Study: Biology and Longitudinal Epidemiology of PETAL COVID-19 Observational Study

Acronym: BLUE CORAL

Protocol: V7

Date: 14 DECEMBER 2021

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Revisions to the Protocol

Protocol Version 1
Date: 5 JUN 2020
Initial protocol

Protocol Version 2
Date: 24 JUL 2020

Substantive protocol changes in Version 2:

1. Revision to the wording of the specimen collection timepoints. This was done to provide clarity to timing of biospecimen collection. As this is an observational study there are not clear study days that the collections can be tied to. Additional detail was provided on the process for collecting biospecimens. Sections 3.2, 4.7, and Appendix B.
2. Revision to the criteria for subjects eligible for post-hospital follow-up: This has been expanded to include Spanish speaking subjects. Sections 3.3.1 and 4.9. Translated assessment documents have been provided.
3. Corrections of erroneous wording:
   - Removal of extra wording; section 4.2 Enrollment first sentence
   - Correction of the number of ADL instruments from 13 to 14; Appendix A

Protocol Version 3
Date: 11 DEC 2020

Substantive protocol changes in Version 3:

1. Added a second paper-based method to obtain subjects consent signature (section 4.3.2)
2. Added the option for attestation of signature for confirmation of informed consent (section 4.3.4).
3. Removed the requirement for image upload of cardiac telemetry from protocol procedures: Images for Repository (section 4.8)

Protocol Version 4
Date: 10 MAY 2021

Substantive protocol changes in Version 4:

1. Update of LTO post hospital enrollment target number from 500 to 1200: (section 4.2, section 4.9 and clarification in section 4.3.6)

Protocol Version 5
Date: 10 JUNE 2021

Substantive protocol changes in Version 5:

1. Added 3- and 6- month follow-up of consented patients regardless of level of ADL or IADL disability at baseline.
2. Language has been added to Section 4.9 Post Hospital Procedures to describe the safety process that the FUNCTION team at U Michigan follow in the event that a subject being interviewed is at risk for harm: “In the event that a respondent demonstrates evidence of severe psychological distress or other immediate risk of harm—especially as demonstrated by any evidence of suicidality—will result in an immediate safety evaluation and, if indicated, provision of information, support, or hand-off to suicide prevention hotline, by the interviewer per current best practice as incorporated in survey group’s Standard Operating Procedures. The results of any such evaluation and any interventions provided will be reviewed with the study project manager and the study PI via email, or by phone if deemed sufficiently high risk by either protocolized evaluation or in the judgement of the interviewer. Responses will be documented in the survey record.” This process has been in place since study start but was not previously described in the protocol.
3. Appendix A: Added new questions to the 6-month survey (PROMIS Fatigue SF7a, headache, sense of smell, three most troubling symptoms, and frequency of calls). These fatigue and symptom questions added to address emerging scientific data about their potential importance as part of the genesis of Post-COVID disability.
4. Deleted medication questions from the 3-month and 6-month surveys. These questions are being dropped because our experience suggested the data they provided were not robust and scientifically valid.

Protocol Version 6
Date: 27SEP 2021

Substantive protocol changes in Version 6:

1. Pg 7: Added American Lung Association, and the National Center for Complementary and Integrative Health as a funder.
2. Pg 8: Updated study duration from 1 to 2 years to reflect addition of 12-month post hospital assessment.
3. Sections 3.2 Overall Approach and 4.2 Post Hospital Procedures: Tables 1 and 6 updated to include 12-month post hospital assessment.
4. Section 4.1 Screening: Updated language to make clear the two types of data collection: 1) Denominator data; used to describe the relationship between enrolled patients and the larger population and 2) screening data: Aggregate data collected on eligible patients and reason for exclusion.
5. Section 4.9 Post Hospital Study Procedures:
    a. Added a 12-month post hospital follow-up with additional surveys (details in Appendix A) to expand on the current qualitative work and long-COVID assessment

   b. Addition of OHSU to assist University of Michigan with the post hospital assessment work.
6. Appendix A: Added new surveys to the 12-month battery, including questions on sleep (PROMIS Sleep Impairment and Sleep Disturbance short forms), healthcare utilization (adapted from OACIC HUS instrument), complementary health (NHIS), tobacco/alcohol/drug use (TAPS), unmet needs and caregiving receipt (PROMIS Instrumental support) durable medical equipment use (NHATS COVID-19), and a novel Long COVID assessment.

Protocol Version 7
Date: 14 DEC 2021

Substantive protocol changes in Version 7:

Overview: Additional interviews, one at 12 months post hospital discharge and the second 3-6 months after, have been added to the post hospital portion of the protocol. These interviews are part of the American Lung Association funded REACH study; a qualitative study consisting of semi-structured interview of COVID-19 survivors and their caregivers. The purpose of this study is to characterize how patients' pre- and post-COVID-19 functional limitations and their social location impact their lived experience of recovering from COVID-19 hospitalization, as well as their health and community service utilization.

Target population: Up to 80 BLUE CORAL subjects and 30 of their caregivers who speak English and/or Spanish. Interviews will be conducted over telephone or a HIPAA-compliant web-based teleconferencing platform. Participants will provide verbal consent at the time of the interview(s).

- Section 4.9 Post-hospital Procedures; Pg 23: Summary and description of the proposed additional interviews. Participants will be given a $60 gift card for each interview completed for their time and effort.

- Section 4.14 Data management, data sharing, quality assurance and security of data; pg 26: paragraph added describing interview approach and qualifications of the interviewers.

- Section 4.15 Privacy and Confidentiality; pg 26: paragraph describing consenting process and how data from transcripts will be stored.

- Pg 32: Appendix C added: Transcript of the semi-structured interview for BLUE CORAL subjects

- Pg 35: Appendix D added: Transcript of the semi-structured interview for BLUE CORAL subjects' caregivers

ABBREVIATIONS

ABG = Arterial blood gas
ADL= Activities of Daily Living
ARDS = Acute Respiratory Distress Syndrome
BAL= Bronchoalveolar lavage
BLUE= Biology and Longitudinal Epidemiology
CORAL= COVID-19 Observational Study
COVID-19= Coronavirus disease due to SARS-CoV2
ED = Emergency Department
FiO_2 = Fraction of Inspired Oxygen
IADL=Instrumental activities of daily living
ICU = Intensive Care Unit
IMV = Invasive Mechanical Ventilation
ISARIC= International Severe Acute Respiratory Illness Consortium
LTO= Long-term outcomes (Post-hospital follow up)
MV= Mechanical Ventilation
NHLBI = National Heart Lung and Blood Institute
PETAL = Prevention and Early Treatment of Acute Lung Injury
P/F = PaO2/FiO2 ratio
$PaCO_2$ = Partial pressure of arterial carbon dioxide
PACU = Post anesthesia care unit
PaO_2 = Partial pressure of arterial oxygen
PBW = Predicted Body Weight
PEEP = Positive End-Expiratory Pressure
POCUS = Point of care ultrasound
Ppl = Plateau pressure
PS = Pressure Support Ventilation
PUI= Person under investigation (Test pending for COVID-19)
RED CORAL=Registry of electronic data for COVID-19
S/F = SpO2/FiO2 ratio
SARS-CoV2= Severe acute respiratory syndrome coronavirus 2
SOFA = Sequential Organ Failure Assessment
SBP = Systolic Blood Pressure
SpO_2 = Oxygen Saturation via pulse oximetry
WHO= World Health Organization

Definitions

Confirmed COVID-19: Defined as a person with a laboratory PCR confirmed SARS-CoV2 infection

CORAL: PETAL Network's COVID-19 Observational Study, which includes RED CORAL (retrospective electronic data repository) and BLUE CORAL (current proposal)

Extubation: Removal of an orotracheal tube, nasotracheal tube, or unassisted breathing with a tracheostomy

Home: Level of residence or health care facility where the patient was residing prior to hospital admission

Invasive Mechanical Ventilation (IMV): Assisted positive pressure ventilation delivered by a nasotracheal, orotracheal, or tracheostomy tube

Mortality at hospital discharge: This includes deaths from all causes at the time of discharge from the hospital

Funder: National Institutes of Health, National Heart Lung and Blood Institute, American Lung Association, and the National Center for Complementary and Integrative Health.

Study Day: The day of presentation to the hospital for admission is study day 1. The day of ICU admission (including unconventional locations and care teams) is ICU day 1.

Study hospital: Defined as the hospital where the patient was enrolled in study procedures.

1. Protocol Summary

Title	Biology and Longitudinal Epidemiology of COVID-19: Observational Study
Short Title	BLUE CORAL
Clinical Phase	Observational Study
Number of Sites	Participating PETAL hospitals
IND Sponsor/Number	Not Applicable
Study Objectives	**Primary Objective** • Describe the clinical characteristics, treatments, biology, and outcomes of hospitalized patients with COVID-19 **Secondary Objectives** • Identify clinical and biologic risk factors and create prediction models for COVID-19 outcomes, including acute respiratory failure, prolonged mechanical ventilation, cardiomyopathy, and death • Create a deidentified repository of clinical, imaging, and biologic data and of biospecimens for rapid sharing with the scientific community
Study Design	Observational study of hospitalized patients with COVID-19
Accrual Objective	1500 patients
Study Duration	2 years
Inclusion Criteria	1. Adult hospitalized within 14 days of a positive PCR test for COVID-19 2. Evidence of acute COVID-19, with fever or respiratory manifestations, as characterized by signs and symptoms such as cough, dyspnea, tachypnea, hypoxemia, and infiltrates on chest imaging.
Exclusion Criteria	1. Lack of informed consent 2. More than 72 hours of continuous hospitalization. 3. Comfort care orders in place at the time of enrollment and/or unexpected to survive for 24 hours 4. Prisoners 5. Previous enrollment in BLUE CORAL
Study Stopping Rules	There are no safety-related stopping rules.

2. STUDY DESCRIPTION

2.1 Background

The initial report of a cluster of 27 cases of pneumonia of unknown etiology in Wuhan, China was made on December 31st, 2019. One week later, the pathogen was identified as a novel coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). By the end of January, there were nearly 8000 cases of coronavirus disease 2019 (COVID-19) in China and 80 travel-related cases confirmed outside China, leading to declaration of "a public health emergency of international concern" by the World Health Organization. In just three weeks more, there were over 70,000 cases and 200 deaths in China and 1000 cases around the world.[1] Since that time, COVID-19 has raged across the earth like wildfire. On March 28th, 2020, there were over 650,000 cases around the world, with over 115,000 in the US, and a global death toll of over 30,000; one week later, these numbers had doubled (over 1.2 million cases worldwide, over 63,000 deaths, and over 300,000 cases in the United States). By May 25th, 2020, worldwide cases skyrocketed to over 5.6 million. Over 1.7 million of these cases occurred in the United States, where over 100,000 have died.

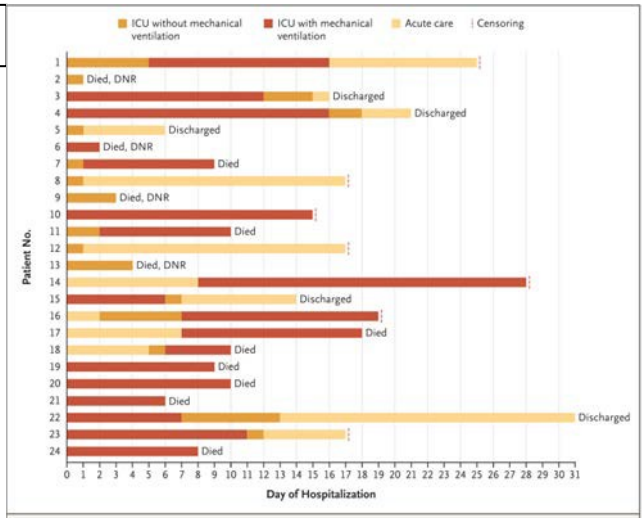
The scientific literature regarding COVID-19 is, unsurprisingly, still in its infancy, and the quality of reported data and studies is highly variable, given the rush to disseminate information during this pandemic. The first large population-level report came from China in late February, describing 44,415 patients with confirmed COVID-19. Most patients were between 30-79 years old, with only 3% of cases in people $\geq$ 80 years. Mild disease was common (81%), although it is not clear if care was received in a hospital setting. Hospitalized patients had signs of lower respiratory infection with cough, shortness of breath, and abnormal chest radiographs. Nearly 20% of patients were critically ill with hypoxemic respiratory failure. Overall case fatality rates was 2.3%, with the oldest and most severely ill at higher risk of death.[1]

Single center reports from China describe high rates of critical illness syndromes among hospitalized patients, with acute respiratory distress syndrome (ARDS) in 22-42%, arrhythmias in 16%, and shock in 11%. [2,3]Early reports describe prolonged respiratory failure and hospitalization, with extended periods of mechanical ventilation. Reports from 1-2 centers in China present clinical risk factors for ARDS and death, describing advancing age, co-morbid hypertension and diabetes, and fever. Patients with poor outcomes were more likely to have abnormal laboratory findings, including neutrophilia, evidence of organ dysfunction (thrombocytopenia and elevated liver enzymes, creatinine, and troponin) and markers of inflammation and dysregulated coagulation (including interleukin-6, ferritin, d-dimer, prothrombin time).[2,4] Case fatality among the severely ill in these Chinese reports is very high, ranging from 49-95%.

The first case series of critically ill patients in the United States is from King County, Washington, where 21 patients with COVID-19 due to community spread were hospitalized at a single hospital between February 20th and March 5th, 2020. All but one developed ARDS, 67%

developed shock, and 33% had evidence of cardiomyopathy. As of March 17th, 14 had died, 5 remained critically ill, and just 2 had left the ICU alive.[5] The second case series, also from Seattle, described 24 critically ill patients, 18 of whom received mechanical ventilation (MV).[6] Median duration of MV was 10 days (interquartile range 7-12), but only four patients had successfully liberated from MV at the time of the report, while three remained ventilator dependent and 8 had died. Although informed by a small number of patients, this report demonstrates major challenges in the care and investigation of severely ill COVID-19 patients; duration of MV and hospitalization is often long, and critical illness may develop later than a week into hospitalization, as shown in **Figure 1.**

Figure 1[5]



Currently, little is known about the epidemiology of COVID-19 in the United States. Best estimates as of mid-March suggested that 20-30% of confirmed COVID-19 cases required hospitalization, and that 5-12% of the overall population with confirmed COVID-19 required intensive care.[7] It is difficult to generalize these findings, given rapid changes in COVID-19 testing and profound evolution of the population at risk from day to day. There are key knowledge gaps regarding clinical characteristics, biology, risk factors, outcomes, and resource utilization for acutely ill COVID-19 patients, especially in the United States. While early studies of remdesivir have shown promise in studies of lowering duration of symptoms in patients early in the course of disease, there are no proven treatments for COVID-19 sequelae, there are no proven treatments, despite high health care utilization and high case fatality, particularly among the elderly and the critically ill. It is unclear how generalizable current knowledge of ARDS biology and treatment may be in COVID-19, since most biomarker profiling and approaches informing prognostication and treatment of ARDS have considered underlying bacterial infections, rather than viral infections. In fact, there are those who have promoted the notion that COVID-19 ARDS might represent a distinct entity from non-COVID-19 ARDS, though more data is necessary to address this fundamental question.

Thus, there exists little understanding of biologic pathways that might be optimal for targeting therapeutics in this deadly syndrome, nor for understanding which patients are at highest risk for ARDS development or prolonged critical illness. Rapid expansion of cases across this country and others necessitates urgent clinical and biologic study of severe acute COVID-19 in order to care for patients, inform and develop treatments, target therapeutics, prognosticate, and understand health system impacts.

2.2 Study Objectives

The epidemiology and biology of patients hospitalized with severe COVID-19 has not been well defined, especially in the American context. There are significant knowledge gaps regarding demographics, clinical characteristics, trajectory of disease, timing of recovery, clinical and biologic predictors of organ failure and death, resource utilization, and post-hospital outcomes. Furthermore, there exists limited understanding of biologic pathways activated by this viral syndrome and which patients are at risk for progression to more severe illness. There are reports of unusual features of COVID-19 critical illness, such as high prevalence of endothelial

dysfunction, thrombosis, and cardiomyopathy as well as catastrophic arrhythmias during recovery, which need further study. In response, the purpose of the BLUE CORAL study is to inform biology, epidemiology, and resource utilization.

2.2.1 Specific Aims

We propose to identify acute and critically ill COVID-19 patients who will undergo detailed clinical and biologic phenotyping with systematic assessment during and after hospitalization, in order to:

a. Characterize the severity and course of acute clinical manifestations of COVID-19
b. Characterize the underlying biology of severe acute COVID-19 via standardized bio-specimen collection
c. Identify risk factors and create prediction models for COVID-19 outcomes, including acute respiratory failure, prolonged mechanical ventilation, cardiomyopathy, and death
d. Describe care processes for hospitalized patients with COVID-19, including resource allocation, utilization of palliative care services, and causes of death
e. Describe the long-term outcomes after COVID-19 and determine the impact of critical illness on these outcomes

The Prevention and Early Treatment of Acute Lung Injury (PETAL) Network is a consortium of academic and affiliated hospitals across the United States, funded by the NHLBI to conduct clinical trials in patients with or at risk for critical illness, including ARDS. Our Network's goal is to improve outcomes of patients with acute and critical illness through research. We have deep expertise in severe acute respiratory infections and critical illness, and the existing infrastructure to rapidly investigate acute and critical illness caused by SARS CoV-2. We are integrated with complimentary efforts in children (PALISI), outpatients (CDC), and the global community (SCCM, WHO/ISARIC). We are perfectly positioned to investigate the burden of disease, severity of illness, clinical course, underlying biology, long-term outcomes, and impact on the health system of severe COVID-19.

3. Research Approach

3.1 Previous Work

There have been no comprehensive studies of epidemiology or biologic profiling of hospitalized patients with COVID-19 in the United States at this time, and only limited reports worldwide. There are growing efforts to create registries of patients with COVID-19 in the United States and around the world, including work by the WHO (ISARIC registry), the Centers for Disease Control (CDC-IVY), the Society for Critical Care Medicine (SCCM-VIRUS), and the pediatric community (PALISI). There are also proposals for bio-specimen collection, including the newly funded COVID Immunophenotyping study by NIAID, IMPACC. This PETAL proposal (BLUE CORAL) is deliberately designed to harmonize and synergize with these existing and proposed efforts.

At the same time, BLUE CORAL is unique, leveraging the expertise of PETAL in order to conduct detailed phenotyping of the biology, clinical course, and outcomes of acutely and critically ill patients with COVID-19, and use this information to understand and improve clinical care, with a particular focus on critical illness. PETAL has successfully completed a large scale observational study of ventilator practices across Network hospitals, [8] and many of the PETAL hospitals, investigators, and staff contributed to a successful observational registry of pandemic H1N1 in 2009-2010 as part of the NHLBI ARDS Network and in conjunction with PALISI.[9] In addition, the NHLBI ARDS Network and now the PETAL Network has a strong history of

collecting and archiving clinically annotated biospecimens that are made available to the broad scientific community to advance understanding of critical illness. The proposed studies are feasible in our hands.

3.2 Overall Approach

BLUE CORAL is a multicenter prospective cohort of 1500 patients hospitalized with severe COVID-19 at participating PETAL Network hospitals. Patients will be eligible for participation both at sites which can contribute to biospecimens and those which cannot. Similarly, patients do not have to be willing or eligible for participation in biospecimens and/or genetics procedures in order to participate in BLUE CORAL. An overview of all study procedures is presented in Table 1.

Table 1: BLUE CORAL study procedures and timing

	Hospital days 1-3	Hospital/ICU days 4-20	Hospital days 21, 28, 60	Hospital discharge	1 mo.	3 mos	6 mos	12 mos
Screening	X							
Enrollment	X							
Informed consent	X							
Data collection	X	X	X	X				
In-hospital survey	X							
Study Labs	X	X						
Biospecimens	X	X						
Images for repository	X	x	X	X				
Post-hospital assessments					X	X	X	X

*Of note, biospecimen collection can extend to ICU day 15+ after enrollment, such that biospecimen collection might extend beyond Hospital day 15 if a patient is transferred to the ICU after initial floor admission.

3.3 Study Population

Inclusion criteria:

1. Adult hospitalized within 14 days of a positive PCR test for COVID-19
2. Evidence of acute COVID-19, with fever or respiratory manifestations, as characterized by signs and symptoms such as cough, dyspnea, tachypnea, hypoxemia, and infiltrates on chest imaging.

Exclusion criteria:

1. Lack of informed consent
2. More than 72 hours of continuous hospitalization.
3. Comfort care orders in place at the time of enrollment and/or unexpected to survive for 24 hours
4. Prisoners
5. Previous enrollment in BLUE CORAL

3.3.1 Study population for post-hospital follow-up

In order to participate in post-hospital follow-up, patients will need to have been enrolled in BLUE CORAL during hospitalization. Additional criteria for participation include

1. Survival to hospital discharge
2. English-speaking or Spanish-speaking
3. Domiciled with access to a working telephone
4. Absence of severe dementia before hospitalization

3.4 Selection of Clinical Sites

BLUE CORAL will recruit at volunteering PETAL Network hospitals (sites). To participate in BLUE CORAL, site personnel must complete training and have capacity for conduct of study procedures as specified in the protocol.

4. STUDY PROCEDURES

4.1 Screening

Research staff will identify and record all COVID+ patients hospitalized during the study period using medical records and lists maintained for clinical operations. This log will include simple information: patient name, medical record number, age, sex, date of admission, and race and ethnicity. This log will be considered a “Denominator Log” and be used to describe the relationship between enrolled patients and the larger population. Patient names and medical record numbers from this log will only be used at the local sites and not transmitted to the Clinical Coordinating Center (CCC). Age, sex, date of admission, race and ethnicity information will be sent securely to the CCC. Research staff will also use the medical records for patients on the log to determine study eligibility. Patients who meet all inclusion criteria for BLUE CORAL will be entered in a separate “Screening Log”. These patients may then be entered individually into REDCap, or research staff can simply track the number of patients who meet each reason for non-enrollment. If using this tracking method, only the number of patients who met each exclusion will be sent to the CCC at the conclusion of the study period, with no identifying information.

If there are multiple patients eligible for BLUE CORAL on a single day, coordinators will prioritize ICU patients first. .

4.2 Enrollment

Eligible BLUE CORAL patients will be enrolled within 72 hours of hospital admission. Target enrollment is 1500 patients overall. If enrollment is slow across the Network, alterations may be made in the approach outlined above. Patients or legal next of kin will be approached to engage in the process of informed consent.

All eligible BLUE CORAL patients may be contacted for detailed post-hospital follow-up. Target enrollment is 1200 patients for post-hospital follow-up Additionally, family members of 100 patients participating in post-hospital assessments will be contacted for participation as well. Informed consent will be obtained by telephone for these potential participants.

4.3 Process of Obtaining Informed Consent

4.3.1 Overview

Prior to conduct of study procedures, informed consent will be obtained from the patient or from a surrogate decision maker if the patient lacks decision-making capacity.

In some instances, bringing a paper consent form and pen to the bedside of a patient with known or suspected COVID-19 and then taking these out of the room would violate infection control principles and policies. Given the infectious risk from COVID-19 and potential shortages of personal protective equipment (PPE), there is a moral and practical imperative to minimize face-to-face contact between patients and non-clinical personnel. The current epidemic also presents unique challenges to obtaining consent from participant's legally authorized representative (LAR). To minimize infectious risk, many institutions are not allowing visitors to enter the hospital. Furthermore, the LAR is likely to have been exposed to the patient and may therefore be under self-quarantine at the time of the informed consent discussion.

Therefore, in addition to the traditional approach of an in-person consent discussion and signed paper informed consent document, we will allow use of "no-touch" consent procedures for this trial. Below, we outline four examples of no-touch consent procedures that may be used: (a) two paper-based approaches; (b) an electronic/e-consent approach; and (c) attestation of informed consent.

4.3.2 Paper-based approach

4.3.2.1 Paper-based approach: Method 1

1. The informed consent document is delivered to the patient or LAR.
    a. If the patient or LAR is on-site, the informed consent document many be delivered to the patient or LAR either by research staff or by clinical staff
    b. If the LAR is off-site, the informed consent document may be emailed, faxed, or otherwise electronically transferred to the LAR (method dictated by institutional policy)
2. Research staff discuss the informed consent document with the patient or LAR either in-person or by telephone or videophone. *This step confirms subject/LAR identity*.
3. If the patient or LAR decides to consent to participate, the patient or LAR signs the paper copy of the informed consent document.
4. A photograph is taken of the signature page of the informed consent document and uploaded into the electronic database (e.g. REDCap).
    a. If using the patient's device (such as a patient's personal cellular phone), a survey link can be sent to their device to allow direct upload of the image into the electronic database (e.g. REDCap).
    b. If using a staff device, it must be approved to store PHI by the local institution. In that case, research personnel can take a photograph of the signature page of the informed consent document either directly or through the window or glass door leading into the patient's room. The photograph can then be uploaded into the electronic database. If a staff device is taken into the patient's room to take a

photograph it must be able to be disinfected according to local institutional practices.

5. Research staff and witness provide signatures within the electronic database (e.g. REDCap) confirming their participation in the informed consent process.
6. The patient or LAR retains the paper consent document. The image of the signature page may be printed and bundled with a copy of the blank informed consent document for research records.

4.3.2.2 Paper-based approach: Method 2

A photograph of the signed ICF can be transmitted to trial staff.

1. An unsigned ICF is provided to the patient by a person who has entered the room.
2. The investigator/designee arranges a telephone call or videoconference call with the patient (and, if desired and feasible, additional individuals requested by the patient [e.g., next of kin]).
3. To ensure the patients are approached in a consistent fashion, a standard process should be used that will accomplish the following:
   a) Identification of who is on the call.
   b) Review of the ICF with the patient by the investigator/designee and response to any questions the patient may have.
   c) Verbal confirmation by the patient that their questions have been answered, that they would like to participate in the trial, and that they have signed and dated the ICF that is in their possession.
4. The patient (or an individual in the room) takes a photograph of the signed and dated ICF and sends it to the investigator/designee.
5. Research staff and LAR/patient provide signatures confirming their participation in the informed consent process.
6. The patient or LAR retains the paper consent document. The image of the signature page may be printed and bundled with a copy of the blank informed consent documents for research records.

4.3.3 Electronic/e-consent approach

1. The electronic informed consent document is opened on a research device or a link for the electronic informed consent document is sent to the patient's or LAR's device.
2. Research staff discuss the informed consent document with the patient or LAR either in person or by telephone or videophone. *This step confirms subject/LAR identity*.
3. If the patient or LAR decides to consent to participate, the patient or LAR signs the electronic informed consent document. This signature may be either:
   a. an actual signature (often tracing a finger on the screen) OR
   b. a username and password specific to the individual signing
4. Research staff and witness provide signatures within the electronic database (e.g., REDCap) confirming their participation in the informed consent process.
5. The image of the signature page may be printed and bundled with a copy of the blank informed consent document for research records.

If a hospital device is provided to facilitate electronic or paper-based consent, that device will be disinfected according to institutional protocols and removed by research staff or clinical staff during the next entry into the patient's room.

This approach complies with relevant regulations and sub-regulator guidance at 45 CFR 46.117, 45 CFR 164.512, 21 CFR 11 Subpart C (11.100–11.300), https://www.hhs.gov/ohrp/regulations-and-policy/guidance/use-electronic-informed-consent-questions-and-answers/index.html, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/informed-consent

4.3.4 Attestation of informed consent

If none of the options outlined above (traditional signature and storage of a paper consent form, electronic photographs of a signed consent page, or e-consent) are available, study personnel may attest to completion of the informed consent process using the procedures outlined below. Importantly, the process of informed consent using this attestation option should not change compared with the traditional method of obtaining informed consent for trial participation except for the method of documenting the consent process in the research record. Rather than storing a paper document with the participant's signature, a member of the research team and an impartial witness will attest to completion of the informed consent process and that the participant signed the informed consent document. This option of attestation of informed consent is not available when obtaining consent through a LAR.
Procedures for attestation of informed consent:

1. An unsigned paper consent form is provided to the patient by a heath care worker or study member.
2. The study member obtaining consent arranges an in-person meeting or three-way call or video conference with himself/herself, the patient, and an impartial witness. If desired and feasible, additional people requested by the patient (e.g., next of kin) may also join this discussion.
3. Study member reviews consent and answers questions in the presence of the impartial witness.
4. Patient signs the paper informed consent document while the witness is listening on the phone or directly observing.
5. Patient provides verbal confirmation that he/she would like to participate in the trial and he/she has signed and dated the informed consent document. This signed informed consent document stays with the patient due to the risk of spreading the virus.
6. Study member and witness attest that other techniques for documenting informed consent were not available for this participant and that the participant provided written informed consent for trial participation by signing a paper informed consent document. An attestation form is available in the BLUE CORAL REDCap toolkit for documenting this attestation. This attestation page with signatures from the study member and witness will be save as evidence of the informed consent process. A signature from the participant will not be saved in the research record.

4.3.5 Non-English language consent procedures

The information for the informed consent discussion will be provided in a formal document (or electronic equivalent) that has been approved by the IRB and in a language comprehensible to the potential participant, using an interpreter if necessary. The information presented in the consent form and by the research staff will detail the nature of the trial and what is expected of participants, including any potential risks or benefits of taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal. Where a patient does not speak English, either a fully translated consent or a short-form consent with qualified interpreter will be employed, using similar “no-touch” principles. Use of an interpreter and the interpreter’s identity will be documented on the electronic consent.

4.3.6 Post-hospital procedures

Patients who provided informed consent during hospitalization will be asked to confirm their interest in participation verbally during follow up calls. Patients participating in post-hospital surveys who were unable to provide informed consent (enrolled via surrogate consent and unable to engage in informed consent before hospital discharge) will participate in the informed consent process by telephone. Those agreeing will provide verbal consent. The same process will be used for family members selected to participate in post-hospital procedures.

4.4 Data Collection

BLUE CORAL includes data collection from enrolled patients’ clinical records. There are three types of forms for each study: admission (hospital/study day 1), daily, and discharge (Table 2). BLUE CORAL elements include all data needed for participation in the ISARIC/WHO registry, in addition to selected variables important for understanding COVID-19 in the context of acute and critical illness in the United States.

Table 2. BLUE CORAL Data Collection Timing & Description

Module	Timing	Data Elements
Admission	Calendar day of presentation to study hospital (Day 1) and 24-hour period	COVID testing, symptoms, demographics, exposures, comorbidities, home medications, vital signs, labs, supportive care & treatments, research trial enrollment, medications, ventilator settings
Daily Data	Days 1-15, 21, 28; ICU days 1-15	Vital signs, labs, supportive care & treatments, research trial enrollment, medications, ventilator settings
Discharge or study termination	Hospital discharge/ study day 60	Disposition, cause of death, care limitations, functional status, infections, organ support at discharge, summative treatments, summative complications, summative diagnostics

The case report form (CRF) is built in RED Cap which can be imported as a local instance or centrally through the PETAL CCC. Since there may be times when study personnel are mandated to work from home due to the ongoing pandemic, BLUE CORAL has many study procedures that are designed to allow off-site completion. All elements that contribute to the COVID ordinal outcome scale are included in daily and summative data collection. Manual data entry of all elements into REDCap may not be required depending on the site's ability to extract data from the EMR.

4.5 In-Hospital Survey

The BLUE CORAL study will obtain pre-hospital information from patients or their caregivers before hospital discharge. The survey consists of questions regarding functional status and health-related quality of life. PETAL study staff members are familiar with the conduct of these surveys as they were used successfully in the ROSE RCT.[10] With high severity of illness, infection control precautions, and absence of family visitation, we anticipate that survey completion will be difficult. Therefore, we have developed multiple approaches to survey completion (telephone, tablet computer, or email with either patients or families) and will attempt to complete as able. Main survey items are presented in Table 6; the full survey is included in Appendix A.

4.6 Clinical Labs

Table 3: Scheduled clinical laboratory assessments

	Enrollment	Hospital day 5-7	Mechanical ventilation day 7
CRP	X	X	X
Ferritin	X	X	X
D-dimer	X	X	X
PT/PTT	X	X	X
Troponin I	X	X	X
CMP	X	X	X

In addition to abstracting the data from all clinically obtained laboratory studies during hospital days 1-15, 21 and 28, and ICU days 1-15, the BLUE CORAL protocol includes scheduled laboratory assessments at standardized times. These labs will be performed—if not done clinically in the preceding 72 hours—on day of enrollment (hospital day 1-3), 4 days later (hospital day 5-7) and on day 7 of mechanical ventilation. Tests include markers of inflammation, coagulation, cardiac injury, hepatic and renal injury, and immunity (Table 3). Most patients are expected to have most, or all, of these laboratories performed as part of clinical care, since many COVID-19 care recommendations include testing of this panel at admission and then every 2-3 days. We considered limiting analyses to clinically obtained values but were concerned that indication bias would prevent meaningful conclusions regarding the utility of these laboratory values as predictors. We also considered conducting these studies as part of the biospecimens/biomarkers work but saw value in (1) having rapid access to results to inform analyses early in the course of BLUE CORAL, and (2) increasing generalizability by obtaining values for all prospective BLUE CORAL patients without restricting to sites capable of biospecimens handling.

4.7 Biospecimens

Biospecimens will be collected with the goals of (a) correlating detailed clinical phenotyping with biological responses in critically ill COVID patients and (b) determining biologic predictors of severe illness and poor outcomes. We anticipate that 1000 of enrolled patients will contribute biospecimens

Table 4: BLUE CORAL biospecimen collection and timing			
	Floor enrollment	Enrolled floor patient transferred to ICU or ICU enrollment (ICU Draw A)	Subsequent ICU Draws B-E (see draw schedule in Appendix B)
Blood	X	X	X
Tracheal Aspirate		X	
Discarded BAL		X	
Urine		X	

BLUE CORAL patients cared for exclusively on the floor will have collection of blood specimens one time only upon enrollment. If floor subjects are transferred to the ICU, they will have samples collected per the ICU schedule detailed below, beginning with ICU transfer. Floor subjects transferred to the ICU who had a floor blood sample drawn can have their initial ICU collection of all specimens for ICU Draw A performed up to 1 calendar day after ICU transfer, as long as the floor blood draw and the first ICU blood draw (ICU Draw A) do not occur on the same calendar day. Subjects enrolled in the ICU will have specimens collected on enrollment (with a +1 calendar day window thereafter). Calendar days are defined as midnight to midnight. For example, if a patient is enrolled on a Monday, they can have samples collected up until midnight Tuesday. Because the initial ICU biospecimen collection day may not correlate with actual ICU day 1 or hospital day 1, the first ICU Draw will be termed “ICU Draw A” to avoid confusion with actual hospital or ICU Days. There will be up to four subsequent ICU draws at scheduled time intervals after the initial ICU Draw A (termed “ICU Draws B-E”, respectively, with a +1 calendar day window for each time point). For the first collection in the ICU (ICU Draw A), ICU subjects will have one-time collection of urine (if Foley catheter present), tracheal aspirate (if intubated), and discarded bronchoalveolar lavage (BAL) specimen (the latter, only if collected for clinical purposes), as per Table 4. Details regarding specimen collection are presented in Appendix B. The blood sampling timing will be coordinated with the study-scheduled clinical laboratory assessments as much as is feasible. If additional funds become available, or we find that clinical lab draws encompass the proposed additional lab draws thus sparing blood volume, additional biospecimen collections may be considered for enrolled patients.

While the majority of the collected biospecimens will be stored and made available to the broad scientific community as has been done with other NHLBI-funded studies, we will use low plasma volumes to perform measurement and analysis of high priority targets that might define subgroups of patients that might optimally respond to specific treatment protocols, as well as identify those at higher risk for worse outcomes. We propose to measure and analyze markers of the hyperinflammatory ARDS endotype (IL-6, sTNFR1, IL-8), given significant prior data in ARDS subjects that have identified this subgroup as one with higher mortality and perhaps more likely to benefit from certain types of anti-inflammatory therapies (e.g., simvastatin)[11]. Moreover, use of IL-6 inhibition therapy and other immunomodulatory therapies prior to RCT data being available in these patients makes this and related targets of high priority to correlate with treatment and clinical outcomes. Finally, the kinetics of the biomarkers are unknown prior to ARDS development and determining whether they also might represent predictors of worsened outcomes in COVID-19 patients is a high priority. Included in this hyperinflammatory panel multiplex assay (without additional sample or cost required) are the following targets which will also be analyzed: ANG2, RAGE, ICAM, and Protein C will be analyzed by ELISA. Additionally, there is increasing appreciation of the need to characterize the metabolite profile of targets downstream of the ACE2 receptor, given that the virus uses this receptor to enter the lung epithelial cells. If there is sufficient blood volume available within our specified maximal blood volume proposed, we will consider future measurement of these analytes that require collection in specific tubes containing protease inhibitors.

There exist other important, relevant targets to examine in these patients, including both early and delayed biospecimens for cardiac biomarkers, markers of coagulation, and the renin-

angiotensin system; banked biospecimens will be available to the community for these studies. These biospecimens are particularly valuable given the need for specialized protocols for collection that we anticipate will be available in a subset of PETAL sites. This biospecimen protocol will be an important and unique resource for many investigators

4.8 Images for Repository

Data collection include abstracting presence of infiltrates as noted on radiologists' reports from chest radiographs and computed tomography (CT) scans. We will collect all clinical radiographs and CT scans available from the course of illness as well as clinically performed cardiac evaluations (Table 5). These images can be collected at any point of the hospitalization and after discharge. Additionally, we will attempt to capture clinically performed point of care ultrasound (POCUS). Members of the study team will need to interact frequently with the clinical team in order to identify when POCUS studies are performed. All image types will be uploaded by study staff into the imaging coordinating center at the American College of Radiology's Center for Research and Innovation. We will use the TRIAD image collection system which removes all identifiers and codes images with study labels in DICOM format. The CORAL Image Repository will be maintained on ACR CRI servers through the course of the study. ACR CRI will receive diagnostic images, create a link between the images and clinical data collected by PETAL, and archive images throughout study duration and after study close to make accessible to researchers.

Table 5: Images for repository

Pulmonary	CXR
	Chest CT
	Lung POCUS
Cardiac	Echocardiograms
	Heart POCUS
	ECGs

4.9 Post-hospital Procedures

BLUE CORAL patients who survive hospitalization, speak English and/or Spanish, are domiciled, and did not have severe dementia before hospitalization may be eligible to enter the post-hospital follow-up study. This study will be conducted by the FUNCTION team at the University of Michigan and the Oregon Health & Science University, led by Dr. Jack Iwashyna, using protocols developed and executed in the PETAL Network ROSE and ongoing CLOVERS studies. Post-hospital follow-up can occur by telephone at 1, 3, 6, and 12 months after hospital discharge.
Patients and family members will provide consent for continued involvement at the time of the first call. The post-hospital data are shown in **Table 6**. Targeted enrollment is 1200 patients.
In addition, family members of 100 patients will be empaneled to assess similar outcomes, in addition to caregiver burden. Participants will receive tokens of $5-10 for completing study tasks. All instruments are included in Appendix A.

In the event that a respondent demonstrates evidence of severe psychological distress or other immediate risk of harm—especially as demonstrated by any evidence of suicidality—will result in an immediate safety evaluation and, if indicated, provision of information, support, or hand-off to suicide prevention hotline, by the interviewer per current best practice as incorporated in survey group's Standard Operating Procedures. The results of any such evaluation and any interventions provided will be reviewed with the study project manager and the study PI via email, or by phone if deemed sufficiently high risk by either protocolized evaluation or in the judgement of the interviewer. Responses will be documented in the survey record.

Table 6: Inpatient and post-hospital surveys

	Hospital	1 month	3 months	6 months	12 months
Contact information	X	X	X	X	X
EQ5D-5L	X	X	X	X	X
Activities of daily living (ADL)	X	X	X	X	X
Instrumental ADLs	X	X	X	X	X
Financial strain/toxicity	X	X	X	X	X
Cardiopulmonary symptoms		X	X	X	X
Medications		X			
Depression (PHQ-9)		X	X	X	X
Anxiety (GAD-7)		X	X	X	X
Cognitive function (MOCA/AD8, Hayling)		X	X	X	
Rehospitalization		X	X	X	X
Fatigue				X	X
Additional symptoms				X	X
Complementary health					X
Unmet needs & caregiving receipt					X
LongCOVID					X
Durable medical equipment					X
Healthcare Utilization					X
ADL/IADL Difficulty					X
Peer support					X
Self-medication (TAPS)					X
Sleep					X

These post-hospital assessments will allow BLUE CORAL to measure the levels and rates of recovery on cardio-pulmonary symptoms as well as the key domains outlined in the NHLBI R24-funded "Improving Long-Term Outcomes" Program[12]; to determine risk factors associated with poor outcomes; to assess the burden of COVID-19 recovery primary spouse or family caregiver of cohort members, stratified by whether the spouse themselves had COVID-19 or not; and to evaluate the association of the COVID-19 Outcome Score with patient-centered outcomes.

Additionally, a small number of BLUE CORAL patients who survive hospitalization and who speak English and/or Spanish, as well as their English and/or Spanish speaking primary caregivers, may be eligible to participate in the American Lung Association (ALA)-funded "REACH" study. This is a qualitative study consisting of semi-structured interviews of COVID-19 survivors and their caregivers in order to characterize how patients' pre- and post-COVID functional limitations and their social location impact their lived experience of recovering from COVID-19 hospitalization, as well as their health and community service utilization. We plan to conduct at least one interview per participant (defined as either a patient or caregiver), with the first interview being conducted between 7-15 months after BLUE CORAL enrollment. We may conduct second interviews 3-6 months after the first interview. Interviews will be conducted over telephone or a HIPAA-compliant web-based teleconferencing platform. Participants will provide verbal consent at the time of the interview(s). Targeted enrollment is up to 80 patients and 30 caregivers. Participants will be given a $60 gift card for each interview completed for their time and effort.

4.10 Human Subjects Considerations

COVID-19 is a global pandemic. Obtaining information about patients with COVID-19 is an important response to a public health emergency. Given that this is a data repository of data that are available in the medical record and already being collected as part of routine care, the risk of the research is loss of confidentiality. In addition, patients will undergo blood sampling, which is part of routine care of hospitalized patients. All adult patients hospitalized with COVID-19 at participating hospitals who meet study criteria are eligible for enrollment regardless of age, gender, ethnicity, race, sexuality, or religion. Previous reports suggest that males may have higher rates of infection than females meaning that males might be slightly over presented – however, distribution of different demographics will be similar to the demographics of admitted patients. Children aged less than 18 years old appear to have milder disease when infected with SARS-CoV2 and in general, are not routinely hospitalized. As such, enrollment will be restricted to adults. However, data will be harmonized with aligned research efforts of pediatric patients.

Research staff will screen hospitalized COVID patients at their site and maintain screening logs via waiver of consent. Informed consent will be obtained from patient or legal next of kin at study enrollment, as described in section 4.3. Patients initially enrolled via informed consent provided by a surrogate will have the opportunity to provide consent for future study procedures before hospital discharge, if able, and upon contact for post-hospital follow-up.

There are concerns that requiring informed consent for participation may bias the demographic characteristics of participants and lead to a non-representative sample. We intend to capture key potential differences between the enrolled population in BLUE CORAL and the larger eligible population by maintaining aggregate data on sex, race, ethnicity, and age of both enrolled and not enrolled patients. We will review these numbers periodically and enact mitigation plans if important differences are noted.

4.11 Risks and Benefits of Participation

The only study procedures which potentially physically impact patients enrolled in the study are blood draws. There are four kinds of potential risk from study blood draws. First, there is a risk

of pain associated with phlebotomy in patients without indwelling vascular access. Second, there are potential concerns about blood loss. Third, there is the risk of use of scarce resources (time, personal protective equipment). And fourth, there exists the potential exposure of nursing, laboratory staff, and research staff to pathogens. We will lessen these risks by coordinating all study blood draws with those scheduled for clinical purposes, which removes concerns of inducing pain, overuse of personal protective equipment, and exposure to clinical staff. We have mitigated risks of blood loss by limiting the number of studies and times of collection, and by only requiring protocolized laboratory assessments if clinical specimens have not been done for 72 hours. Biospecimen collection will require no more than 50 ml total in 7 days and no more than 81 ml total over 2.5 weeks. Additionally, no more than one draw per day, and no more

than 2 draws per week will be performed, to limit blood volumes. Institutional and PETAL guidelines protecting patients from blood loss will be carefully followed [13]. All coordinators and clinical laboratory personnel will be required to have appropriate training for safe handling of specimens per their local institution's protocols for biosafety handling of COVID specimens. These study procedures are not different from typical processes of care for acutely ill patients.

Non-physical risks include invasion of privacy and stress. Data will be secured and protected. Patients and surrogates will have the opportunity to refuse participation in both in the hospital and in the follow-up period. BLUE CORAL is an observational study; there are no clinical benefits to participation. However, many patients report benefits of altruism through study participation. This study has the potential to help future patients with COVID-19 and those stricken in future pandemics.

4.12 STUDY WITHDRAWAL OR DISCONTINUATION

At the time of study enrollment, patients can choose if they wish to participate in biospecimens collection and genetic studies. Patients may opt out of these aspects of BLUE CORAL but still enroll in the study. Once enrolled, patients may choose not to participate in study procedures, including surveys, blood collection, and post-hospital phone calls. BLUE CORAL study staff will ask for permission to return for completion of future procedures (either in- or post-hospital), since often refusals are situational and not philosophical. All chart-abstracted and previously collected data elements and biospecimens will be retained.

4.13 STATISTICAL CONSIDERATIONS

It is anticipated that there will be thousands of patients eligible at PETAL hospital for entry into the registry and cohort. This proposal is to collect data on 1500 patients. It is possible that all patients will be included during the first wave of the COVID-19 pandemic in 2020. It is also possible that cases decrease quickly (hopefully!) and that more patients are enrolled in a second wave, as is currently expected for fall 2020. It is difficult to predict what proportion of included patients will be acutely ill, critically ill, receiving mechanical ventilation, developing ARDS, receiving prolonged mechanical ventilation, and dying during initial hospitalization—early reports have been small and incomplete. Describing these aspects of the clinical epidemiology, with special attention to ARDS and cardiac complications, and course of acute severe COVID-19 is an important early contribution from this work.

Overall, the expected mortality for the overall cohort may be around 20% (300 patients). We anticipate sufficient power to evaluate at least 20 variables for association with these outcomes of respiratory failure, prolonged mechanical ventilation, and death. We will focus on key demographic factors, such as age, sex at birth, comorbidity, race/ethnicity, and pre-morbid functional status. We will develop multivariable models to evaluate the association of additional laboratory and physiologic variables with these outcomes and compare with existing risk prediction models. If able, we will also look at the associations with specific treatments, such as IL-6 antagonists and antivirals, with outcomes, adjusting for potential confounding factors. These analyses will help inform analyses for the prospective cohort. In addition, in the biospecimen cohort, we will investigate the distribution of the hyper- and hypo-inflammatory phenotypes that have been described in patients with ARDS[11]. We will evaluate the association of these phenotypes with mortality, both in the population with respiratory failure and the overall COVID-19 population.

The sample size of 1000 patients with biospecimens collection was selected to include enough patients with respiratory failure and death to determine the association between hyper- or hypo-inflammatory phenotype. For example, if 70% of COVID-19 patients express the hyperinflammatory phenotype, then 1000 patients would provide 85% power to detect a 10% difference in mortality.

4.14 Data management, data sharing, quality assurance and security of data

Data collected by study staff will contain identifiers. For transmission of data to the PETAL CCC, subjects will be assigned a unique study number. Those subjects that consent to the post hospital follow up study will have contact information collected and shared with the FUNCTION group so that they may be contacted for the study assessments. BLUE CORAL data is designed to be shared in order to facilitate rapid knowledge generation and dissemination, including plans to contribute data to the WHO/ISARIC COVID-19 registry. BLUE CORAL data, images, and biospecimens may be shared with other projects provided that human subjects' protections are followed. BLUE CORAL case report forms, data dictionaries, and REDCap builds will be available on the public-facing PETAL website. The BLUE CORAL committee will work with the PETAL CCC and Steering Committee to create a solid approach to early data sharing that accelerates knowledge while minimizing potential threats of invasion of privacy. Sharing of data and biospecimens will be reviewed by the PETAL Network Natural History Committee and/or Pathogenesis Committee, according to current PETAL protocol.

ISARIC data elements from all completed cases will be regularly shared with ISARIC's Oxford Data Coordinating center. The PETAL Network will receive reports from ISARIC describing numbers and features of the cases contributed. In addition, these data will be easily shared with other efforts to understand COVID-19 and will be expeditiously made publicly available.

Data quality and consistency of approach to data collection is very important. We will follow the previously successful approach to multi-faceted quality assurance which includes: (1) use of Manuals of Operation for training and reference, (2) regular meetings between local Investigators and study coordinators to answer questions and ensure consistency in evaluations across study sites, (3) conferences between all Investigators for the same purposes, (4) ongoing quality assurance review and training updates, (5) data entry into a database with extensive automated checks of data validity, and (6) ongoing review of descriptive statistics by Investigators with detailed review of selected data. We will use best practice physical and electronic security and back-up procedures as well.

For the REACH qualitative study, we will use a semi-structured interviewing approach using an interview guide (see Appendix C and Appendix D for patient and caregiver interviews respectively). Trained research coordinators and investigators with previous experience in qualitative research will conduct these interviews using institutionally approved online platforms or by phone.

4.15 Privacy and Confidentiality

Data will be collected into the HIPAA compliant REDCap database. Only study personnel will have access to the REDCap database. Data from PETAL sites will be transferred via REDCap to the CCC at Massachusetts General Hospital. These data will include identifiers, in order to conduct post-hospital telephone visits. Identifiers will only be shared in accordance with all relevant human subjects' protections.

For the REACH qualitative study, participants will provide verbal consent to be interviewed and

audio recorded. Interviews will be downloaded in a password protected secure folder behind the OHSU firewall. Transcripts will be de-identified and imported into qualitative data analysis software (e.g., Atlas.ti) behind OHSU's firewall for maintenance and analysis.

4.16 Record Retention

Six years after the primary manuscript is published or after data collection ends, whichever is last, any identifiable data in the database will be deleted and the data will be transferred to an NIH controlled, de-identified database.

- Activities of Daily Living (ADLs) and Instrumental ADLs about patient (14 items)
- AD8 about patient (8 items)
- Healthcare utilization about patient (1 item)
- Demographics (2 items)

ICU Draw A (will include blood, plus urine (if Foley placed), tracheal aspirates (if intubated), discarded BAL where feasible): First ICU Draw, obtained within 1 calendar day of ICU transfer for an enrolled floor patient transferred to the ICU, or within 1 calendar day of enrollment if the patient is enrolled in the ICU.

- ICU Draw B (blood only): 2 calendar days after ICU Draw A (+ 1 calendar day)
- ICU Draw C (blood only): 5 calendar days after ICU Draw B (+ 1 calendar day)
- ICU Draw D (blood only): 2 calendar days after ICU Draw C (+ 1 calendar day)
- ICU Draw E (blood only): 5 calendar days after ICU Draw D (+ 1 calendar day)

No further biospecimen are collected for subjects who transfer out of the ICU, are discharged, or die prior to the end of the sampling period.

Tracheal aspirates (ICU Draw A collection from intubated patients only): Collected into a sputum trap (aiming for an approximate volume of 3 ml) during a clinically indicated suctioning of the patient. Three mls of Zymo DNA/RNA shield will be added to the sputum trap prior to removal from the patient's room (to inactivate the virus) and then handled as per the institution's approved SOP for biospecimen collection in COVID-19 subjects.

Discarded BAL specimens (ICU Draw A collection from intubated patients only): Discarded material will be obtained from BALs only if performed for clinical indications. Three mls of Zymo shield DNA/RNA shield will be added to the sputum trap (with approximately 3 ml of BAL fluid) prior to removal from the patient's room (to inactivate the virus) and handled for aliquoting as per the institution's approved SOP for biospecimen collection in COVID-19 subjects.

Urine (ICU Draw A collection for subjects with an indwelling Foley catheter): Will be collected using protocols as per the local institution's approved SOP for biospecimen collection in COVID-19 patients.

PROCESSING AND SHIPMENT:

After processing, samples will be frozen and stored as per the institution's approved SOP for biospecimens in COVID-19 subjects.

Samples collected at PETAL Network sites will be labeled with a coded ID number and shipped and stored in the PETAL central biorepository.

DNA Extraction Plan:

DNA extraction from PAXgene tubes will be coordinated by the PETAL Network to make aliquots available to the broad scientific community.

Appendix C. Semi-structured Interview

"I am a researcher from the Oregon Health & Science University in Portland, OR. We are conducting this study because we want to learn about your experience recovering from COVID-19. Because you were hospitalized for severe COVID-19, we believe you can help us understand what may be important to others who must transition back to their daily lives after severe COVID-19.

This interview will take between 30-40 minutes, but it may take more time than that depending on how long your responses are. If that's the case, does your schedule permit us to go beyond 40 minutes if needed?

The interview will be audio-recorded for accuracy. All responses are confidential (private), and you can pass on any question you prefer not to answer. It is possible that some questions may be hard to answer or trigger an emotional response. You do not have to answer any questions you do not wish to discuss, and you can also stop the interview at any time. Answering these questions is voluntary and you may choose to end the interview at any time. Do you have any questions before we get started?"

"Thank you for your time. [START AUDIO RECORDER]. This is [NAME OF INTERVIEWER]. Today's date is [DATE]. I am with participant [STUDY ID#]. Please state your name and confirm you consent to be recorded."

Pre-Interview Checklist:

1. *Pre- & and post-COVID disability status using Activities of Daily Living (ADLs) and Instrumental ADLs (14 items)*
2. *Pre-COVID medical conditions*
3. *Race; Hispanic ethnicity; Gender*
4. *Date of hospital admission; Date of hospital discharge*

Patient Background/Social Location

Tell me a bit about yourself and your background.

Probe (*establish social location*): *What communities do you identify with?*

Reframe: *What's important to you in terms of how you identify (e.g. race, ethnicity, rurality, occupation)? Where do you live? What kind of work do you do? Tell me about your educational background.*

What was your life like before your COVID-19 hospitalization?

Probes: Your general well-being? Any chronic medical conditions? Effect on life and daily activities?

Patient's acute COVID-19 Story

Tell me your story about being diagnosed and treated for COVID-19, including your hospitalization.

Do you have any specific stories about how the hospital's pandemic policies affected your hospital experience? Probes: family visitation? masking? social distancing? COVID-19 testing? Ability to communicate with your care team and your loved ones?

If you could tell another patient something about how to handle being hospitalized with COVID-19, what would it be?

How did your (*chronic condition*) affect your COVID-19 illness experience?

How did your (*social location: e.g. race, ethnicity, or identity mentioned in personal background*

section) impact your COVID-19 illness experience?

Patient's Post-Acute Sequelae of SARS-CoV-2 Story

Now, I would like to hear about your recovery experience. There are many ways to define recovery. Recovery can include your recovery in terms of your COVID-19 symptoms or your medical treatment after being discharged from the hospital; changes in your health and well-being; changes in your ability to participate in aspects of your everyday life such as school, work or family responsibilities; how the illness impacted your sense of self, including your spirituality or how the illness impacted your ability to maintain social relationships with your family, friends, peers and significant others.

Tell us about your recovery from the COVID-19 hospitalization (see dates listed above)

Probes: persistent COVID-19 symptoms; return to work or school; return to leisure activity; impact on: social roles with family; friends; peers; impact on sense of self; spirituality.

How would you characterize your health now?

Probes: Physical; Emotional; Cognitive; Social

Tell us about the kinds of health care services you engaged in after your COVID-19 hospitalization?

Probes: Primary Care services? Specialty Services (e.g. Pulmonary, Renal,)? Rehabilitation Services (like physical, occupational or speech therapy)? What else?

Please share a specific story that captures some of the challenges you experienced in getting the healthcare you needed after your COVID-19 hospitalization. Can you also share a positive experience in getting healthcare after your COVID-19 hospitalization?

After your COVID-19 hospitalization, as part of your recovery process, did you seek the help of any community or public health services (e.g. housing services, social services, case management, food bank services, etc)?

Probes: Talk about some of the challenges you experienced in accessing these services. Can you share some positive experiences in accessing these community services?

What changes did you have to make in your home environment in order to live more comfortably after the illness?

Probes: what challenges have you encountered in adjusting to these changes? Positive aspects to adjusting to these changes?

Can you discuss the role of loved ones, family members or caregivers in your recovery process?

What have been your most significant barriers to recovery? What has most helpful in facilitating your recovery?

How did (*your chronic condition*) impact your recovery process?

How did (*your social location: e.g. race, ethnicity, or identity mentioned in personal background section*) impact your COVID-19 recovery process?

Is there something else about your background that impacted your recovery?

What does being a COVID-19 survivor mean to you? Do you think of yourself as a COVID-19 survivor?

If you could tell another patient something about how to handle the recovery process after COVID-19

hospitalization, what would that be?

Thank you for your time. In case there is anything we need to ask you about later, would you be willing to be re-contacted in the future for follow-up interviews on this topic? We are also interested in learning more about the experience of a family member or caregiver who was involved in your recovery. Is there someone who helped you who we could contact to see if they are interested in an interview? Could you provide us with their name and phone number and/or email address?

Appendix D. Caregiver Semi-structured Interview

"I am a researcher from the Oregon Health & Science University in Portland, OR. We are conducting this study because we want to learn about your experience caring for a loved one who is recovering from COVID-19. We believe you can help us understand what may be important to others who must transition back to their daily lives after severe COVID-19.

This interview will take between 30-40 minutes, but it may take more time than that depending on the duration of your responses. If that's the case, does your schedule permit us to go beyond 40 minutes if needed?

The interview will be audio-recorded for accuracy. All responses are confidential, and you can pass on any question you prefer not to answer. It is possible that some questions may be difficult to answer or trigger an emotional response. You do not have to answer any questions you do not wish to discuss, and you can also stop the interview at any time. Your participation is voluntary and you may choose to end the interview at any time. Do you have any questions before we get started?"

"Thank you for your time. [START AUDIO RECORDER]. This is [NAME OF INTERVIEWER]. Today's date is [DATE]. I am with participant [STUDY ID#]. Please state your name and confirm you consent to be recorded."

Background/Social Location

Tell me a bit about yourself and your background.

> Probes (*establish social location*): *What communities do you identify with? Reframe: What's important to you in terms of how you identify? Where do you live? What kind of work do you do? Tell me about your educational background.*
>
> *Reframe: What's important to you in terms of how you identify?*

Caregiving Story; Roles and Responsibilities

Tell me your story of your loved one's illness (including the COVID-19 hospitalization) from your perspective.

Do you have any specific stories about how the hospital's pandemic policies affected your experience?

> Probes: family visitation? masking? social distancing? COVID-19 testing? Ability to communicate with the care team and your loved ones?

Please tell me about your roles *(& responsibilities)* during the illness and recovery process.

> Probes – how did these roles change during periods of transition (e.g. from home to hospital, after hospital discharge, etc.)

How did these caregiver roles and responsibilities affect your relationship with *your loved one*? How did these roles impact your own health and well-being?

> Probes: Physical; Emotional; Cognitive; Social
>
> *Reframe: Has your role as a caregiver created opportunities for you to grow as a person?*
>
> *Probes:* your relationship with others; your personal strength; your spirituality; or your appreciation of life

How did (*your social location: race, ethnicity, rural*) impact your ability to be an effective caregiver to your loved one?

If you could tell a family member or caregiver of someone else with COVID-19 one key pearl of how to handle their loved one's hospitalization, what would it be?

How did your (*social location: e.g. race, ethnicity, or identity mentioned in personal background section*) impact your COVID-19 illness experience?

Post-COVID-19 Health Care and Community Service Utilization

Can you share a specific story that captures some of the challenges your loved one experienced in getting the healthcare they needed after their COVID-19 hospitalization? Can you share some positive experiences in accessing these services?

What do you think have been the most significant barriers to your loved one's ability to engage in health care services during their recovery process? What has been the most helpful health care service to aid in your loved one's recovery?

As a result of your loved one's illness & recovery, have YOU had to seek the help of any community or public health services (e.g. housing services, social services, case management, food bank services, etc)?

> *<u>Reframe:</u> From your perspective, what has been the most helpful community or public health service for you or your family during your loved one's recovery process?*

How did (*social location: race, ethnicity, rural*) affect your ability to connect with recovery-related services?

Thank you for your time. In case there is anything we need to clarify later, would you be willing to be re-contacted in the future for follow-up interviews on this topic?

5. REFERENCES

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