Study: Functional, imaging, and respiratory evaluation in CORAL: FIRE CORAL

Acronym: FIRE CORAL

Protocol Version: 2.3

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Summary of Revisions to the Protocol

1. Protocol V1.0 date 25 JAN 2021
Initial protocol

2. Protocol V2.0 date 15 MAR 2021
Substantive protocol changes in Version 2:

- Addition of exclusion 5, patient self report of pregnancy. The purpose of this exclusion is to ensure that women who are pregnant after hospital discharge are not scheduled for a FIRE CORAL visit that includes a CT scan. Women of child-bearing age will be asked about their pregnancy status. If pregnant, they will be excluded.
- COVID testing consent changed from electronic consent to verbal consent. This testing is a standard clinical requirement at many institutions and therefore, by itself, it is not considered to be part of screening. Using verbal consent less burdensome to the subject while still ensuring the subject is informed. Changes: Section 3.4 Study Procedures (pgs 7-8); removed language related to electronic consent and replaced it with "verbal" consent.

3. Protocol V2.1 date 9 APR 2021
Substantive protocol changes in Version 2.1:

- Revision of Section 3.4.5 to remove collection of any images or data from outside of the site's healthcare system, as this would require additional consent, which would be burdensome to staff and subjects. In addition, removed collection of rehospitalization information. Rehospitalization is already collected as part of BLUE CORAL.

4. Protocol V2.2 date 24 MAY2021
Substantive protocol changes in Version 2.2:

- Modification to the inclusion criteria **Section 3.2: Study population**, Inclusion criterion 1 has been modified to allow subjects who participated in either the 1 month or the 3-month post-hospital telephone assessment to be eligible for the FIRE CORAL study. Previously only those subjects who participated in the 1-month call were eligible. This change was made to enable subjects who may have missed the 1-month call to be included. Severely ill subjects, who are being prioritized, are more likely to still be in a rehab facility at the 1-month mark and thus would miss this call. Equivalent languages in Section 3.4.1 Screening and Figure 1 in the Study Enrollment and Informed Consent were updated accordingly.
- Cleaned up left-over language in the **Non-English language consent procedures** section that referenced no-touch consent.
- Removal of the "public facing" language from the **Data management, data sharing, quality assurance and security of data** section. Data and related information will be shared with the public via the NHLBI process.

5. Protocol V2.3 date 12 August 2021
Substantive protocol changes in Version 2.3:

- Extension of eligibility for the first visit to anytime within 3-9 months after hospital discharge.
- Modification to the 6 month visit:
    - Removal of FIRE-2 designation and need for abnormal CT to qualify

    - Extension of the time window to 6-9 months post-discharge. This visit will only be done with those participants who complete a first visit prior to 6 months. It will be done at least 2 months after prior visit.
    - Increase in the number of subjects completing the 6 month visit from 40 to up to 60.
- Addition of an in-person assessment visit at 12 months (up to 80 subjects total). Allow option for initial contact to be made in writing (email, text, etc.).
- Clarification of visit payments to make clear subjects are reimbursed for each visit that involves diagnostic studies.
- Remove requirement to upload CT reports.
- The modifications to the protocol were made to address the difficulties of long term follow up and allow for more subjects to be potentially eligible who are just outside the visit window. Additionally, it will be useful from a scientific standpoint to have data on a larger sample over a longer period of time to understand post-COVID variability.
- Modifications were made accordingly to the following sections:
    - Section 2 Study Objectives and Specific Aims (pg. 6),
    - Section 3 Research Approach (pg. 7), Table A (pgs. 7-8) and Exclusion Criteria (pg. 8)
    - Section 3.4 Study procedures (pgs. 8-9)
    - Consent for follow-up COVID testing (pg. 9)
    - 3.4.2: In-person study procedures (pg. 10)
    - Section 6 Data Management and Analysis (pg. 13)

1. Background

The NHLBI PETAL Network-sponsored observational study of hospitalized patients with SARS-CoV2 infection, CORAL, was designed to inform the epidemiology of COVID-19. CORAL includes the detailed retrospective evaluation of data from the electronic health records of 1503 COVID-19 patients hospitalized at PETAL Network hospitals from 3/1/20 through 4/1/20 (RED CORAL). Additionally, CORAL includes an ongoing prospective study recruiting 1500 patients hospitalized with COVID-19, involving the collection of biological specimens, standardized laboratory evaluations, and patient and/or family surveys, in order to provide a more detailed description of the biology and epidemiology of COVID-19 (BLUE CORAL). BLUE CORAL includes post-hospital telephone follow-up of 800 survivors of COVID-19 at 1, 3 and 6 months after hospital discharge, in order to describe recovery and persistent life impacts of the disease. RED and BLUE CORAL are positioned to make meaningful contributions to our current knowledge of the COVID-19 disease course in the acute setting. However, many important knowledge gaps exist, particularly regarding recovery and long-term outcomes among COVID-19 survivors that are not addressed by the existing protocols.

Early reports suggest that many patients have persistent symptoms lasting months after infection with SARS-CoV2. One US study of 274 symptomatic outpatients with COVID-19 reported that 35% had not returned to their normal state of health 2-3 weeks after initial testing; cough, fatigue, and shortness of breath were the most commonly reported enduring symptoms. (1) An Italian report of 143 patients hospitalized with COVID-19 described that only 13% of patients were symptom-free 60 days after initial symptom onset; in that study, fatigue, dyspnea, joint pain, chest pain, and cough were the most common enduring symptoms. Nearly half reported persistent impairment of health-related quality of life. (2) There is considerable discussion of this phenomenon—coined “long COVID” or “COVID long haulers” in the lay press and, increasingly, in the medical literature. (3) With over 8 million Americans having tested positive for SARS CoV2 by October 2020 and infections on the rise, the public health impact of delayed recovery is enormous. However, the etiologies of these persistent symptoms and impairments remain unclear.

While a growing number of investigations are focused on patient-reported outcomes—including BLUE CORAL—few have reported the results of objective assessments after hospital discharge. In a small study of 110 non-ICU patients with COVID-19 who were hospitalized in China between February and March 2020, pulmonary function tests were performed at the time of discharge. (4) Investigators identified impaired diffusing capacity in nearly half of patients (47% had DLCO less than 80% predicted), reduced total lung capacity (TLC) in 25% of patients, and 5% had reduced FEV1/FVC ratio. Abnormalities in DLCO and TLC were both associated with severity of initial COVID-19 pulmonary manifestations. In another study of patients hospitalized with COVID-19 in China, serial computed tomography of the chest was performed during admission, and again at 2 and 4 weeks after discharge. (5) This report describes improvement in ground glass opacity, consolidation, and subpleural lines over time, with 65% of patients’ CT scans demonstrating full recovery by 4 weeks post-discharge. There have been no reports of pulmonary function testing or CT imaging following hospitalization among patients with COVID-19 in the United States, and data evaluating the relationship between PFTs, imaging, and “long haul” symptoms are lacking. Furthermore, to our knowledge, there are no reports describing integrative functional assessments, such as 6-minute walk tests, or results of biospecimen collection in the months after hospital discharge. There remains a large knowledge gap in understanding the post-hospital outcomes

after hospitalization with COVID-19, the etiology and biology of persistent impairments, and the risk factors associated with delayed or incomplete recovery.

2. Study Objectives and Specific Aims

Just as Herridge and colleagues heralded an era of focus on recovery from the acute respiratory distress syndrome with a carefully conducted longitudinal cohort study of 109 patients, performing pulmonary function tests and 6 minute walk tests at 3, 6 and 9 months after hospital discharge, (6) we propose to add crucial in-person objective assessments to a subset of patients enrolled in the BLUE CORAL study in order to describe recovery after COVID-19. By adding Functional, Imaging and Respiratory Evaluation to the BLUE CORAL study, "FIRE CORAL" will address the following specific aims:

1. To describe the prevalence of abnormalities of pulmonary function, chest imaging, and functional status in 80 patients hospitalized with COVID-19 at 3-9 months after hospital discharge.
2. To determine the trajectory of recovery of pulmonary function and functional status between 3 and 12 months after covid-19.
3. To identify clinical and biologic factors associated with persistent impairment of pulmonary function, chest imaging, and functional status after hospitalization with COVID-19.
4. To determine the independent association between patient-reported outcomes of impaired recovery with objective measures of pulmonary function and persistent inflammation.
5. To create a repository of biospecimens that permits longitudinal analysis of biomarkers spanning hospitalization to post-hospital discharge.

By accomplishing these aims, the PETAL Network will address key information gaps and contribute foundational knowledge to the epidemiology and biology of COVID-19, and extend the value of the existing BLUE CORAL study by including in-person assessments and biospecimen collection at 3, 6 and 12 months after hospitalization in a subset of patients participating in BLUE CORAL's telephone-based collection of post-discharge patient-centered outcomes.

3. Research Approach

3.1: Overview

The current proposal, FIRE CORAL, will identify 80 patients enrolled in the post-hospital assessment component of the BLUE CORAL study who are able to participate in in-person assessments at participating PETAL Network sites. All FIRE CORAL patients will be scheduled for up to3 return visits during the 12 month after hospital discharge time period for a battery of systematic assessments (detailed in Table A) including pulmonary function (spirometry, lung volume, and diffusing capacity), chest imaging (non-contrast computed tomography – participant's first visit only), function (6-minute walk testing and short performance physical battery), respiratory questionnaires and biospecimen collection. If participants complete their first study visit prior to 6 months after hospital discharge, they (up to 60 total) will be given the opportunity to return for an additional visit 6-9 months after hospital discharge, scheduled at least 2 months after the prior visit. Up to 80 participants who complete at least one visit within the 3-9 month after hospital discharge time point will complete a 12-month visit.

Table A: Study procedures for BLUE CORAL, BLUE-LTO, & FIRE CORAL

Hospital	**Hospital**	**Hospital d/c**	**1-month post d/c**	**1-9 months post d/c**	**3-9 months post d/c**	**If first visit completed prior to 6 months post d/c – additional visit at 6-9 months post d/c (> 2 months from first visit)**	**12 months post d/c (window 11-15 mo) (> 2 months from previous visit)**	**3, 6 & 12 months post d/c**
Enroll in BLUE CORAL	x							
Select for BLUE LTO		x						
BLUE LTO phone surveys			x					x
Select for FIRE CORAL				x				
Biospecimen collection	x				x	x	x	
Chest CT scan					x			
Spirometry					x	x	x	
Lung volumes					x	x	x	
DLCO					x	x	x	
6-minute walk test					x	x	x	
Short performance physical battery (SPPB)					x	x	x	
Respiratory Symptom Assessment					x	x	x	

Definitions:

- BLUE CORAL- 1500 patient prospective study beginning during acute SARS-CoV2 infection hospitalization
- BLUE-LTO- 800 patient subset of BLUE CORAL participating in post-hospital telephone follow up via U of Michigan
- FIRE CORAL- 80 patient subset of BLUE CORAL LTO, returning for in person assessments

3.2: Study population

Inclusion criteria:

1. Patient enrolled in BLUE CORAL and participated in either the 1-month and/or the 3-month post-hospital telephone assessment
2. Patient enrolled at a site at or near where in-person procedures are available
3. Eligible for in-person follow up and/or testing based upon local site's specific COVID infection control criteria

Exclusion criteria

1. Unable or unwilling to return to clinical site for completion of study procedures around 3-9 months post-index hospitalization
2. Not selected for FIRE CORAL (only a subset of eligible patients will be selected)
3. Concern from investigator about patient's ability to participate in follow up testing
4. Not able to follow instructions as reported by surrogate or investigator
5. Patient self report of pregnancy at the time of screening call or follow up visit

3.3: Selection of clinical sites

All PETAL Network clinical sites participating in BLUE CORAL with capabilities of performing study procedures will be eligible to participate in FIRE CORAL on a volunteer basis.

3.4: Study procedures

3.4.1: Screening

Screening for potential candidates for FIRE CORAL will be performed by the BLUE CORAL LTO center at the University of Michigan, since completion of the 1-month and/or 3-month post-hospital assessment is an eligibility criterion. Volunteering clinical sites will be notified of potentially eligible FIRE CORAL patients via disclosure of PETAL study ID only. In-person assessments will be coordinated by the local clinical site. Initial contact by the site may be done by phone, email, text message, or other messaging service, using included template. Screening of potentially eligible subjects will be done via phone utilizing the included phone script to introduce the study to potential candidates and determine adequacy for inclusion. Consent for contact for screening and eligibility purposes is included in the consent process for the parent BLUE CORAL study in which patients must be participating in order to be eligible for inclusion in the current study.

Process of Obtaining Informed Consent

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.

Consent for follow up COVID testing if necessary for in-person follow up per local site-specific infection control procedures:

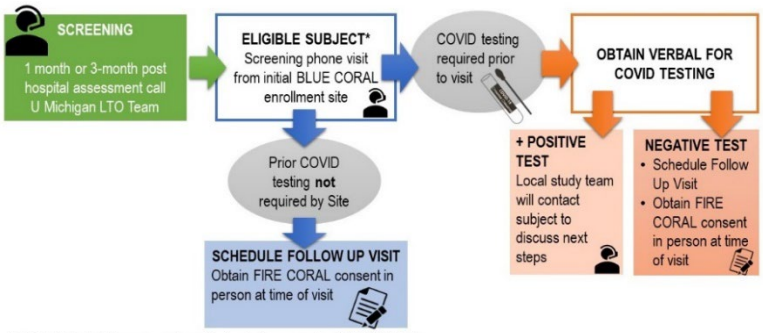
Given the infectious risk from COVID-19, patients and/or surrogates may be in different phases of quarantine and/or COVID recovery at the time of their scheduled follow up. Institutional infection control processes limit follow up procedures for patients with known prior COVID infection requiring documentation of cleared infection prior to potential procedures. As such, patients, according to local

site infection control procedures may be required to undergo a repeat COVID test prior to in-person follow up visit or study procedures. To minimize the burden for patients and/or surrogates who may be ineligible for subsequent testing based on persistent COVID-positivity, we will allow use of "no-touch" consent procedures to obtain verbal consent for COVID testing at the time of eligibility screening. This consent will be separate from the main study consent which will occur at the time of the first study visit.

Study enrollment and Informed Consent

Enrollment into the full FIRE CORAL study will occur at the time of the first in-person assessment, where the informed consent process will occur. The informed consent document will be signed by the participant or surrogate before beginning any study procedures.

Figure 1 Overview of screening/enrollment & consent process:



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 CIRB 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 study 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. Use of an interpreter and the interpreter's identity will be documented during the consenting process.

3.4.2: In-person study procedures at the 3-9 & 12 month post-discharge time points

FIRE CORAL consists of a battery of in-person assessments designed to objectively measure pulmonary function, residual abnormalities on lung imaging, and functional status. Enrolled subjects will undergo the following assessments at the visit(s) occurring approximately 3-9 months post-discharge, as well as the 12-month visit. Chest CT will only be performed at the subject's first visit. Subjects will be compensated $100 after completion of each study visit with required diagnostic studies.

Chest CT 	Computed tomography of the chest without contrast will be performed for all FIRE CORAL patients. This will be performed in the clinical radiology department according to common protocol. Recommendations for CT specifications are listed in the Appendix. Clinical CT interpretation will occur according to the site-specific radiology protocol. Images will be subsequently uploaded to the American College of Radiology image repository for a secondary quantitative read to be performed at National Jewish Hospital according to their post-COVID-specific research protocols.
Spirometry 	FIRE CORAL patients will have FEV1, FVC, and FEV1/FVC ratio performed according to clinical standards in using the clinical site's Pulmonary Function Laboratory.
Lung Volumes 	FIRE CORAL patients will have lung volume testing performed according to clinical standards in using the clinical site's Pulmonary Function Laboratory.
Diffusing capacity 	FIRE CORAL patients will have single breath DLCO measured according to clinical standards in using the clinical site's Pulmonary Function Laboratory.
6-minute walk testing 	FIRE CORAL patients will have 6-minute walk testing performed according to clinical standards in using either the clinical site's Pulmonary Function Laboratory or research staff with expertise in 6MWT performance. Percentage of distance covered as expected for age will be calculated based upon the 6MWT distance obtained.
Functional Testing 	FIRE CORAL patients will undergo functional testing using the Short Performance Physical Battery (SPPB) functional scale. This scale is well-validated in survivors of critical illness and is comprised of three components: 4-meter gait speed, tandem-stand and timed sit to stands.
Respiratory Symptom Assessment 	FIRE CORAL patients will undergo detailed respiratory symptom screening to understand the ongoing effects of COVID19 on pulmonary symptomatology. Patients will undergo respiratory symptom screening using the St. George's Respiratory Questionnaire and screening for fatigue symptomatology using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale.
Biospecimen collection 	FIRE CORAL patients will have up to 15 mL of blood collected, either by clinical or research personnel, which will include 6 mL of plasma, 2.5mLfor DNA PaxGENE, and 2.5mL for RNA PaxGENE.

3.4.3: Substitution of clinically available studies:

Patients who receive pulmonary function testing or high-resolution CT scan (including expiratory and prone images) within 1 month of the designated time point with results and imaging accessible will not need to undergo repeat testing. Results of clinically obtained studies will be collected and utilized for study purposes to minimize radiation exposure and testing fatigue for study subjects.

3.4.5: Medical records review

Images and data from any chest CTs, as well as data from any PFTs or 6 minute walk tests the subject underwent within the site's healthcare system in the 10 years prior to the follow up visit will be collected.

4. Human Subjects Considerations

This is an observational protocol with no direct benefits to participants. Indirect benefits are primarily altruistic, for participants will be providing key information to the global community about recovery from Covid-19. Risks include stress, threats to privacy, and potential minimal physical harm from procedures. Risks of biospecimen collection include pain and minimal bleeding at the phlebotomy site. Risks of pulmonary function testing include dyspnea and symptoms of claustrophobia. Risks of 6-minute walk test include pain, fatigue, and fall risk. Risks of computed tomography include discomfort and low-dose radiation exposure. Additionally, CT screening may identify incidental findings that may require additional intervention or evaluation. This information will be relayed to the subject and their designated primary care provider per local radiology protocol at the time of identification for additional management to be determined by the primary physician. All of these risks will be minimized by careful adherence to clinical best practices and protocols. Safety concerns will be reported to the PETAL DSMB and reviewed regularly.

Study withdrawal and discontinuation:

At the time of study enrollment, patients can choose if they wish to participate in biospecimen collection and genetic studies. Patients may opt out of these aspects of FIRE CORAL but still enroll in the remainder of the study. Once enrolled, patients may choose not to participate in study procedures, including CT scans, pulmonary function testing, strength testing and/or respiratory questionnaires. FIRE CORAL study staff will ask for permission to return for completion of future procedures since often refusals are situational and not philosophical. All previously collected data elements and biospecimens will be retained for participants opting to withdraw mid-study.

Reporting of Adverse Events or Unanticipated Problems Involving Risk to Participants or Others

Adverse events are not anticipated, since FIRE CORAL is an observational study. Adverse events from the BLUE CORAL study are collected by PETAL Network/NHLBI protocol. If a patient experiences an unexpected adverse event related to the FIRE CORAL protocol, it will be reported directly to the PETAL CIRB, NHLBI, and PETAL DSMB within their established timeframe for such reporting.

5. Data management, data sharing, quality assurance and security of data

Data collected by study staff may contain personal health identifiers. For transmission of data to the PETAL CCC, subjects will be assigned a unique study number. PETAL study numbers of subjects that complete one-month and/or three-month long-term follow up and are potentially eligible for FIRE-CORAL participation will be provided by the FUNCTION group to the approved FIRE-CORAL study staff at participating sites. FIRE CORAL case report forms, data dictionaries, and REDCap builds will be available on the PETAL website. The FIRE-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. After study publication, data and remaining biospecimens will be deposited in an NHLBI repository and will be shared according to the NHLBI repository protocol.

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 to ensure data safety and integrity.

6. Biospecimen handling

Collection Plan: Plasma (6 ml), and RNA (PAXgene tubes) (2.5 ml) and DNA (PAXgene tubes) (2.5 ml), using protocols as per the local institution's approved SOP for biospecimen collection in COVID-19 subjects. Consent for biospecimens and genetic analyses will be obtained as part of a layered consent at the time of enrollment.

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 50 enrolled patients will contribute biospecimens.

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 broader scientific community.

7. Data management and analysis

Reports from all clinical assessments will be stored locally. CT scans will be promptly uploaded to the American College of Radiology image repository.

Primary analyses are descriptive. We will describe the prevalence of abnormalities of pulmonary function, chest imaging, and functional status in 80 patients hospitalized with COVID-19 at 3-9 months after hospital discharge. Among patients who return for a 12-month visit, we will describe the trajectory of recovery of pulmonary function and functional status between first and last study visits. We will identify clinical and biologic factors associated with persistent impairment of pulmonary function, chest imaging, and functional status after hospitalization with COVID-19, using data collected during and after hospitalization. We will also attempt to determine the independent association between patient-reported outcomes of impaired recovery with objective measures of pulmonary function and persistent inflammation. All analytic plans will be agreed upon by the FIRE CORAL committee after review of the distribution of abnormalities from the first 40 completed visits.

Privacy and Confidentiality

Data will be collected directly into a HIPAA compliant REDCap database. Only approved study personnel will have access to the REDCap database. Source documents from pulmonary function testing and/or radiology (CT scan) reports will be retained at the participating sites. Data from the participating PETAL sites will be entered into the RED Cap database at the CCC at Massachusetts General Hospital.

8. References

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