Manual of Operating Procedures

Study Title: ***F****unctional,* ***i****maging, and* ***r****espiratory* ***e****valuation in* ***CORAL***

Acronym: ***FIRE CORAL***

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MOP Purpose:

The purpose of this document is to provide step-by-step guidance for sites to implement and successfully complete this study.

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1. Participating 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.

Current Participating Sites:

1. University of Colorado Hospital
2. Stanford University Hospital
3. Oregon Health and Science University
4. Wake Forest Baptist Health
5. Intermountain Medical Center
6. Montefiore Medical Center
7. University of Kentucky
8. Harborview Medical Center
9. UCLA
10. Cleveland Clinic Foundation
11. Baystate Medical Center

2. Study Summary

2.1. Study Population

FIRE CORAL will identify 80 participants 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 participants will return to the local PETAL site for a research visit between 3-9 months after hospital discharge for systematic assessments including pulmonary function (spirometry, lung volume, and diffusing capacity), chest imaging (non-contrast computed tomography), physical function (6-minute walk and Short Physical Performance Battery testing), and biospecimen collection.

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 (e.g. lack of transportation, domiciled in skilled nursing facility or LTACH, subject not interested)

2. Not selected for FIRE CORAL -only a subset of eligible patients will be selected. (e.g. all available appointment slots full so patient not contacted by site
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
6. Not excluded, not enrolled

6.1.1 Unable to contact

6.1.2 Subject agrees to participate, but site unable to arrange necessary study follow up testing within eligibility window

2.2. Study Timeline: BLUE CORAL, BLUE-LTO, FIRE CORAL

FIRE CORAL participants will have at least one visit between 3-9 months after discharge. Participants who complete their first study visit prior to **6 months** after hospital discharge will be eligible for a follow up visit between 6-9 months after discharge. All participants who complete at least one study visit between 3-9 months after discharge are eligible to return for a follow up visit 12 months after discharge. All follow up visits must occur at least 2 months after the previous one.

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

2.3. Screening and eligibility

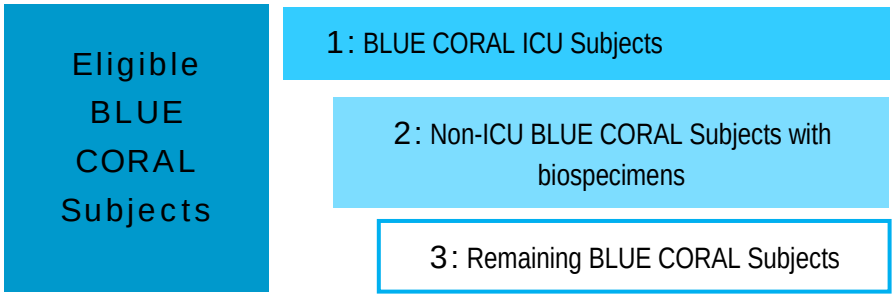
Eligibility:

FIRE CORAL participants will be eligible for enrollment upon completion of the 1 or 3-month post hospital discharge telephone visit for the BLUE CORAL study (Figure 1). Participants who survive hospitalization, speak English and/or Spanish, are domiciled, and do not have severe dementia or severe disability before hospitalization may be eligible to enter the FIRE CORAL study.

The FUNCTION team at the University of Michigan, led by Dr. Jack Iwashyna will notify participating FIRE CORAL sites when a participant completes the 1 or 3-month BLUE CORAL LTO visit. The FUNCTION team will provide the participant's PETAL ID number to the designated local participating PETAL site FIRE CORAL contact. The local PETAL site will contact FIRE CORAL candidates by telephone or, using the Written Initial Contact Template, by email, text message, or other messaging service. Initial screening of FIRE CORAL candidates will be done by telephone to determine eligibility, initiate informed consent discussion (to be completed at time of study visit) and schedule initial study visits.

If multiple subjects are eligible at the same time, site study coordinators will determine whether subjects were in the intensive care unit during BLUE CORAL hospitalization prior to reaching out to eligible subjects. All subjects who were in the ICU will be prioritized for study participation, followed by any non-ICU subjects who had biospecimens collected as part of BLUE CORAL. Sites will choose the order in which to contact remaining subjects per local workflow.

Enrollment Prioritization:

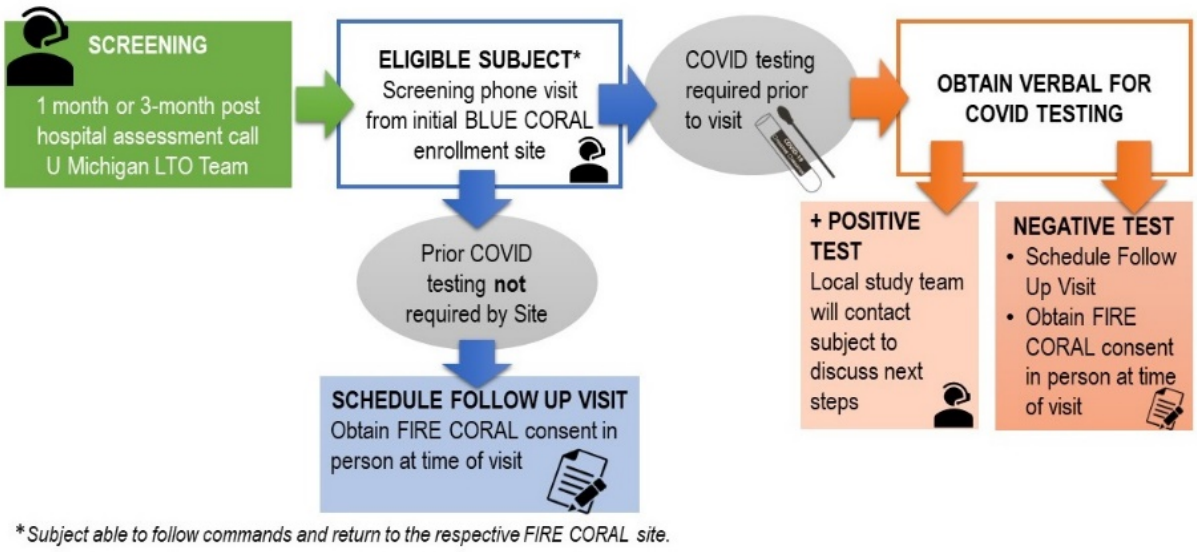


The **FIRE CORAL REDCap Screening Form** should be completed for all eligible subjects (those who completed 1 or 3-month BLUE CORAL surveys).

Screening:

Local study teams will use the cIRB approved FIRE-CORAL Screening Script when contacting eligible candidates. Teams will emphasize the voluntary nature of study participation, describe study participation, potential risks and benefits and clarify questions to the candidate's satisfaction. Women of child-bearing age will be asked about their pregnancy status. If pregnant, they will be excluded (due to risk of radiation from CT scan). If candidate expresses interest, study team will proceed to next steps. Immediately after the call, copies of the consent materials will be sent via email, or standard mail if no email address is available, to the participant. Study staff will schedule in person visit based on participant availability ascertained during call. Once visit has been arranged at the site, study team will call participant, confirm follow up appointment date, and answer any questions. One week prior to the visit, the participant will be contacted to remind them of appointment and ensure no issues with follow up. At that time, they will also be sent a follow up information sheet with site-specific instructions for in person follow up via email.

Figure 1 details the screening and enrollment process.



Subject able to follow commands and return to the respective FIRE CORAL site.

Study teams will follow local institutional procedures for scheduling clinic study visits. It is possible that study participants will be scheduled for clinically indicated visits at local sites at the same follow up intervals as FIRE CORAL procedures. Study visits should be scheduled to coincide with clinically indicated visits whenever feasible to limit multiple visits required of participants. Additionally, local sites should follow local institutional policy to administer study visits when coinciding with clinical visits. Often, study procedures will take place after the clinical visit. Study teams should collaborate with local clinical teams to clearly differentiate between clinical and study procedures. A protocol-specified procedure may occur as a part of clinically indicated care. Results from clinically indicated procedures may be used for study purposes, based on local policy, to prevent duplicate participant procedures.

3. Pre-Visit COVID-19 Testing

Local PETAL study sites may require COVID testing at a certain interval prior to research visits, confirming negative COVID results, prior to in-person study clinic visits. Each PETAL site will follow local requirements for scheduling testing visits and confirming and documenting results. This test will be paid for by the study if the participant chooses to be tested at the study site. Participants may choose to be tested at another location. The study will not pay for tests done at other locations. COVID testing participation consent will be obtained prior to testing via verbal consent (see Screening Script). Consent for the test itself will occur at the testing site, by testing site staff at the time of the test.

If participants test positive for COVID-19 at their pre-study visit screening, they may still be able to participate in a limited number of assessments, determined by local policy.

Transportation to obtain COVID-19 test and to study visits will be the responsibility of the research participant, unless local sites have transportation procedures available. Transportation costs and arrangements will not be provided by or paid for by the study team.

Local sites will keep a screening and enrollment log. Enrollment will be tracked through the CCC and University of Colorado. Sites will provide CCC with an updated subject tracking sheet each week.

4. Enrollment and Informed Consent

Subject Consent: Enrollment in FIRE CORAL 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 participant or legally authorized representative (LAR) before beginning any study procedures.

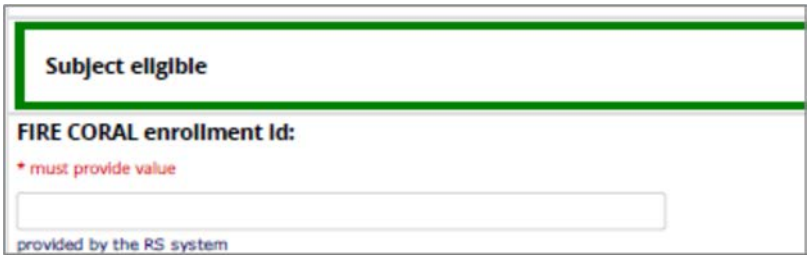
A paper consent form approach with original, wet-ink signatures will be used for informed consent. Informed consent document will be reviewed with the participant or LAR at the first in-person assessment, with any questions addressed prior to signature.

The original fully executed consent document will be kept by the study team. A copy of the fully executed consent document will be given to the participant or surrogate upon enrollment.

Enrollment of subjects: Subjects will be enrolled into FIRE CORAL in the same manner as BLUE CORAL, by registration via the PETAL RS system.

Registration Steps:

1. Once informed consent is obtained, access the PETAL RS system: https://rs2.partners.org/rs/login to obtain a FIRE CORAL study ID number (format will be "site number-F-subject number" or "XXF-XXXX")
2. Register consented subjects on the same day as consent
3. Enter the FIRE CORAL study ID number in REDCap on the Screening Form:



Spanish Speaking participants:

Spanish speaking participants are included in BLUE CORAL LTO assessment calls and therefore are eligible for FIRE CORAL participation. An IRB-approved Spanish FIRE CORAL Part 1 Master Consent document is available centrally. Local participating sites will be responsible for translating the FIRE CORAL Part 2 Local Context Consent using a qualified translator service. The local site will submit the translated Part 2 consent document, along with a translator declaration statement of language fluency, to the PETAL Network Coordinating Center for submission to the Vanderbilt central IRB prior to use.

Study procedures will be conducted using qualified fluent study personnel or Spanish language interpreters per local site policies. Interpreter services may be remote via telephone/video conferencing or using face-to-face personnel as available. During functional testing administration, it is recommended that sites utilize on-site, face-to-face interpreter services, as available and feasible.

6 Minute Walk Tests are routinely performed by Pulmonary Function Test clinic personnel at some sites. Spanish instructions for the 6 Minute Walk Test are often available in this setting. Sites should complete testing as appropriate and available at their locations.

English and Spanish-translated versions of surveys and questionnaires are provided to study teams.

4. In-person study procedures at the 3-9 month post-discharge time point

Study visits consist of respiratory assessments, radiology procedures, survey/questionnaire interviews, biospecimen collection and functional testing. It is recommended to complete all procedures in a single visit for efficiency purposes, however, if necessary, studies may be completed on multiple visits due to time constraints or participant/research team preference. All study interventions may be performed in any order based on local feasibility and study team preference. Figure 2 demonstrates a typical study day workflow that can be modified by sites based on feasibility.

Figure 2: *Study day workflow*

5. Personal Protective Equipment (PPE)

Participating study sites will follow local institutional guidelines for use of personal protective equipment during in-person study visits. Study teams will be responsible for instructing study participants regarding participant requirements for PPE during study visits.

6. Medical Records Review

Participants who receive clinically indicated pulmonary function testing or high-resolution CT scan (including expiratory and prone images) within 1 month of the designated study visit time point, with results and imaging accessible to study teams, 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.

7. Respiratory Assessments

7.1. Chest CT:

Computed tomography of the chest without contrast will be performed for all FIRE CORAL patients. This will be performed in local site's clinical radiology department according to common protocol. 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. Site study personnel will ask women of child-bearing age their pregnancy status at the follow up call one week prior to the in person visit. Any patients who are pregnant will be excluded.

Investigator Review of Radiology Reports:

Copies of clinical reports from the hospital radiologist will be reviewed by the site investigator.

Documentation steps:

1. **Site investigator:** Review the CT report for incidental findings
2. **Investigator or Coordinator:** Capture date/time of review; name of investigator reviewing, and if incidental findings date/time primary care provided was notified on provided source document
3. **Date and sign** the source document and retain with your study files

7.2. Pulmonary Function Tests (PFTs / Spirometry):

FIRE CORAL patients will have **FEV1, FVC**, and **FEV1/FVC ratio** measured according to clinical standards, using the clinical site's clinical or research Pulmonary Function Laboratory. Local pulmonary labs may provide site-specific patient instructions prior to performing PFT testing.

Lung Volumes: Lung volume testing will be performed according to clinical standards using the clinical site's Pulmonary Function Laboratory.

Diffusing Capacity: Single breath diffusing capacity of the lungs for carbon monoxide (DLCO) will be measured according to clinical standards using the clinical site's Pulmonary Function Laboratory.

Data Entry: Spirometry, lung volumes and diffusing capacity results will be entered into FIRE CORAL REDCap electronic case report forms. Reasons for incomplete testing will be documented by study teams.

7.3. 6 Minute Walk Test (6MWT):

6-minute walk testing (6MWT) will be performed according to clinical standards using either the clinical site's Pulmonary Function Laboratory or via research staff with training in 6MWT performance. The percentage of distance covered as expected for age will be calculated based upon the 6MWT distance obtained.

Instructions for the 6 Minute Walk Test are provided. Safety assessments will be completed prior to administering the 6MWT following provided guidelines. Reasons for not performing testing will be documented by study teams.

8. Respiratory Symptom Assessment:

Detailed respiratory symptom screening to understand the ongoing effects of COVID-19 on pulmonary symptomatology will be collected. Participants will undergo:

1. respiratory symptom screening using the **St. George's Respiratory Questionnaire (SGRQ)**
2. screening for fatigue symptomatology using the **Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)** scale.

Assessments will be administered by trained study personnel in-person or via telephone after study clinic visits. Administration and participant instructions are provided on the test forms.

8a. St. George's Respiratory Questionnaire (SGRQ)

The St. George's Respiratory Questionnaire (SGRQ) is an index designed to measure and quantify health status in patients with chronic airflow limitation. It has been shown to correlate well with established measures of symptom level, disease activity and disability.

It is recommended that participants self-administer the SGRQ. Ask the participant to complete it as honestly as possible and emphasize that there are no right or wrong answers; only the answer that best applies to them.

The SGRQ should be administered in the participant's language for fluency.

8b. FACIT-F

The FACIT scales are designed for participant self-administration but may also be administered by interview format. For self-administration, patients should be instructed to read the brief directions at the top of the page. After the participant's correct understanding has been confirmed, he/she should be encouraged to complete every item in order without skipping any. Some participants may feel that a given question is not applicable to them and will therefore skip the item altogether. Participants should be encouraged to circle the response that is most applicable. If, for example, a participant is not currently receiving any treatment, they should circle "not at all" to the question "I am bothered by side effects of treatment."

FACIT-F Form F should be administered in the patient's language of fluency.

9. Functional Testing - SPPB

Functional testing using the Short Performance Physical Battery (SPPB) functional scale will be performed by trained local physical therapy, rehabilitation staff or research staff.

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.

Instructions and documentation requirements for the SPPB are provided. Safety assessments will be completed prior to administering the SPPB following provided guidelines.

Reasons for not performing or completing testing will be documented by study teams.

10. Biospecimen Collection

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.

Up to 11 mL of blood will be collected, either by clinical or research personnel, which will include 6 mL of plasma, 2.5mL for DNA PaxGENE, and 2.5mL for RNA PaxGENE. Please see the FIRE CORAL Lab Manual for information on collection and processing. Sample Collection data will be completed for each sample collection. Data will be entered into REDCap.

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.

11. Follow Up Visit Assessments

All follow up visits (6-9 month and 12 month) will include the same assessments done at the initial visit, with the exception of a CT scan. **Only the initial visit will include a CT scan.**

12. Data Entry, Case Report Form completion

Data entry and any documentation upload to FIRE CORAL REDCap will be completed within 2 weeks of visit.

12.1. Protocol Deviations:

A **protocol deviation** is an event or incident that occurs off protocol, with or without the permission of the Coordinating Center, but has minor or no impact on subject safety. Should a protocol deviation occur, **a Protocol Deviation Report** should be completed for each deviation. Reports should be entered into REDCap within 72 hours of the event.

12.2. Adverse Events:

Adverse events are not anticipated since FIRE CORAL is an observational study. However, participants should be monitored closely during study visit interventions.

If a patient experiences an unexpected adverse event related to the FIRE CORAL protocol, it should be reported to the FIRE CORAL protocol leads and PETAL Coordinating Center within 24 hours after the site researcher learns of the adverse event. The Adverse Event form in REDCap should also be completed. The adverse event may also need to be reported to the site's local IRB. Local guidelines should be followed to determine this.