, BNP, and Ferritin. These inflammatory markers suggest the utility of HBOT in patients suffering from severe respiratory distress given its ability to reduce inflammation and improve tissue oxygenation. To our knowledge, the only investigations into this treatment modality have been performed in Wuhan [6]. These patients have shown clinical signs of improvement in imaging studies and other symptomatic measures. In addition, HBOT has been shown to be an effective method to improve clinical outcomes in conditions that directly cause hypoxic injury such as systemic sclerosis [27-28], ischemia-reperfusion injury [29], and malignancy [30].

Currently, two other centers have already been granted IRB approval to study HBOT in COVID-19, NYU Langone (New York, NY) and Karolinska Hospital UCSD (San Diego, CA). A third group is currently under IRB review (UPMC, Pittsburgh, PA). In our study we have chosen to use portable hyperbaric chambers over fixed hyperbaric chambers for ease of deployment, lower cost and reduced risk of infectious spread due to patient transport as compared to a fixed HBOT chamber.

Rationale

Covid-19 is a novel respiratory pathogen with alarming rates of transmission and morbidity and mortality. The predominant presentation is fever, cough or other common upper respiratory symptoms. Some patients with COVID-19 present with hypoxemia, and some who present with the impending 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 (or cytokine storm) leads to increased capillary permeability.[5] Hyperbaric oxygen may have a positive role if delivered before patients develop respiratory failure thus decreasing the need for ventilators. Of note: hyperbaric oxygen will not interfere with any other adjunctive therapy such as hydroxychloroquine, azithromycin, remdesivir, favipiravir, anti-IL-6 therapies, etc.

2) Study Design:

This is a single (multi) center prospective randomized control trial to evaluate the safety and efficacy of hyperbaric oxygen therapy (HBOT) as an emergency investigational device for 40 treating patients with a novel coronavirus disease-COVID-19. Patients that meet inclusion criteria will be consented by the hyperbaric physician. Patients will be evaluated and treated in the COVID unit. Patients will be matched into groups and followed through completion of their hospital stay. Patients will enroll as subjects with the knowledge that most will not receive hyperbaric oxygen therapy.

The goal will be to have 40 subjects in the treatment arm. All study personnel will always have proper PPE. The subject will then be placed into the portable chamber and when the chamber is closed the subject will remove any respiratory filter/mask that was placed. The subject will receive 90 minutes of hyperbaric oxygen at 2.0 ATA, without air breaks, every 24 hours, for a maximum of six (6) treatments as determined by the treating physician.

Upon completion of treatment the subject will continue to receive care consistent with accepted COVID-19 guidelines. There is no restriction on other therapies a study patient may receive. An interim analysis after the first five subjects in the treatment arm will be conducted for all endpoints. During the interim analysis of the first five subjects in the treatment arm and after the intervention portion of this study, a chart review will be performed to compare the outcomes of intervention subjects versus age and gender matched control subjects who received standard of care. After the intervention portion of this study, we will create a comparison cohort from chart review of 120 subjects who received standard treatment and were matched with 20 HBOT subjects in 3:1 ratio, such that the comparison group will consist of 120 standard of care subjects.

Target Population

The proposed study aims to prevent respiratory failure and thus decrease the need for ventilators through the use of HBOT in patients who have tested positive for COVID-19 in the emergency department or other in-patient unit.

Two target populations offered HBOT:

- 1) Symptomatic COVID patients (HBOT alternative to ventilation given that reports from NY show these patients do poorly in ventilation) who are not yet in distress
- 2) COVID patients where rapid decline has been initiated and documented through a cytokine storm, but not yet deemed needing intubation

Recruitment

We will recruit a cohort of 40 COVID19- positive patients without respiratory distress to undergo HBOT at Mon Health Medical Center. This agency has agreed to provide access to potential subjects using the recruitment procedures outlined below as well as access to subject clinical data. All contact with prospective subjects will be through core study personnel (i.e., list of personnel). Information about the study will be relayed to potential subjects through written materials distributed as part of their hospital visit. This information sheet will give potential subjects (and their family member/caregiver) the option to either (1) contact the study directly or (2) request to be contacted by the research staff (via signed consent to be contacted for more information). Based on their interest, they will be contacted

by the study coordinator or other trained research staff member, informed of study's parameters and requirements, and screened with a standard telephone script for inclusion or exclusion. 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 to the COVID unit maintaining all local and customary precautions based on the most current hospital protocol.

Inclusion Criteria

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

1. All sexes, age > 18 years - 90 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 made by the treating physician based on a combination of physical exam, laboratory, and radiographic findings
3. Respiratory compromise defined by SpO2 <93% on room air
4. No untreated pneumothorax

Exclusion Criteria

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

1. Pregnancy - women of childbearing potential age must have a negative serum or urine pregnancy test prior to initial HBO treatment.
2. Untreated Pneumothorax - The study team will check for untreated pneumothorax by checking the results of a clinically indicated X-ray.
3. Intubated patients
4. Unstable patients or patients undergoing rapid clinical respiratory deterioration with increasing O2 requirements as determined by the primary treating physician.
5. Patients with MAP<65, HR<50, seizure disorder, or on hemodialysis.
6. Patients with previous lung fibrosis
7. CT- or spirometry-verified severe COPD with emphysema
8. Contraindications for HBOT according to local guidelines
9. Body mass greater than 135kg

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

Primary Objective

Evaluate whether HBOT can reduce mortality rate in patients due to COVID-19 compared to standard of care. The outcome measurement will be mortality rate, case fatality rate, or recovery rate.

Secondary Objectives

Evaluate whether HBOT can reduce need for mechanical ventilation or duration of ventilation in patients with COVID-19, or to reduce the length of hospital stay and cost compared to standard of care. Outcome measurements may include mechanical ventilation rate, duration of mechanical ventilation, days of hospitalization, direct costs, and indirect costs.

Planned Intervention
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. It is hypothesized that in addition to treating hypoxia, HBOT may also improve negative inflammatory responses due to COVID-19 infection.

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

Total Number of Participants and Sites
Recruitment will end when approximately 40 participants are enrolled in the HBOT group.

Primary Study Endpoints
The primary endpoint will be subject mortality.

Secondary Study Endpoints
The secondary endpoints will be whether a subject needed invasive mechanical ventilation and the number of days on a ventilator for those who did receive ventilation. The rate of subjects 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.

3. Study Population:
Patients greater than 18 years of age diagnosed with COVID19 and under respiratory distress.

Sample Size
Using a sample of 160 subjects, 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 subjects 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 subjects.

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

1. All sexes, age > 18 years - 90 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
5. Documented informed consent according to ICH-GCP and national regulations.

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 with previous lung fibrosis
5. CT- or spirometry-verified severe COPD with emphysema
6. Contraindications for HBOT according to local guidelines
7. Body mass greater than 135kg
8. Unstable patients or patients undergoing rapid clinical respiratory deterioration with increasing O2 requirements as determined by the primary treating physician.
9. Patients with MAP<65, HR<50, seizure disorder, or on hemodialysis.

Other conditions are all relative contraindications that need to be discussed with the treating physician and the hyperbaric medicine physician. We will not be including minors because subjects who do not have the capacity to consent will not be enrolled.

Research Materials

The following will be collected from medical records if was done as part of standard of care:

1. Medical history will be obtained from medical records
2. Medication history: complete and/or currently taken
3. Physical examination including vital signs, height, weight, and organ systems
4. Blood oximetry test
5. Blood tests including chemistry, CBC, liver function tests, PT, PTT, BUN, and
6. creatinine.
7. Blood tests to determine markers of inflammation (D-dimer, IL-6, vitamin
8. D 25OH, BNP, CRP, ESR, plasmin, and troponin, AMDA, ferritin)
9. Imaging and diagnostic testing acquired during the hospitalization.

4) Participant Recruitment:

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.

Use of EHR 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. EHR data will be used to determine if subjects meet study eligibility criteria. Any recruitment information sent by email will utilize encrypted HIPAA-compliant email protocols.

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 nelcampg@monhealthsys.org or 304-598-1200 ext. 1451.

5) Informed Consent:

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.

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 can provide informed consent, the hyperbaric oxygen physician investigator 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.

EHR data will be used to determine if subjects meet study eligibility criteria as well as to determine if they have a legally authorized representative or 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 stepchild, 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.

Costs and Remuneration
Subjects enrolled in this trial will not reimbursed for their participation. The patient nor their insurance company will be held accountable to pay for the HBO treatment.

6) Risks and Benefits

Known Potential Risks
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 (barotrauma), 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 measures 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, medical conditions 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 the chamber will be set up specifically for COVID-19 positive patients and will be thoroughly cleaned according to accepted protocols after use in order to prevent 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.

Known Potential Benefits

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

Data Storage and 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 device 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 the IRB archives of the Mon Health Medical Center 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 the Mon Health 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 Medicine 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 Mon Health Medical Center.

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%.

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. The same will be done to evaluate a potential difference in the length of hospital stay. Slope coefficient along with 95% confidence interval will be reported as an estimate of difference between HBOT and SOC groups.

Sample Size

Using a sample of 160 subjects, 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 subjects 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 subjects.

Planned Interim Analysis

An interim analysis of all endpoints will be performed after the first 5,10, 20, and 40 subjects treated with HBOT complete the study compared to matched cohort of subjects from case review maintaining a 3:1 ratio to the extent possible. Data and follow-up from other similar existing

trials will also be reviewed at the time of each interim analysis to look for any critical information gleaned to date that would suggest modification of the design of this study.

Termination Criteria

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

- If any subject experiences a death which is likely to be attributable to the use of HBOT.
- Technical or safety issues with the Portable Hyperbaric Chamber.
- Recommendation of the Principle Investigator based on safety concerns or unanticipated clinical outcomes.
- Any complication from another similar study that has led to termination of that trial.

8) Data Quality Control and Database Management

Research Use of Stored Data

- Data will be stored using codes assigned by the investigators. Data will be stored on secured Mon Health Medical Center approved software. 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.

Future Use of Stored Data

Data collected for this study will be analyzed and stored at the Mon Health Medical Center. 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.

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 and then securely destroyed.

- 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 secured CICOM software.
- Subject-coded data will be stored for up to three years post manuscript publication, and then securely destroyed.

- 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 CICOM software.
- 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 CICOM software 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. CICOM-supported and password protected devices will be used to access project data while using secure connections.

9) Data Safety Monitoring

Data Safety Monitoring Plan (DSMP)

Safety oversight will be under the direction of the co-Principal Investigators and co-Investigators. After the first 5 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 5,10, 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.

10 Device Set Up and Safety

Acquisition, delivery, and set up the HBOT chamber will be coordinated with the hospital plant and care unit managers so as to not disrupt patient care. All technical manuals and device specifications will be supplied by the device manufacturer/distributer. The hospital biomedical engineers (or similarly assigned personnel) will review safety of device deployment in the hospital. Any and all regulations and precautions with regard to electrical safety, infection control, fire prevention, will be tasked to the appropriate hospital staff.

11) List of Contributors

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12) Approved trials for the use of HBOT in COVID-19

1- Safety and Efficacy of Hyperbaric Oxygen for ARDS in Patients With COVID-19 - Full Text View - ClinicalTrials.gov
2- https://clinicaltrials.gov/ct2/show/NCT04332081

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