Early Continuous Positive Airway Pressure (CPAP) in COVID-19 Confirmed or Suspected Patients
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EARLY CPAP IN COVID-19 INFECTED OR SUSPECTED PATIENTS

(PAP-COVID STUDY)

MANUAL OF PROCEDURES

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1 - GENERAL STUDY INFORMATION

1.1 INTRODUCTION

There is surge in COVID infected patients in New York City with a shortage of hospital beds, ICU beds and ventilators. Strategies to reduce the need for all of the above are immediately needed. Further, few interventions are targeted in COVID infected patients early in the course of their disease and especially in the community/home settings. Respiratory decompensation appears to occur later in the disease process (i.e. 7-10 days after becoming symptomatic) therefore many patients are sent home from the Emergency Room only to decompensate later at home. Some patients die at home and others are returning to the Emergency Room with advanced hypoxemic respiratory failure. There is no treatment offered to this population of patients, i.e. COVID suspected or confirmed and with respiratory symptoms or abnormal chest x-ray at the time of presentation. Based on experience across the globe, these patients are likely to worsen at home. We therefore propose a prospective, single-center, parallel group, open-label, randomized clinical trial to assess the efficacy of continuous positive airway pressure therapy (CPAP) (FDA approved and often used for treatment of sleep apnea) in COVID confirmed or suspected patients with abnormal chest x-ray or respiratory symptoms who do not require hospital admission and are discharged home from the emergency room. CPAP delivers positive pressure ventilation through a non-invasive facemask and can therefore be used at home. There is limited evidence on the use of CPAP for viral pneumonia resulting in acute respiratory distress syndrome (ARDS), as it offers no clear advantage over mechanical ventilation. However, in the last two decades, two viral pandemics (SARS 2003 and H1N1 2009) have triggered investigation into the use of CPAP due to severe shortage of mechanical ventilators. The success rate of CPAP was as high as 84% in H1N1 infected hospitalized individuals with lower severity of illness. Further, CPAP use in COVID-infected patients with respiratory abnormalities has shown promise in other countries such as England, China and Italy.

1.2 DESIGN AND OBJECTIVES

STUDY DESIGN

This is a prospective, single-center, parallel group, open-label, randomized clinical trial, where we will investigate the efficacy of continuous positive airway pressure therapy (CPAP) in COVID suspected or confirmed patients who are sent home from the emergency room with mild pneumonia or respiratory illness but who do not require hospital admission. We propose a randomized controlled trial of CPAP (n=100) vs. control (n=100) in COVID-19 suspected or confirmed patients with pneumonia or respiratory illness. The overarching aim of this proposal is to determine if early use of CPAP at home will reduce the need for hospitalization or death in COVID-19 suspected or confirmed patients. We will include adult patients (age>18), oversampling when possible for obese patients who live alone or have more than one bedroom at home, with serologically confirmed or under investigation for acute COVID-19 infection, who have one or more of the following: fever (>38ºC), sore throat, myalgia or flu-like illness AND have one or more of the following additional symptom or diagnostic criteria: abnormal chest x-ray, new onset cough, mild hypoxemia at rest (saturation less than 96%), abnormal lung exam, chest tightness or shortness of breath AND who are without need for hospital admission. Patients with preexisting pulmonary diseases such as advanced COPD, advanced parenchymal lung disease, history of pneumothorax etc. will be excluded (see inclusion and exclusion criteria for more information). Participants in both arms will be shipped a pulse oximeter to monitor oxygen

saturation and a disposable home sleep apnea monitor (WatchPAT) to track blood oxygen level continuously for 12 hours with data feed into a cloud based platform. Additionally, 100 patients will be randomized to receive CPAP at fixed pressure of 8 cm in women and 10cm in men and obese men and women will start be set at 10cm. of water pressure for 72 hours continuously (except for daily activities such as eating, grooming etc). We will adjust pressures in the range of 8-10cm depending on patient's comfort and related assessments in follow up period. However, the range of the pressure will remain constant throughout the study. While the study protocol will end at 72 hours, patients who wish to continue CPAP will be allowed to do so for symptomatic benefit up to 7 days from randomization. All CPAP recipients will be given a full-face mask and will be asked to stay in quarantine for the duration of the protocol to avoid risk of infecting family members with aerosol (information on this presented below). We hypothesize that early CPAP in COVID infected patients who have respiratory abnormalities will decrease the risk of subsequent hospitalization or death in 14 days from randomization.

OBJECTIVES

Aim 1: Given the expected shortage of ventilators to treat COVID-19 suspected or confirmed individuals with severe acute respiratory distress syndrome (SARS)/ARDS, we propose a prospective, single-center, parallel group, open label, randomized clinical trial of CPAP (n=100) vs. control (n=100) in COVID-19 suspected or confirmed patients with abnormal chest x-ray or respiratory symptoms. The overarching aim of this proposal is to determine if early use of CPAP at home reduces the need for hospitalization admission or death in COVID-19 suspected or confirmed patients. We will include adult patients (age>18), oversampling when possible for obese patients who live alone or have more than one bedroom at home, with serologically confirmed or under investigation for acute COVID-19 infection, who have one or more of the following: fever (>38ºC), sore throat, myalgia or flu-like illness AND have one or more of the following additional symptom or diagnostic criteria: abnormal chest x-ray, new onset cough, mild hypoxemia at rest (saturation less than 96%), abnormal lung exam, chest tightness or shortness of breath AND who are without need for hospital admission, i.e. being sent home. Patients with preexisting pulmonary diseases such as advanced COPD, advanced parenchymal lung disease, history of pneumothorax etc. will be excluded (see inclusion and exclusion criteria for more information). Participants in both arms will be shipped a pulse oximeter to monitor oxygen saturation and a disposable home sleep apnea monitor (WatchPAT) to track blood oxygen level continuously for 12 hours with data feed into a cloud based platform. Additionally, patients in the treatment arm (n=100) will be randomized to receive CPAP at fixed pressure: 8 cm water pressure in women and 10cm water pressure in men. All obese patients (BMI>=30) will be treated with a fixed pressure of 10cm of water pressure (both men and women). The CPAP pressure will be adjusted based on patient's comfort but will not deviate from the range of 8-10cm noted above. The treatment will be prescribed for 72 hours continuously (except for daily activities such as eating, grooming etc). While the study protocol will end at 72 hours, patients who wish to continue CPAP will be allowed to do so for symptomatic benefit up to 7 days. All CPAP recipients will be given a full-face mask and will be asked to stay in quarantine for the duration of the protocol to avoid risk of infecting family members with aerosol. We hypothesize that initiation of early CPAP in COVID infected patients with respiratory abnormalities will decrease the risk of subsequent hospitalization or death in 14 days from randomization. Patients will be followed for 28 days and as a secondary endpoint we will assess 28 day mortality as well as to assess for late impact of CPAP.

Aim 2: Younger Americans with COVID-19 infection have a higher rate of hospitalization and need for mechanical ventilation compared to younger citizens of other countries. One potential explanation is high obesity prevalence. Obstructive sleep apnea is present in over 50% of obese individuals and obesity further compromises lung compliance and ability to handle increased ventilatory demand seen in COVID-19 patients with related lung injury. Further, COVID infected individuals with OSA may be at higher risk for progression from mild pneumonia to ARDS however this remains to be determined. Therefore in Aim 2, we will determine if obstructive sleep apnea (OSA) is associated with increased hospitalizations and mechanical ventilation in COVID-19 suspected or confirmed patients. This will be achieved primarily through our control group (not receiving PAP therapy but will receive home sleep apnea testing). This is of vital importance as the primary treatment of OSA is CPAP and there are more than 8 million CPAP users in the United States. This treatment can therefore be leveraged to treat mild respiratory distress in COVID infected OSA patients in the face of a crisis with hospital and ventilator shortage. We hypothesize that obese patients with COVID-19 infection are more likely to be hospitalized or receive mechanical ventilation compared to non-obese individuals with COVID-19 infection. In exploratory analysis, we will also assess if OSA is an independent risk factor for hospital admission or death in our control group. We expect obesity and OSA to be correlated and will determine the independent impact of each of these on our primary endpoint.

Aim 3: To leverage EHR to determine a risk score to predict readmission to the Emergency room in COVID-infected or suspected patients. This aim will be done simultaneously while Aims 1 and 2 are ongoing and will be implemented in real-time to identify high-risk patients.

1.3 SAMPLE SIZE, TIMELINE, AND ENDPOINTS

SAMPLE SIZE

We anticipate that approximately 200 patients will participate in this study. Randomized clinical trial of CPAP (n=100) vs. control (n=100) in COVID-19 suspected or confirmed patients with abnormal chest x-ray or respiratory symptoms.

TIMELINE

We anticipate that accrual will occur over a 1-3 month period, beginning as soon as IRB approval is obtained. The study will last until we have 100 participants in each group, and each group completes all phases of the trial.

ENDPOINTS

Primary endpoint:
The primary efficacy endpoint is a non-weighted composite endpoint comprised of the following components;

- All-cause mortality within 14 days of randomization
- Hospital Admission (including ED visit) within 14 days of randomization
- Oxygen saturation less than 90 during the 72-hour observation period from randomization
- Absolute reduction in oxygen saturation of more than 4% during the 72-hour observation period from randomization

Secondary endpoints:

- Time to ICU admission within 14 days of randomization

- Time to intubation and mechanical ventilation within 14 days of randomization
- Time to death within 14 and 28 days of randomization
  - Degree of improvement in oxygen saturation within 14 days of randomization
  - Improvement in respiratory symptoms of cough, shortness of breath, etc via respiratory symptom questionnaire within 14 days of randomization
  - Adverse events and conversion rates of COVID family members in CPAP vs control within 14 days of randomization
  - Percent of patients electing to continue CPAP for greater than 72 hours
  - Time to hospital admission or ED visit within 14 days of randomization

1.4 STUDY PHASES

SCREENING PHASE

Eligible participants will be identified by:

1) **Precision Recovery Program.** This program is a Sinai-wide initiative which is remotely monitoring patients who are sent home from the emergency room. This is similar to our protocol and therefore working with the precision recovery program will be a synergistic effort. **We will exclusively recruit from their pool of patients when possible**, as the precision recovery program will hand out our fliers to their participants, and therefore will ensure that the patient does not get a cold call from us.
2) **Emergency room staff members.** Members of the research team (primarily Emergency Room department, in these following two locations: main ED, and surge space (Martha Stewart)) will identify and provide flyers to the patients as discussed above.
3) **Via EPIC screening.** Subjects will also be identified using the EPIC database of COVID confirmed/suspected patients lists to see if patients meet our inclusion criteria.

At the time of introducing the study to the patient, the inclusion/exclusion criteria will be reviewed by the study team member.

ENROLLMENT PHASE

For all participants, this phase occurs from the time of consent through on average a period of about 28 days. All participants will be followed until their 28 day participation. Procedures are outlined in the "Study Procedures" section. The enrollment phase may continue past these points for participants requiring ongoing monitoring of an AE.

CLOSE-OUT PHASE

The closeout phase includes confirming that all queries are addressed, the dataset is finalized, locked and analyzed, all documentation is appropriately stored, and the study is closed with the Institutional Review Board (IRB).

1.5 PROTOCOL AMENDMENTS

The objectives of the PAP-COVID study are most likely to be achieved if the protocol does not require alteration. Any changes in the protocol would result in some degree of heterogeneity of the data, which may complicate the analyses and may compromise the scientific integrity of the study. However,

occasions may arise in which protocol changes are necessary. Therefore, changes in the protocol will be considered only if they are required to ensure safety or will significantly enhance the scientific validity or feasibility of the study. Any member of the PAP-COVID study team may request a change to any portion of the study protocol. The staff member wishing to change the protocol should present the proposed changes(s) in writing to the PI, who will then contact other relevant personnel. The Executive Committee will then jointly decide on the appropriate mechanism (letter, conference call, or meeting) to handle the proposal depending on the implications of the proposed change. Proposed changes will be presented to all study members via conference call or formal meeting to allow all members to benefit from the scientific debate generated in these discussions. Proposed changes can be implemented only after the PI and relevant personnel reach a majority vote. Once a proposed change has been approved, the Research Manager will coordinate all activities required to implement the change via the issuance of a protocol amendment document and revised protocol. Substantive changes to the protocol and ancillary proposals must be submitted to the Data Monitoring Committee (DMC) for review and approval before implementation can occur.

2 – STUDY ORGANIZATION

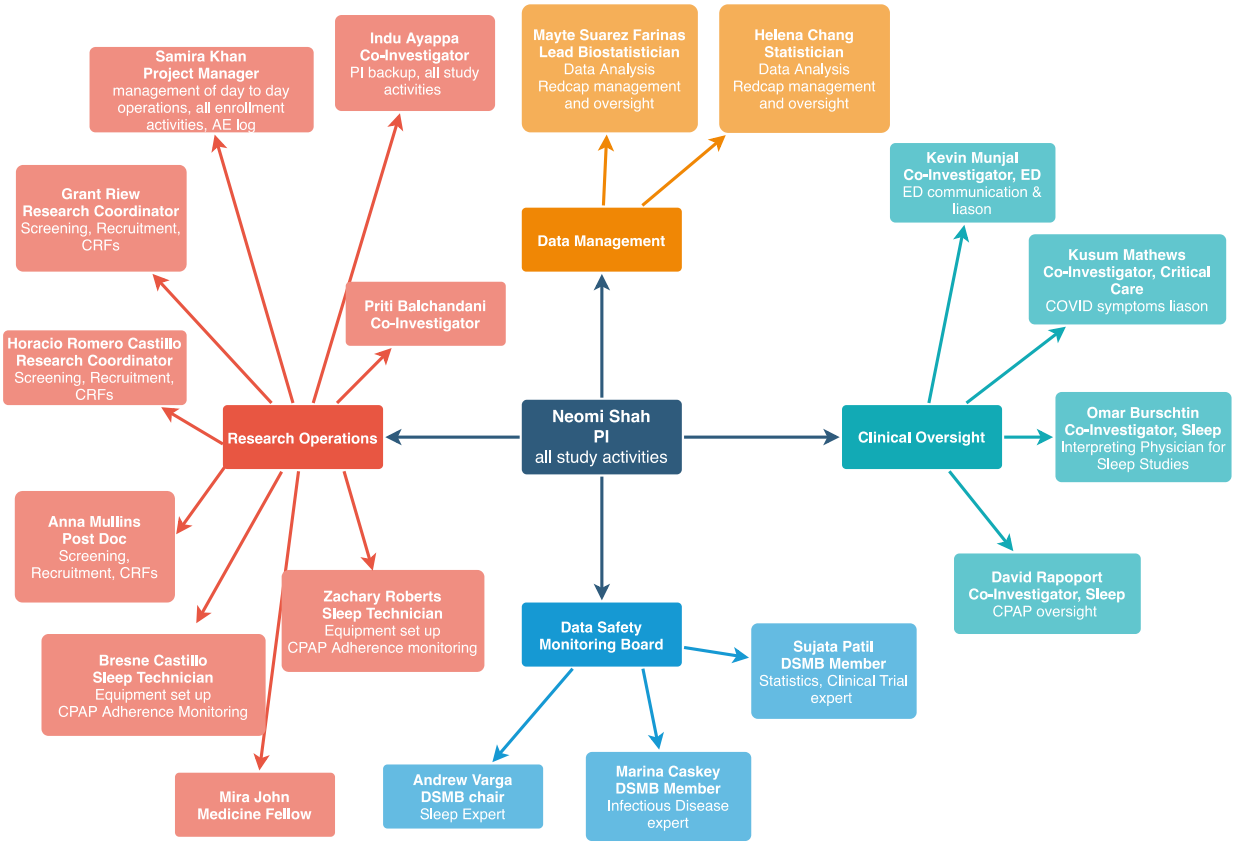
2.1 PROJECT MANAGEMENT

STUDY PERSONNEL

- **Neomi Shah:** PI; all study activities
- **Samira Khan:** Project Manager; management of day to day operations, all enrollment activities, AE log
- **Indu Ayappa:** Co-Investigator; PI backup, all study activities
- **Priti Balchandani:** Co-Investigator
- **Kevin Munjal:** Co-Investigator, ED; ED communication & liaison
- **Kusum Matthews:** Co-Investigator, Critical Care; COVID symptoms liaison
- **Omar Burschtin:** Co-Investigator, Sleep; interpreting physician for sleep studies
- **David Rapoport:** Co-Investigator, Sleep; CPAP oversight
- **Mayte Suarez Farinas:** Lead Biostatistician; data analysis RedCAP management and oversight
- **Helena Chang:** Statistician: Data Analysis; RedCAP management and oversight
- **Andrew Varga:** Sleep Expert
- **Marina Caskey:** Infectious Disease Expert
- **Zachary Roberts:** Sleep Technician; equipment set up, CPAP adherence monitoring
- **Bresne Castillo:** Sleep Technician; equipment set up, CPAP adherence monitoring
- **Sanjana Inala:** Research Coordinator; screening, recruitment, CRFs
- **Michelle Rolak:** Research Coordinator; screening, recruitment, CRFs

COMMITTEES

- **Executive Committee:** Neomi Shah, Indu Ayappa, Samira Khan
- **Research Operations:** Neomi Shah, Indu Ayappa, Samira Khan
- **Data Management:** Neomi Shah, Indu Ayappa,Mayte Suarez Farinas, Helena Chang
- **Clinical Oversight:** Neomi Shah, Indu Ayappa, Kevin Munjal, Kusum Matthews, Omar Burschtin, David Rapoport
- **Data Monitoring Committee:** Neomi Shah, Indu Ayappa, Sunjata Patil, Marina Caskey, Andrew Varga



2.2 MEETING SCHEDULES

Each of the major committees will meet on a regular basis: Usual meeting (by phone or video conference) intervals are as follows, but may vary at the discretion of the Chair, depending on the study needs:

- **Executive Committee:** Every two weeks by conference/Zoom call
- **Research Operations:** Every week by conference/Zoom call
- **Data Management:** Monthly or more frequent intervals, as needed, by conference/Zoom call
- **Clinical Oversight:** Monthly or more frequent intervals, as needed, by conference/Zoom call
- **Data Monitoring Committee:** The DMC will meet prior to trial initiation to discuss the Charter, review and approve the study protocol prior to study initiation, review any other relevant documents, and make recommendations to the sponsor and study team regarding possible modifications. Future meetings will review the accumulating data on safety and, study quality and will be scheduled approximately three times during the course of the trial (after 25%, 50% and 100% of patients reach the primary endpoint at 14 days post-randomization). Meetings will be conducted via zoom. A DMC meeting will require a quorum.

To aid communication, a study OneDrive will be developed which will include areas for posting study documents, interactive study progress reports, quality control reports, and a publications hub.

2.3 CLINICAL SITES

Subjects are at-home patients discharged or denied entry to the ER at any Mount Sinai hospital. All study contact (ie. recruitment, consent, explanation of study procedures) will occur remotely via telephone and video calls. Study devices will be shipped to the patients' home. The patient will then use the devices in their own homes.

3 – STUDY OVERSIGHT

3.1 DATA MONITORING COMMITTEE (DMC)

DESCRIPTION

This Charter is for the Data Monitoring Committee (DMC) for the Early Continuous Positive Airway Pressure (CPAP) in COVID Confirmed or Suspected Patients study (PAP-COVID Study).

This Charter defines the primary responsibilities of the DMC, it's relationship with other trial components, its membership, and the purpose and timing of its meetings. The Charter also provides the procedures for minimizing conflicts of interest and ensuring confidentiality of emerging data and deliberations of the DMC, as well as statistical monitoring guidelines to be considered by the DMC, if any. It will also address the content of the Open and Closed Reports that will be provided to the DMC.

REPORTS

For each DMC meeting, interim safety reports including reports of all mortalities, household COVID conversions, and adverse events will be prepared by the trial statistical team. In addition to the pre-scheduled meetings, the DMC Chair will receive and review reports of all mortalities, unexpected serious adverse events, and COVID conversions within 72 hours of the Investigator becoming aware of the event as well.

ADDITIONAL INFORMATION

More information regarding DMC membership, responsibilities, and operations can be found in the DMC Charter (separate document).

3.2 INSTITUTIONAL REVIEW BOARD

This study is to be conducted according to U.S. and international standards of good clinical practice, applicable government regulations and institutional research policies and procedures. The final study protocol and any amendments will be submitted to the IRB and Mount Sinai COVID-19 Research Protocol Committee. The decision of the IRB concerning the conduct of the study will be made in writing to the PI and a copy of this decision will be provided to the sponsor before commencement of this study.

4 – SCREENING AND RECRUITMENT

4.1 SCREENING AND RECRUITMENT OVERVIEW

Overall recruitment should focus on patients with known or suspected COVID-19 who are experiencing symptoms, and have been discharged from or denied admission to the ED.

4.2 RECRUITMENT SOURCES

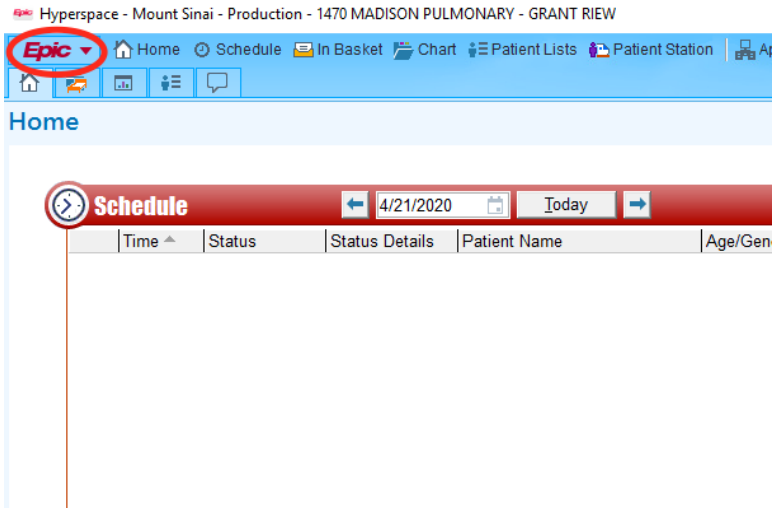
Eligible participants will be identified by:

4) **Precision Recovery Program.** This program is a Sinai-wide initiative which is remotely monitoring patients who are sent home from the emergency room. This is similar to our protocol and therefore working with the precision recovery program will be a synergistic effort. **We will exclusively recruit from their pool of patients when possible**, as the precision recovery program will hand out our fliers to their participants, and therefore will ensure that the patient does not get a cold call from us.
5) **Emergency room staff members.** Members of the research team (primarily Emergency Room department, in these following two locations: main ED, and surge space (Martha Stewart)) will identify and provide flyers to the patients as discussed above.
6) **Via EPIC screening.** Subjects will also be identified using the EPIC database of COVID confirmed/suspected patients lists to see if patients meet our inclusion criteria.

4.3 SCREENING PROCEDURES

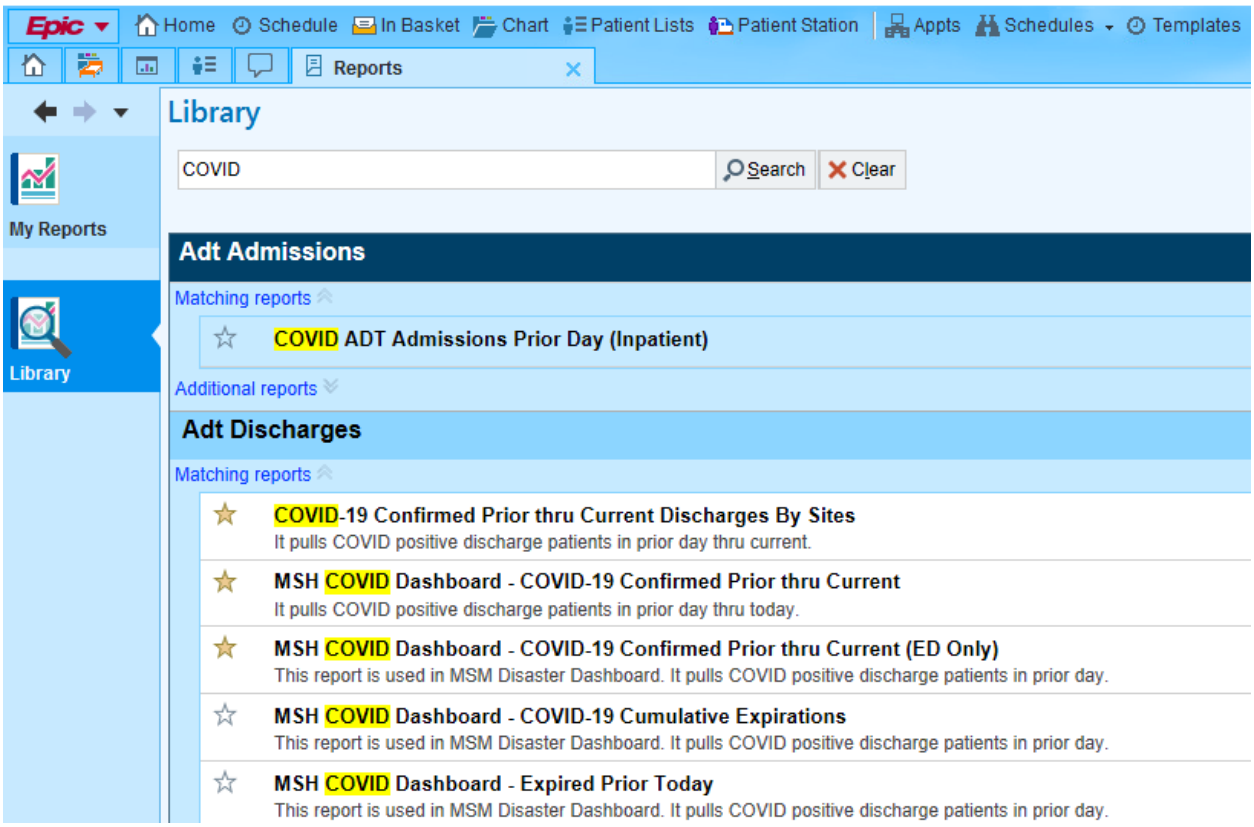
EPIC screening procedures are as follows:

1) Click on Epic logo dropdown top left corner

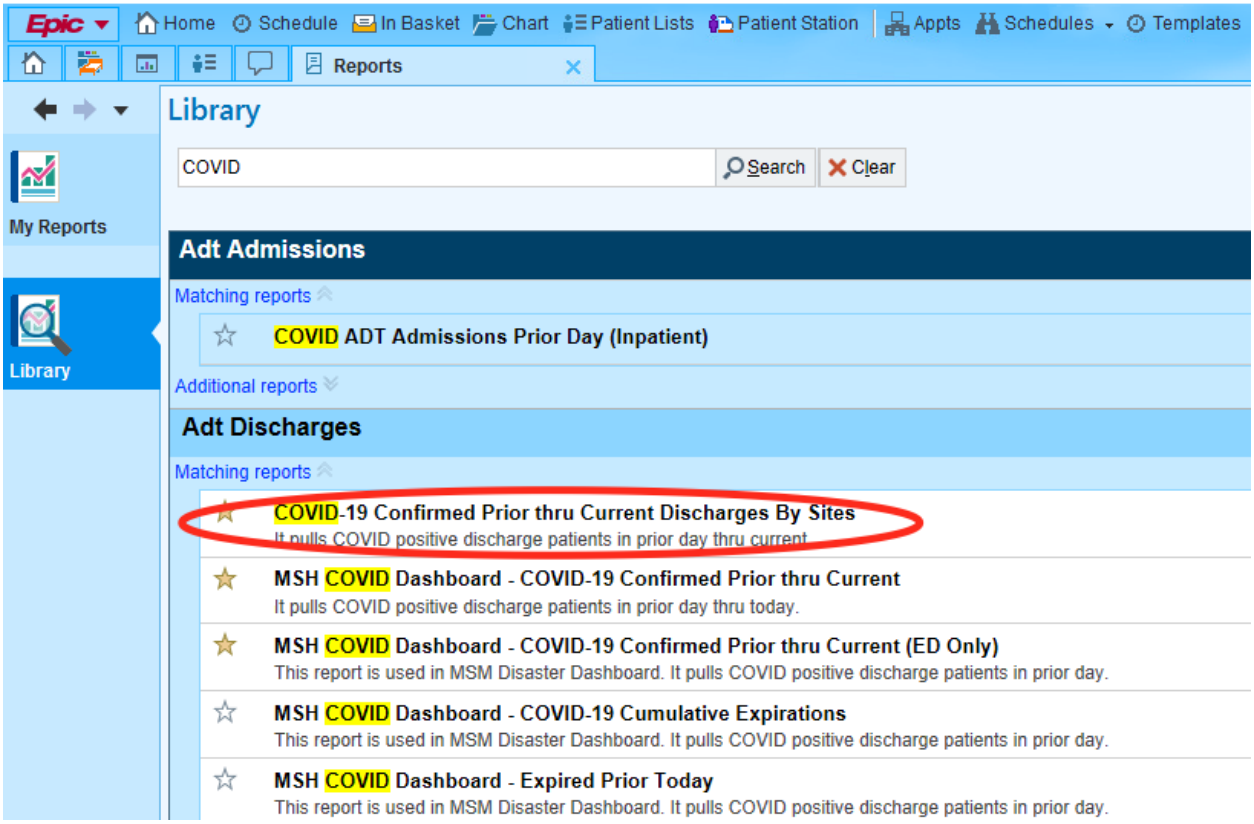


2) Reports → My Reports

3) Click Library left hand side
4) Search “COVID”



5) “Star” COVID-19 Confirmed Prior thru Current Discharges by sites
    a. This shows you positive discharge patients



6) "Star" COVID-19 Confirmed Prior thru Current
    a. This shows all COVID from MSH
7) "Run" the report
8) Open patient chart, go to Notes, and read ED Provider Notes (symptoms)
    a. Check for inclusion/exclusion criteria in chart
        i. (ALL EXCLUDED PATIENTS ADD TO RIPPLE, add note for exclusion)
    b. Call patient to see if interested

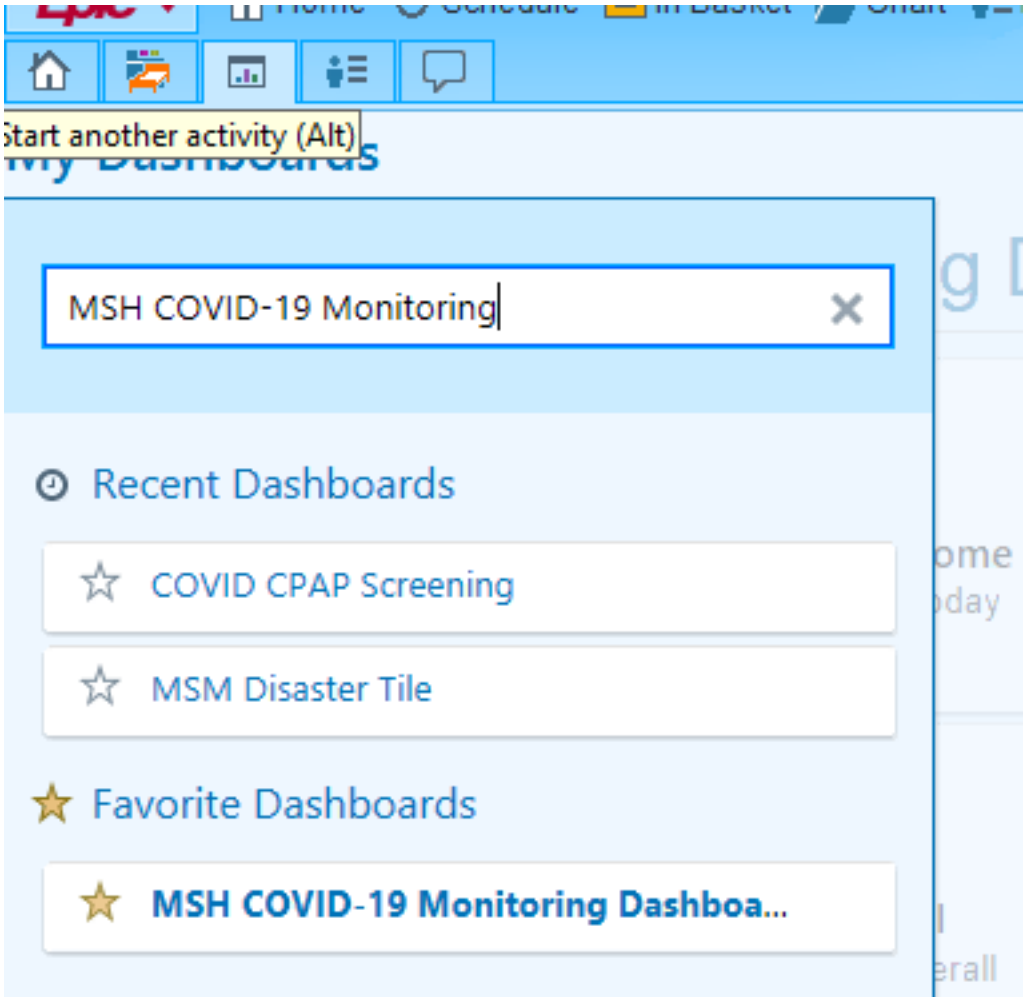
Once contacted patient,

1) If interested, input in OnCore and begin study
2) If not interested, add to Ripple and add a note saying not interested

Dashboard (MSH COVID Statistics)

EPIC → Reports → My dashboards

1) My dashboards
2) Search: "MSH COVID-19 Monitoring"



3) Star "MSH COVID-19 Monitoring Dashboard"
4) Run report
5) Scroll down to bottom, click "MSH ED SURGE"
6) Double click to see patients

4.4 RECRUITMENT AND RETENTION OVERSIGHT

RECRUITMENT TRACKING

Tracking will occur through online software: Oncore and Ripple. Patients who enroll will be tracked in Oncore. Patients who decline to enroll, or are ineligible will be recorded in Ripple to prevent double calling.

5 – PARTICIPANT POPULATION AND ELIGIBILITY

5.1 DESCRIPTION OF POPULATION

This study will involve participation of adults with confirmed or suspected COVID-19 and abnormal chest X-ray or clinical symptoms. Adults ≥ 18 years of age, of both genders and all racial and ethnic groups will be eligible for participation. Inclusion and exclusion criteria refer to the participant only.

5.2 ELIGIBILITY CRITERIA

Eligibility criteria are listed on the Eligibility [ELIG] CRF, and below.

INCLUSION CRITERIA

1. Adults > 18 years old
2. Patients living alone or with more than one room at home
3. COVID-19 confirmed or suspected
4. To be discharged home or already discharged
5. One or more of these: fever (>38ºC), sore throat, myalgia or flu-like illness
6. One or more of the following: abnormal chest x-ray, new onset cough, mild hypoxemia (saturation between 92-96%), abnormal lung exam, chest tightness or shortness of breath

EXCLUSION CRITERIA

1. Unable to self quarantine for 72 hours if in the CPAP arm
2. Preexisting pulmonary diseases such as advanced COPD, advanced parenchymal lung disease, history of pneumothorax etc.
3. Claustrophobic and unable to tolerate CPAP mask
4. Evidence of hypercapnia
5. Recent heart of lung surgery within 3 months
6. Individuals without access to smart phones or wireless connection or internet access
7. Prior history of aspiration
8. Speech or swallowing impairment (risk of aspiration)
9. History of stroke with significant neurologic deficit
10. Advanced symptomatic heart failure
11. Unable to provide informed consent
12. Household with young children and child care responsibilities
13. Household with high-risk individuals (defined as over 60 or with comorbidities (e.g. heart disease, diabetes, pulmonary)

6 – INFORMED CONSENT

6.1 INFORMED CONSENT OVERVIEW

Each coordinator is responsible for ensuring that informed consent is obtained from each participant according to the guidelines of the central IRB, and all applicable local hospital and regulatory requirements. The consent procedure will include ongoing review of vital status and hospitalizations

through regular review of the EMRs from the local medical center(s), as well as the request of records from outside medical institutions when hospitalizations are reported at those institutions. Specifically, the following must be accomplished during the informed consent process:

The participant must be informed that participation in the study is voluntary, and that refusal to participate will involve no penalty or loss of benefits;

- The participant must be informed that the study involves research;
- The participant must be informed of any alternative procedures;
- The participant must be informed of any reasonable foreseeable risks;
- The participant must be informed of any benefits of participating in the research;
- An outline of safeguards to protect confidentiality must be included, as well as an indication of which parties are allowed to review the record;
- The participant must be informed of their right to withdraw without penalty. This discussion should be balanced with a discussion of the effect/s withdrawals have on the study, and the responsibility that the participant has, within limits, to continue in the study if they decide to enroll;
- The participant must be informed of their right to have questions answered at any time, and should be given adequate time to consider the study obligations and discuss the study with family members or other prior to consenting;

INFORMED CONSENT ADMINISTRATION

After patients have verbally agreed to participate in the study, they will complete an e-consent. The research staff will walk the patient through the e-consent and explain the study, risks and benefits in detail to the participant. The Mount Sinai approved Phone Consent process will be utilized, including having a witness present or having the patient send back signed documents in the case a witness is not able to be present.

Once deemed eligible, the study coordinator will provide the participant with a copy of the ICF. The study coordinator will explain in lay persons' terms the nature of all procedures. After the participant has had a chance to ask questions, the ICFs must be signed and dated.

Ample time should be given to allow the participant to read the ICFs, process the information, and ask questions. If the participant wishes to take the ICFs home before reaching a decision, they may do so. At the subsequent visit, the PI and/or other investigator should answer any questions raised by the participant. The participant should be made aware of their responsibilities throughout the screening process, during the baseline visit, after the randomization assignment, and throughout the study period. The importance of continued follow-up should be stressed and balanced with a discussion of the effect of withdrawal on the study.

The ICFs must be signed and personally dated by the participant (if a witness is not present), and by the principal investigator or designated staff member obtaining consent. The staff member obtaining consent and signing the ICF does not need to be a physician. The participant should not be asked to sign the ICF if they have any doubts about enrolling, or if the study staff member believes that the participant does not understand what participation would involve. Under no circumstance is any study information to be collected or study procedures performed other than those described for screening in Section 4.3, before the participant has signed the ICF. The study coordinator will maintain the original, signed ICFs in the participant's Source Document Binder with other study documentation, and provide a copy of the signed ICFs to the participant who

should be urged to retain the document for future reference. To ensure confidentiality, the study coordinator will not send copies of the ICFs signed by the participant to the DCC or other core groups.

HIPAA AUTHORIZATION FORM

Medical records will be screened in order to identify eligible patients. We will only be contacting patients if they meet the inclusion criteria, thus would be unable to obtain HIPAA authorization from them prior to viewing PHI. We are requesting a waiver for recruitment purposes only and will obtain full HIPAA Authorization from subjects who sign the consent form.

MEDICAL INFORMATION

All patients will be within the Mount Sinai health system, and their medical records will be screened in order to identify eligible patients. Waivers and signing for full HIPAA authorization will be obtained.

6.2 CONFIDENTIALITY

Confidentiality is strictly maintained throughout the study. All study personnel have been trained about the importance of confidentiality and steps toward guarding it have been incorporated. In order to protect the privacy interests of subjects, we will ensure that all data will be entered into a secure and password protected electronic database (REDCap, OnCore, Ripple). Only study-related personnel will have access to the data and subject identifiers. All data will be collected electronically. When coding data, subject names will be stored separately from all other data, and ID codes are substituted for subject names.

6.3 ASSIGNMENT OF ID CODES

Each participant will be assigned an ID code upon consent. This code will be entered into Redcap and will be used for all communication purposes. Only the PI, Research manager, and research coordinator will be able to link ID codes to each participant.

7 – STUDY PROCEDURES

7.1 VISIT SCHEDULE

Study Procedures:

1) Patients will be screened as described earlier
2) Eligible patients will be provided a flyer by ED provider when possible but may also be contacted by telephone once they have been discharged. (Of note: we are being approached by patients who are discharged from the hospital with COVID pneumonia who continue to experience shortness of breath and are requesting a CPAP without having prior knowledge of this study).
3) Research will be introduced to the patient, and if they agree to participate, a telephone consent will be conducted (according to IRB requirements including witness). Once patients have enrolled in the study, their PMD will also be notified of their participation. The patient will also be added to the study on EPIC, so that all treating physicians are aware of the patient's participation in our study.
4) Once patients have enrolled in the study, a pulse oximeter and a disposable WatchPAT One device will be mailed to the patients (within 24-48 hours of discharge). Orders placed before noon will be delivered the same day by a local durable medical equipment company we are working with. Orders placed past noon, CPAP delivery will be done the subsequent day or upto 48 hours if outside the New York area. Patients who are randomized to the treatment arm will receive a CPAP machine and three full-face masks in addition to the above noted equipment.
5) Patient will then be instructed via facetime or other video platform on CPAP setup and use, face mask fitting (those randomized to CPAP), and use of the WatchPAT One and pulse oximeter (for both CPAP and control arm). All participants will wear the WatchPAT one for one night whereas the oximeter will stay on continuously and the patient will report the saturation to us via follow up survey.
6) Patients randomized to receive CPAP will be asked to stay in isolation throughout the duration of the study i.e. 72 hours. They will be required to stay in a different room with the door shut and windows open (weather permitting). We will also ask the patient to stop using CPAP during meals or other daily activities. Subjects not on CPAP machine will also be instructed to sleep in a room with windows open (weather permitting).
7) Patients will use the CPAP machine as instructed for 72 hours.
8) All patients will be contacted every 6-12 hours to complete follow up assessments. These follow ups will be done via a phone call. If the timing of these follow ups fall between 10pm-6am, the follow up will be deferred until after 6am. After 72 hours, all patients will then be contacted daily until day 14 from randomization. After day 14, research staff will continue to monitor the medical charts for any visits to the hospital. One last contact will be made on day 28.
9) After 72 hours, patients will be asked to discontinue using the CPAP and pulse oximeter. If patients wish to continue to use the CPAP, they may do so for up to 7 days from time of randomization.
10) The research staff will continue to call all patients daily (after the 72 hour mark) to assess symptoms.
11) The patients can also choose to monitor their oxygen saturation beyond the 72 hours of treatment.
12) CPAP download is available continuously however we will download data on usage, pressure, leak daily and make adjustments to the mask or CPAP pressure as needed for patient comfort. For patients experiencing significant trouble tolerating high pressure, we will decrease CPAP from 8-10 cm to a fixed CPAP of 5 cm for 2-4 hours after which we will raise it back to 8-10cm for the

duration of the study. If the patient is not able to tolerate the pressure again, we will reduce it back to 5cm of water pressure for several hours before increasing the pressure. This will be continued until the patient withdraws or 72 hours are completed, whichever occurs first.

13) Patients will be asked to track their own oxygen saturation using the provided pulse oximeter and report it when we contact them for the 6-12 hour follow up calls/surveys.
14) The sleep apnea test will provide continuous oxygen and breathing data for a period of 12 hours during the 72 hours and will also provide information on oxygen saturation while the patient is asleep.

The outline of the forms that correspond to the study visits can be found in the Appendix, Figure 1. All of these forms are subsequently included in the following appendicies.

7.2 SCREENING VISITS

PRELIMINARY SCREENING

A research coordinator will conduct preliminary screening prior to contacting patient.

SCREENING VISIT

Upon reaching out to patient, the coordinator will confirm enrollment eligibility with the patient prior to consenting.

7.3 VISIT 1

Visit 1 is performed by the coordinator. It consists of the following forms:

- Phone consent
- Enrollment Eligibility Form
- ER Admission Data Form
- Demographics and Subject History Form
- Participant Contact Form
- Medications Form
- CPAP and WatchPAT Assignment Form
- PROMIS questionnaire Form
- Randomization Form
- Respiratory Questionnaire Form

1. Once the Mount Sinai team has randomized patient, we will email covid19cpap@communitysurgical.com with demographics and equipment ordered.
2. Community surgical will call patient to confirm address and information, they will then initialize the WatchPAT.
3. The pin used will be the DOB in the following format: MMDD
4. The pin will be written on the WatchPAT box as well
5. Community surgical will then deliver the equipment box to the patient. Patient will receive documents to sign via docusign.

6. Once delivery has been made, community surgical will notify PI
7. Community surgical will register patient on encoreanywhere – once patient has been registered it will take approximately 24 hours before we are able to see the patient on our end

7.4 VISIT 2 (EQUIPMENT SET UP CALL)

Visit 2 is done by the sleep technicians. It consists of the following forms:

- CPAP Set Up Form
- WatchPAT and POX Set Up Form

7.5 6-12 HOUR CHECKINS (UP UNTIL 72 HOURS)

The subsequent check-ins are done by the coordinator. They consist of the following forms:

- Follow-up Questionnaire
- Respiratory Questionnaire Form
- CPAP Adherence Form
- CPAP Use Form

7.6 DAILY CHECKINS (DAYS 4-7)

After 72 hours, check-ins occur daily. For patients on CPAP, the forms to be filled out are:

- Follow-up Questionnaire
- Respiratory Questionnaire Form
- CPAP Adherence Form
- CPAP Use Form

For patients not on CPAP, the forms to be filled out are:

- Follow-up Questionnaire
- Respiratory Questionnaire Form

7.7 DAILY CHECKINS (DAYS 8-14, 28)

After 7 days, check-ins continue to occur daily. For patients on CPAP, the forms to be filled out are:

- Respiratory Questionnaire Form
- Interval Assessment Form
- Investigator Statement Form (Day 28)

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8 – WITHDRAWLS AND DROP-OUTS

8.1 REFUSAL OF PARTICIPATION

A record will be kept of all participants who are ineligible, or approached but are not interested in participation in the study prior to the signing the ICF. This is to prevent double calling patients. The MRN and reason for ineligibility/disinterest will be logged in Ripple. We will let the patients we call know their MRN will be stored in Ripple. This data will be deleted when the study is over.

8.2 WITHDRAWALS

Participants whose participation in the study is terminated prematurely (before final participant completes their 28-day endpoint visit) at their own discretion or that of the investigator are considered withdrawals. The withdrawal request can be made during a phone contact. When possible, willing participants will have follow-up data collected, including electronic medical record data.

REASONS FOR WITHDRAWAL

Participants are free to withdraw from the study at any time. The various reasons for withdrawal may include:

- Experiencing an AE;
- Dissatisfaction with treatment;
- Significant concurrent illness;
- Loss of interest in the study;
- Relocation.

Participants may also be withdrawn from the study by the investigators, for protocol non-compliance or other reasons at the discretion of the site PI. All withdrawals should be reported following the procedures below.

PROCEDURES FOR WITHDRAWAL

Once it has been established that a participant is going to be withdrawn from the study, the study coordinator should complete the End of Study CRF. If the participant has been randomized, the study coordinator should also complete the Treatment Stop CRF.

Study Stop Resulting from Withdrawal

Once withdrawal is established the study coordinator fills out the End of Study CRF by recording:

- That the participant did not complete the study per protocol;
- The last study visit the participant completed;
- The date participation stopped (the day withdrawal was established); • The primary reason cited for ceasing participation;

The End of Study CRF must be completed in Slice within 24 hours of withdrawal. This will allow the DCC to begin the data archival process.

8.3 DROP-OUTS

Participants who drop out will be distinguished from those who withdraw based on whether they actively withdraw versus passively dropped out by not responding to phone interviews.

PROCEDURES FOR DROP-OUTS

Participants who do not answer or respond to phone calls will be considered possible drop-outs. Following a missed visit, the study coordinator must:

- Immediately place a call to the participant in an attempt to re-establish contact and leave a voice message if possible detailing the importance of contacting study staff in order to gather critical data, whether or not they intend to continue participation.
- Query the Mount Sinai Expired list, frequently.
- Continue to call twice a day for 7 days until you hear from patient. If patient misses 2-3 consecutive calls, check the emergency contact.
- Once the participant has not responded and the emergency contact is unavailable, the PI should be notified. The End of Study form may be filled out given the situation.

8.4 VISIT WINDOWS AND MISSED VISITS

VISIT WINDOWS

Check-ins should occur based on the "schedule" form.

MINIMIZING MISSED VISITS

To minimize the occurrence of missed appointments, the participant should be provided with the following when appropriate:

- Visit Schedule of in-window visits generated and provided at the baseline visit;
- Text reminders to patients to fill out forms

9 – RANDOMIZATION

9.1 ELIGIBILITY FOR RANDOMIZATION

Only participants who have successfully completed the entire screening process will be eligible for randomization. The following will be assessed to confirm eligibility:

- The inclusion and exclusion criteria will be reviewed, checked, and verified by completing the Screening and Eligibility CRF during the screening and baseline visit prior to randomization.

The PI and study coordinators will be the only people who has authorization to access the randomization database. The study coordinator must complete the Screening and Eligibility CRF in RedCAP to receive the computer-generated randomization code. The randomization code will not be assigned until all the questions have been answered and automatically crosschecked in the system with previously entered data to confirm eligibility. The randomization process is an administrative task that occurs after all the screening and baseline data have been collected and entered into RedCAP. The study coordinator may randomize the subject at the end of the baseline visit with the participant present or within 12 hours of the baseline visit.

9.2 RANDOMIZATION PROCEDURES

ELECTRONIC RANDOMIZATION

The PI and Research Manager will be responsible for randomization. Once patient has been deemed eligible and coordinator has entered in the appropriate documents, the PI will review with the research manager and sign off. An automatic electronic randomization process has been built in to the redcap database.

10 – PROTOCOL DEVIATIONS AND ADVERSE EVENTS

10.1 PROTOCOL DEVIATIONS

Deviations are variances from the IRB (and sponsor when one exists) approved protocol/protocol related materials that have not been pre-approved and 1) imposed no increase in risk to the participant and 2) did not result in a negative consequence and is not anticipated to result in a negative consequence in the future.

Violations are variances from the IRB (and sponsor when one exists) approved protocol/protocol related materials that have not been pre-approved and 1) imposed an increase in risk to the participant and/or 2) resulted in a negative consequence or is anticipated to result in a negative consequence in the future.

REPORTING PROTOCOL DEVIATIONS

All protocol deviations must be reported using the Protocol Deviations CRF. Note that a protocol deviation that is also an AE should be reported as an AE rather than a deviation.

Reasons for deviation:

- Informed Consent not obtained/signed/dated
- Incorrect version of Informed Consent obtained/signed/dated
- Eligibility Criteria not met
- Randomization not performed as required
- Not all required testing/assessments completed
- Follow-up visit/testing/assessments done outside of visit window
- Follow-up visit not done/missed
- SAE submitted to Sponsor and/or EC outside the required timeframe
- Not all required testing/assessments completed **and** follow-up visit/testing/assessments done outside of visit window

10.2 ADVERSE EVENTS AND UNANTICIPATED PROBLEMS

Ad adverse event is considered “unexpected” if it is not listed in the protocol, or Informed Consent Forms or is not listed at the specificity, severity or rate of occurrence that has been observed; or, is not consistent with the risk information described in the general investigational plan or elsewhere.

ADVERSE EVENTS

An AE is any unfavorable or unintended sign, symptom or disease occurring in a participant at any stage of the study, whether or not considered related to the study.

CLINICAL ENDPOINTS

Any reported AEs that meet the following are also clinical endpoints and will be reported on the End of Study form. DMC Project Manager will review all AEs to determine if they also meet

clinical endpoint criteria. If criteria are met, the DMC Project Manager will ensure all documentation need for endpoint review is received by the site study coordinator.

	Anticipated Adverse Events (AAE)		Unanticipated Adverse Events (UAE)	
	○ Headaches ○ Fever ○ Chills ○ Loss of appetite ○ Nausea ○ Vomiting ○ Fatigue ○ Muscle or body aches ○ New loss of taste or smell ○ Sore throat ○ Congestion or runny nose ○ Diarrhea ○ Decrease in oxygen saturation (that is not associated with shortness of breath or difficulty breathing)	○ Oxygen saturation less than 90 during the monitoring period ○ Absolute reduction in oxygen saturation of more than 4% **associated with shortness of breath or difficulty breathing** ○ Persistent pain or pressure in the chest ○ Any worsening of COVID symptoms that lead to an Emergency room visit, hospital admission, ICU admission, intubation, or mechanical ventilation	○ Any Adverse effect on the health or safety caused by, or associated with, the CPAP or progression of underlying COVID that was not previously identified in the product labeling, published literature or study protocol	○ Any event that results in death ○ Conversion of family members to COVID positive in the CPAP group
Reporting	None	Redcap	None	Redcap, DSMB, IRB

10.5 DISCONTINUATION

DISCONTINUATION – TREATMENT STOP/DISCONTINUATION

Participants may require additional/alternative therapies that may or may not be exclusionary criteria and are designed to minimize the potential risks to participant's safety which can result in discontinuation of the study treatment. Discontinuation can be observed during either routine interim follow-up phone calls or visits, or as a result of study contact by the participant or the participant's physician. If the participant is deemed a 'discontinuation – treatment stop', the Treatment Stop CRF must be completed, arrangements for the return of the concentrator must be made, and the participant should still be followed-up per protocol, despite no longer receiving the study intervention, if agreed. Discontinuation – treatment stop in PAP-COVID are defined as follows:

• The participant's physician has identified a change in signs or symptoms that in his/her opinion are related to ongoing symptoms of COVID-19 and therefore warrant alternative treatment, such as permanent supplemental oxygen

URGENT MEDICAL REFERRAL

Patients have 24/7 access to the Precision Monitoring Program doctors. These doctors include:

- Dr. Christopher Kellner (Dept. of Neurosurgery)

- Dr. Johanna Fifi (Dept. of Neurosurgery)
- Dr. Mariam Zakhary (Dept. of Rehab and Human Performance)
- Dr. Dayna McCarthy (Dept. of Rehab and Human Performance)
- Dr. Eliana Cardozo (Dept. of Rehab and Human Performance)
- Dr. Vincent Huang (Dept. of Rehab and Human Performance)
- Dr. Kirk Lercher (Dept. of Rehab and Human Performance)
- Dr. Gerardo Miranda-Comas (Dept. of Rehab and Human Performance)
- Dr. Joseph Gladstone (Dept. of Orthopedics) tentative

10.6 SURVEILLANCE

At each contact with the participant, the investigator must seek information on AEs, clinical endpoints, and urgent medical referrals. Information on all events/problems should be recorded immediately. All events/problems occurring during the study period must be recorded and reported. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause and the event is not a defined clinical endpoint. Monitoring events/problems is a constant task given to all study personnel, and should be accomplished using all available sources, including (but not limited to):

- Spontaneous reports by the participant;
- Observations by key study personnel;
- Reports to study staff by the participant or medical care providers;
- Possible AE documented in records or progress notes.

In addition to receiving reports of potential AEs, the study coordinator should develop and implement a plan to monitor for AEs consistently and routinely through proactive measures such as:

- Review participant's records for additional information;
- Communicate with participant's medical providers if necessary.

In addition to these avenues of monitoring, AEs will be monitored more formally through several means of surveillance, including:

- At each follow-up visit, data will be collected that includes assessment of interim symptoms, concomitant medication use and any new illnesses or conditions that have occurred from the time of the previous visit.
- Research data will be interrogated to identify whether any questionnaire data exceed values that indicate an abnormality.

10.7 REPORTING ADVERSE EVENTS

HOW TO REPORT AN ADVERSE EVENT

In response to an adverse event, the research coordinator must fill out the Adverse Event Case Report Form and notify the PI. The PI will provide further instructions on a case-by-case basis.

10.8 FOLLOW-UP OF ADVERSE EVENTS

DURING THE STUDY

We will obtain signatures on a medical release form at enrollment, and then obtain any medical records throughout the duration of the patient's experience of the adverse events. We will be regularly checking in with the patient and appropriately documenting all progress until the adverse event has been resolved.

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11 – DATA MANAGEMENT

11.1 REDCAP

We will store all data collected from forms on RedCAP.

11.2 ONCORE

All participant data will be stored on OnCore Clinical Trial Management Software.

11.3 RIPPLE

All patient data for those who are ineligible or declined to participate will be stored in ripple.

11.4 ENCOREEVERYWHERE

All CPAP monitoring and compliance/adherence data will be stored on EncoreEverywhere.

11.5 CLOUDPAT

All sleep data will be stored on CloudPAT for the DMC to download and interpret.

12 – QUALITY ASSURANCE

12.1 QUALITY ASSURANCE PROCEDURES AND RESPONSIBILITIES

Quality control measures will be implemented at several levels to ensure that all centers and personnel meet and maintain comparable high levels of technical performance. Quality control will be optimized by multiple levels of training, monitoring, and feedback activities including coordinator training and certification of personnel for all specialized testing and monitoring procedures.

COORDINATOR TRAINING

After protocol and Manual of Procedures development, a training session will be held virtually on Zoom. Attendees will include study investigators, study coordinators, as well as the leaders of each subcommittee. Joint introductory sessions will be held that include a review of the entire protocol and study organization and allow study personnel to become acquainted. Specifically, but not exclusively, this training will ensure that all personnel understand the study's goals and objectives, as well as PAP-COVID specific data collection and procedures, to ensure that the study is conducted appropriately. Breakout sessions will focus on specific aspects of data collection and database management; anthropometry; AE monitoring and reporting; recruitment and retention; and data entry and data management. Some sessions will be audio-recorded and/or videotaped for future references by staff. Time will be allotted to document proficiency in specific procedures, which may require combinations of observation by the trainer and written exams. In addition to the initial coordinator training, ongoing training of study staff will be conducted. This training, in the form of conference calls, is designed to maintain a current level of project knowledge regarding developments taking place after the initial coordinator training.

12.2 DATA INTEGRITY

INSPECTIONS AND AUDITS

Participation as an investigator in this study implies acceptance of potential inspection by applicable Institutional compliance and quality assurance offices. The investigator will permit study-related monitoring, audits, and inspections by the IRB, and Mount Sinai compliance and quality assurance groups of all study-related documents (e.g. source documents, regulatory documents, data collection instruments). The investigator will ensure the capability for inspections of applicable study-related facilities.

DATABASE AND SYSTEMS MANAGEMENT

The PI will routinely monitor data entered by the coordinators. The DMC and statisticians will check for data quality.

DATA RECOVERY

We will routinely backup the RedCAP databases so we have physical copies of the data.

13 – REGULATORY COMPLIANCE

13.1 RECORD KEEPING AND SOURCE DOCUMENTS

Source data consists of all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original (source) documents and data records include:

- Hospital records;
- Clinical and office charts;
- Laboratory notes;
- Evaluation checklists;
- Pharmacy records;
- Death records;
- Recorded data from automated instruments;
- Copies or transcriptions certified after verification as being accurate and complete;
- Photographic negatives;
- Digital pictures;
- Microfilm or magnetic media;
- X-rays;

All patient information will remain in OnCore and RedCAP.

RECORD RETENTION

It is the investigator's responsibility to retain essential study documents for at least seven years after the study is discontinued.

13.2 INSTITUTIONAL REVIEW BOARD

It is the responsibility of the Principal Investigator (PI) to work with the IRB in initiating protocol approval and re-approval, notification of protocol and/or ICF changes, AEs, and termination of the study according to the appropriate IRB requirements.

13.3 CONTINUING REVIEWS

The study is expected to last less than one year, and before any continuing reviewing will be needed. In the event that we need to extend the study, a continuing review will be submitted in accordance with Mount Sinai's IRB policies.

APPENDICES

FORMS

SCREENING FORM

Effective Date: 5/19/2021
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Screening Form

1. Source of participant's referral? (check one)

☐ Mount Sinai Main ED

☐ Mount Sinai ED Surge Space

☐ ED Precision Recovery Program

☐ ☐ EPIC

☐ ☐ other means, specify: _____

Demographics and Subject History Form :

2. Patient's demographic information was obtained via:
   ☐ Chart Abstraction ☐ Oral Interview
3. participant's current age? _____
4. What is the participant's biological sex?
   ☐ Male ☐ Female
5. What is the participant's race (check all that apply)?

☐ American Indian or Alaska Native

☐ Asian

☐ Black or African American

☐ White or Caucasian

☐ Native Hawaiian or Other Pacific Islander

☐ Other (please specify): _____

☐ Unknown or Not Reported

6. What is the participant's ethnicity?

☐ Hispanic or Latino

☐ Not Hispanic or Latino

7. What is participant's BMI? _____

Enrollment Eligibility Form:

ER ADMISSION DATA FORM

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ER Admission Data Form

*This is abstracted from the chart, data from the date of their admission to the ER prior to baseline

1. Date of admission to the ER: _____
2. Time of admission to the ER: _____
3. Number of days since symptom onset: _____
4. Source of COVID infection:
    - ☐ Unknown
    - ☐ Known
        - ☐ Occupational
        - ☐ Household
        - ☐ Other: _____
5. Did patient have any of the following symptoms (y/n):
    - ☐ Fever (y/n)
    - ☐ Cough (y/n)
    - ☐ Shortness of breath (y/n)
    - ☐ Chest tightness (y/n)
    - ☐ Sputum (y/n)
    - ☐ Nasal congestion (y/n)
    - ☐ Sore throat (y/n)
    - ☐ Chills (y/n)
    - ☐ gastrointestinal symptoms (y/n)

Vital signs in the ED

6. Temperature Fahrenheit: _____
7. Oxygen saturation: _____
    - ☐ Without supplemental oxygen
    - ☐ With supplemental oxygen
        - ☐ How much supplemental oxygen? _____
        - ☐ What method of oxygen: nasal canula, face mask, high flow nasal canula
8. Blood pressure: _____/_____
9. Pulse: _____

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VISITS FIGURE

VISITS FIGURE

	Visit 1	Visit 2 Equipment Set Up Call	6-12 hrs	18-24 hrs	30-36 hrs	42-48 hrs	54-60 hrs	66-72 hrs	Daily Days 4-7 (CPAP only)	Daily Days 4-7 (no CPAP)	Everyone Days 8-14, 28	Event Driven
Phone consent with witness (Consent Form)	✓											
Screening	✓											
Enrollment Eligibility Form	✓											
ER Admission Data Form	✓											
Demographics and Subject History Form	✓											
Participant Contact Form	✓											
Medications Form	✓											
CPAP and WatchPat Assignment Form	✓											
PROMIS questionnaire Form	✓											
Randomization Form	✓											
CPAP Set up Form		✓										

WatchPAT and Pox Set up Form		✓										
Follow-up Questionnaire			✓	✓	✓	✓	✓		✓	✓		
Respiratory Questionnaire Form	✓		✓	✓	✓	✓	✓		✓	✓	✓	
CPAP Adherence Form (Downloaded)			✓	✓	✓	✓	✓		✓			
CPAP Use Form (For Patient)			✓	✓	✓	✓	✓		✓			
WatchPAT Download Form												
Adverse Event Report Form												✓
Discontinuation Form												✓
Interval Assessment Form											✓	
Protocol Deviation/Violation												✓
End of Study Form												✓
Investigator Statement Form (Day 28)											✓	

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