Clinical Protocol Synopsis

1. Title

Addressing psychological distress symptoms among serious illness survivors of a viral pandemic with a completely self-directed, symptom-responsive mobile mindfulness intervention (NCT identifier pending)

2. Background

Rigor of prior research: Cardiorespiratory failure patients suffer from persistent psychological distress—as COVID-19 patients likely will.[1,2]

>2 million patients are treated in ICUs annually in the US for cardiorespiratory failure caused by pneumonia, sepsis, and congestive heart failure, among others.[3] After discharge, patients experience clinically important symptoms of psychological distress—depression, anxiety, and post-traumatic stress disorder (PTSD)—symptoms that are both common (50-70%) and persistent.[4-11] Pneumonia, the second-most common cause of hospitalization, places its survivors at high risk for persistently worsened health status and lasting depression, anxiety, and PTSD symptoms. Currently acute infection with the severe acute respiratory syndrome novel coronavirus 2 which leads to coronavirus disease 2019 (COVID-19) is causing the largest pandemic of pneumonia in over 100 years.[12,13] COVID-19 is a mild disease for ~80% of patients, but 10-20% of patients are hospitalized with pneumonia. Of those hospitalized, up to 88% require respiratory support such as mechanical ventilation.[14,15] COVID's specific post-hospital outcomes have not been clearly described; not even 100 days have transpired since the disease was first defined. Yet since patients will be recovering from severe disease during a global state of emergency and economic stress, COVID-19 likely puts them at even higher risk of distress than other forms of cardiorespiratory illness.[1,2]

Conceptual orientation and rigor of proposed research: The LIFT mobile mindfulness intervention is a scalable approach for improving COVID-19 patients' psychological distress.

The COVID-19 pandemic represents a unique threat to patient-centered care given new norms of 'social distancing,' limited healthcare resources that serve as barriers to distress assessment and timely treatment, and economic devastation of those impacted by it.[16-18] Clinical resources are stretched thin as health systems are overwhelmed with the stresses of caring for massive numbers of COVID-19 patients, forcing the cancellation of outpatient clinics. Most research institutions have banned study staff from conducting clinical research that includes direct patient contact. These barriers require a novel approach that we believe can be effectively provided by this Supplement proposal.[19]

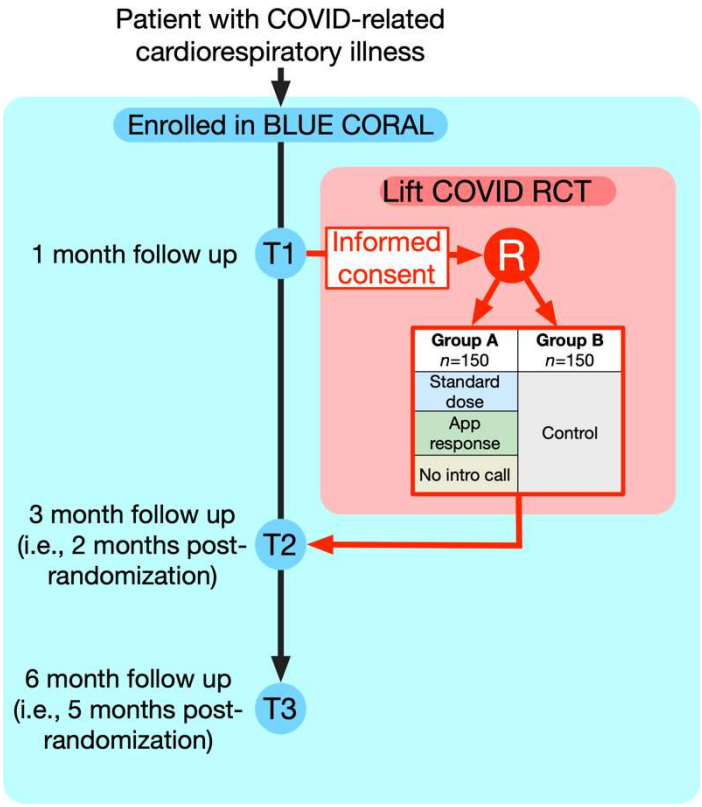
LIFT is ideally positioned to overcome barriers to both the timely delivery of mind-body therapy as well as research participation during a pandemic like COVID-19. Its tested mindfulness content promotes a practice of non-judgmental awareness that can alleviate distress by uncoupling emotional reactions and habitual behavior from unpleasant symptoms, thoughts, and emotions—content that improves symptoms of depression, anxiety, and PTSD.[20-24] LIFT's 'touchless deployment' allows automated screening, consenting, intervention activation, and data collection without direct patient contact. Additionally, LIFT is a self-guided mobile app that works on any device, giving it the flexibility and scalability required in a pandemic. LIFT is a scalable solution for overcoming barriers to addressing COVID patients' distress—and our research network is ideal for conducting an RCT to test it.

3. Focus of the Study and Specific Aims

BLUE CORAL and LIFT COVID study designs (Figure)

LIFT COVID is a 300-participant, two-arm, parallel groups RCT with 6-month follow up nested within the NHLBI PETAL Network's **BLUE CORAL** observational study of patients hospitalized with cardiorespiratory manifestations of COVID-19. The PETAL data coordinating site, the University of Michigan, will screen participants, conduct informed consent, and conduct all follow up interviews. Participants with symptoms of depression (PHQ-9 ≥5) 1 month after hospital discharge will be randomized to either the LIFT intervention (Standard Dose, App-based Symptom Response, No intro

Call) or usual care control. Follow up interviews will be done 1, 3, and 6 months post-discharge (i.e., 0, 2, and 5 months post-randomization), as per BLUE CORAL's current timeline.



Specific aims for LIFT COVID RCT

Aim 1: In an RCT nested within the NHLBI's PETAL BLUE CORAL cohort study of 1,500 planned participants, to test the clinical impact of LIFT (n=150) vs. usual care control (n=150) among recently discharged patients recovering from serious COVID-19 infection.

Hypothesis: Compared to control at 3 months post-discharge (i.e., 2 months post-randomization [T2]), LIFT will reduce symptoms of depression (primary outcome; Patient Health Questionnaire-9 [PHQ-9] as well as secondary outcomes of anxiety (General Anxiety Disorder [GAD-7]) and PTSD (Post Traumatic Stress Scale [PTSS]).

Aim 2: In an RCT nested within the PETAL BLUE CORAL cohort study, to test the clinical impact of LIFT (n=150) vs. control (n=150) at 6 months post-discharge.

Hypothesis: Compared to control, LIFT will reduce symptoms of depression, anxiety, and PTSD and 6 months post-discharge.

Aim 3: Among RCT intervention participants, explore barriers and facilitators to LIFT intervention implementation and dissemination in the context of a pandemic.

Approach: Using qualitative analysis of semi-structured interviews from 25 purposively sampled participants enrolled from Supplement Aim 1, we will explore perceptions about barriers to accessing, using, and applying LIFT effectively in a pandemic. This could improve LIFT processes in the future.

4. Study population

4.a. BLUE CORAL eligibility

Eligible BLUE CORAL patients will be enrolled within 72 hours of hospital admission or COVID-19 confirmation by PCR. Target enrollment is 1,500 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.

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

4.b. LIFT COVID eligibility

There will be 300 BLUE CORAL patients selected for detailed post-hospital assessment—these will be the target population for the LIFT COVID RCT. If there are more eligible patients, patients may be selected randomly or according to enrichment strategies which will be informed by the composition of the cohort. Informed consent will be obtained by telephone for these potential participants.

Inclusion criteria:
1. Enrolled in BLUE CORAL
2. Survival to hospital discharge
2. English-speaking
3. Domiciled with access to a working telephone and smartphone, tablet, or computer with wifi or internet connection
4. Absence of severe dementia or severe functional disability before hospitalization or at time of 1 month post-discharge interview

Exclusion criteria:
1. PHQ-9 <5 at time of interview 1 month post-discharge
2. Suicidal ideation at time of interview 1 month post-discharge

5. Screening

PETAL research staff will identify potentially eligible COVID+ patients hospitalized during the study period using medical records and lists maintained for clinical operations. A log of hospitalized COVID+ patients during the study period will be compiled by participating sites. This log will include simple information: patient name, medical record number, age, sex at birth, date of admission, admission location (ward or ICU), race and ethnicity, and BLUE CORAL enrollment or reason for non-enrollment. This log will 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). Research staff will use the medical records for patients on the log to determine study eligibility. Patient names and medical record numbers will be removed from screening logs, which will then be uploaded by each site into REDCap. This information will be used to describe basic characteristics of the entire population of patients with COVID-19 hospitalized at participating hospitals during the BLUE CORAL study period. If there are multiple patients eligible for BLUE CORAL on a single day, coordinators will prioritize ICU patients first. The screening log will be updated with the results: enrolled, declined, not attempted, ineligible.

6. Process of Obtaining Informed Consent

6.a. BLUE CORAL

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 two examples of no-touch consent procedures that may be used: (a) a paper-based approach; and (b) an electronic/e-consent approach.

Paper-based approach

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.

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.
6. 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

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 selected for participation 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.

6.b. LIFT COVID RCT

Screening

1. At the time of the 1 month (T1) BLUE CORAL post-discharge interview, the FUNCTION staff will conduct the PHQ-9 survey.
2. For those with a PHQ-9 score ≥5, the research staff will discuss the informed consent document with the patient by telephone or videophone.

Informed consent

Verbal process

1. During the phone call, a formal DUHS Central IRB-approved telephone script for informed consent will be followed for LIFT COVID by the FUNCTION staff.
2. If the patient decides to consent to participate, the study team will record the participant's name, their contact information, and the date and time of consent. This information will be entered in the study data system.
3. If the patient requests to be called back at a different time to discuss consent, a study team member will do so. Per the patient's direction, the study team will follow the protocol for either the verbal process above or the electronic consent process described below.
4. If the patient declines, this will be noted in the study database.

Electronic consent process

1. For those who prefer completing electronic informed consent, they will do so by following a unique URL sent via an email to a study-specific REDCap e-consent form. Their signature will be done by tracing their finger on the screen. The e-consent form will be retained in the research data system.
2. Research staff and witness provide signatures within the electronic database confirming their participation in the informed consent process per Duke policy.
3. A copy of the signed/dated consent form will be provided to the participant.

There may be instances related to obtaining informed consent that the FUNCTION staff is unable to complete the outlined processes above. Should this occur, the FUNCTION staff will communicate with sister sites, Oregon Health & Sciences University (OHSU) and University of Colorado-Denver (UCD). OHSU and UCD may be asked to complete the recruitment and informed consent process, as well as initiate app registration as further outlined in the sections below.

7. Data Collection

7.a. BLUE CORAL 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.

The case report form (CRF) is built in REDcap 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.

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. 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.

BLUE CORAL patients who survive hospitalization, speak English, are domiciled, and did not have severe dementia or severe disability before hospitalization may be eligible to enter the post-hospital follow-up study (BLUE CORAL). This study will be conducted by the FUNCTION team at the University of Michigan, led by Dr. Jack Iwashyna, using protocols developed and executed in the PETAL Network ROSE and ongoing CLOVERS studies. Sister sites, Oregon Health & Sciences University (OHSU) and University of Colorado-Denver, led by Drs. Terri Hough and Marc Moss, respectively, may be asked to conduct the study visits as needed. Post-hospital follow-up will occur by telephone at 1, 3 and 6 months after hospital discharge (Table 1). Patients will provide consent for continued involvement at the time of the first call.

Table 1: Data collection timing and content for BLUE CORAL and LIFT RCT participants.

	Hospital	1 month* (T1)	During intervention[1, 2]	3 months* (T2)	6 months* (T3)
Contact info	X	X		X	X
PHQ-9 depression (primary outcome)		X	X	X	X
GAD-7 anxiety		X		X	X
EQ-5DL quality of life	X	X		X	X
ADL / IADL limitations	X	X		X	X
Financial strain	X	X		X	X
Cardiopulmonary symptoms		X		X	X
Cognitive function (MOCA/AD8, Hayling)		X		X	X
Rehospitalization		X		X	X

* Timing is from the time of hospital discharge
[1] Collected via the Lift mobile app weekly
[2] These data collected only for LIFT RCT participants. This will be done via the app platform.

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; 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.

7.b. LIFT COVID Surveys

As shown in Table 1, participants enrolled in the LIFT COVID intervention arm will also complete the PHQ-9 survey weekly within the LIFT mobile app for the duration of the 4-week intervention.

7.c. List of all BLUE CORAL and LIFT COVID surveys

Inpatient

- Recent living status (1 item)
- Days hospitalized in month prior to COVID-19 admit (1 item)
- EQ-5D-5L baseline (5 items)
- Activities of Daily Living (ADLs) and Instrumental ADLs baseline (13 items)
- AD8 (8 items, completed by caregiver)
- Household Financial Strain (7 items)
- Occupation and Industry (2 items)
- Number of People in Household (1 item)

Post-hospital patient surveys

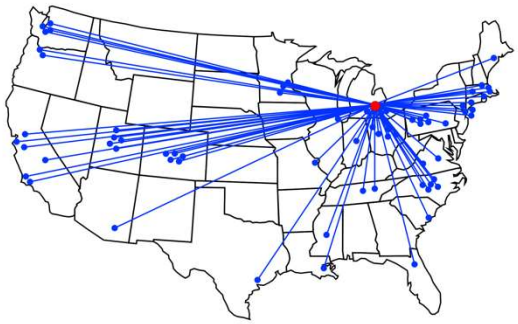
- COVID-19 Recovery (1 item)
- EQ-5D-5L (5 items)
- Activities of Daily Living (ADLs) and Instrumental ADLs (13 items)
- Financial Toxicity (12 items)
- Cardiopulmonary symptoms and respiratory support (13 items)
- Patient Health Questionaire-9 (9 items)
- Generalized Anxiety Disorder-7 (7 items)
- Healthcare utilization (1 item)
- Demographics (2 items)
- Montreal Cognitive Assessment MOCA-Blind
- Hayling Test of Executive Function
- Select Current Medications, matched to those collected in-hospital

8. Randomization.

Figure 1 shows the general approach to screening, informed consent, and randomization. PETAL sites will obtain informed consent for the BLUE CORAL observational study. At the time of the 1-month post-discharge follow up call from the University of Michigan, potential participants will be first screened on the for sufficient distress (i.e., PHQ-9 ≥5). For those who meet the cutoff, the staff will describe the LIFT trial and obtain informed consent by phone. For those who provide informed consent, the delegated study staff will enter the data required for randomization (contact information, stratification variable data) into the Shibboleth password-protected Lift app platform study staff dashboard. This will enable auto-randomization by the LIFT platform. Randomization will be stratified by age, gender, and baseline PHQ-9 score.

At this point, an automated SMS text message and/or email (per user preference) will be sent to the participant that alert them to their treatment group. For intervention group participants, it will also provide a link to download the LIFT app platform and a unique ID code to activate it. After download

Figure 1. Screening, consent, and randomization for the LIFT COVID RCT



Step 1: screening by PETAL / FUNCTION. The PHQ-9 will be administered by the University of Michigan FUNCTION staff by phone 1 month post-discharge for BLUE CORAL observational study. This will be the baseline (T1) data collection for LIFT.

Step 2a: consent from PETAL / FUNCTION. If PHQ-9 eligibility cutoff met, University of Michigan FUNCTION staff obtains informed consent during the phone call.

Step 2b: consent from Duke center if needed. If potential participant wishes to think about it, contact data passed to the LIFT sites for either follow up phone call or email-/text-based approach. If participant agrees, LIFT team then sends email and/or text. Participant clicks link in email / text to download the mobile app platform.

Step 3: randomization. University of Michigan or LIFT teams add contact data and key variables required for stratification for consented participant to Lift mobile app platform dashboard. The LIFT platform then automatically randomizes the participant into one of the two LIFT COVID groups (LIFT app vs. traditional care control).

Step 4: intervention. Intervention participants receive Lift app access. After T3 (6 month post-discharge) BLUE CORAL survey, traditional care control participants can access Lift if they wish via an email automatically sent from the LIFT platform.

and activation with the unique ID, the participant's experience will be automated.

9. LIFT COVID RCT procedures

Aims 1 and 2.

LIFT is a self-directed mobile app platform based on a solid conceptual model that guides participants through a 1-month program. LIFT content includes 4 weekly app-based sessions as previously tested in a pilot RCT (NCT02701361).[21] Each session is composed of three parts: 1. Video presentation describing rationale (3-5 min.), 2. Audio guided meditation (8-10 min.), and 3. Other relevant in-app exercises (e.g., tips to help apply mindfulness to daily life). Each week a participant completes the PHQ-9 depression symptom survey within the app. While the parent U01 factorial trial is comparing 8 versions of LIFT that differ on 3 factors (NCT04038567), the LIFT COVID RCT will use the version of LIFT that includes no introduction call, app-based response to symptoms changes during the intervention period, and standard dose. The app-based approach to non-responders, defined as those whose PHQ-9 score has increased in comparison to the previous week or whose PHQ-9 score is ≥20, uses the app's logic to display hovering messages and notifications within the app that may be applicable to the user. Depending on whether emotional or somatic depression symptoms are dominating the PHQ-9 score for the individual, a unique video is shown within the app that features the study interventionists leading a brief exercise in which the participant is coached by the interventionist in the application of mindfulness for the symptoms the participant has endorsed. The app-based approach to non-responders has 8 unique videos, 2 for each week (i.e., one tailored to emotional symptoms, one tailored to somatic symptoms).

Aim 3 procedures (cross-sectional focus groups)

The goal of Aim 3 is to understand the barriers and facilitators to the successful use of the LIFT app from a patient's perspective within the context of a pandemic. We will use a stratified purposive design to sample 25 participants (~2 / mo.), a number sufficient for theme saturation,[25] after 3 months post-discharge. The procedures will include a ~30-minute semi-structured one-on-one interview conducted by phone (based on participant preference and availability) by an experienced coordinator that will explore app access, use, and content.[26,27] Theoretical sampling will ensure sufficient variability in characteristics that may influence experiences, stratifying cases by response to LIFT (high vs. low), LIFT use (high vs. low), demographics (age, gender), and baseline distress (moderate vs. high).[28-31]

10. Statistical design, analyses, sample size, and power:

Aims 1 and 2

The goal of the parent U01 trial analysis is to determine which LIFT components (i.e., factors) have the greatest salutary effects on MOST optimization criteria of feasibility, usability, and clinical impact.

Analyses for the LIFT COVID RCT's Aims 1 and 2 are designed to compare the clinical impact on psychological distress symptoms (depression, anxiety, PTSD) LIFT (n=150) vs. control (n=150) among COVID-19 patients. All participants will be analyzed by their assigned group, regardless of adherence or crossover status. Briefly, we will test the primary study hypothesis that the PHQ-9 score is lower (i.e., fewer depression symptoms) for LIFT recipients compared to control 3 months post-discharge with a general linear model using SAS PROC MIXED (SAS Institute, Cary NC). An unstructured covariance matrix will be specified to account for the correlation between longitudinal repeated measures. Similar analyses will be performed in Aim 2 for the GAD-7 and PTSS, as well as for all other outcomes at 3 and 6 months.[32,33] Procedures for missing data will include (as needed) sensitivity analyses, multiple imputation PROC MI),[34] and estimates combined using Rubin's rules as implemented in PROC MIANALYZE.[35,36]

Goal and procedures for Aim 3

Supplement Aim 3 will add an additional 25 COVID-positive LIFT recipients to the 75 included in the parent U01's Aim 3, with the goal of understanding barriers and facilitators to the successful use of the LIFT app in a pandemic.[37-39] We will use a stratified purposive design to sample 25 participants, a number sufficient for

theme saturation.[40] The procedures will include a 30-minute semi-structured telephone interview conducted by an experienced coordinator to explore app access, content, and use.[26,27] Theoretical sampling will ensure variability in potentially influential characteristics: response to LIFT (high vs. low), demo-graphics (age, race, gender), and baseline distress (moderate vs. high).[28-31] Analyses will be nearly identical to the U01 and will use modified grounded theory methods (e.g., open and axial coding, consensus building on codes, member checking) [28,30,31,41,42] to inductively and iteratively develop frameworks.[43-46]

Sample size and power considerations

For Supplement Aim 1, we will randomize 300 patients. Even with a 40% dropout rate (i.e., 180 at 3 months) and conservative assumptions (SD=6.0, ρ=0.5, two-sided test, type-I error of 5%), this sample size will provide a power of 80% to detect a differential between-group PHQ-9 improvement at 3 months as small as 2.5 units, substantially less than the minimal clinically important difference (MCID) of 5.0 units.[47] Calculations were based on mixed-models tests for a difference in slopes using PASS 16 Software (v16.0.5; Kaysville UT).

11. Subject Participation Duration: It will require 5 months for participants to complete the entire study from the time of randomization, including the month-long intervention and follow up surveys.

12. Study Duration: We estimate that from the time the RCT opens to enrollment it will require 1 year to complete all study activities.

13. Costs to the Subject: There are no costs to participants.

14. Compensation

Participants will receive $20 for each completed survey, up to a total of $60, for participation in the LIFT COVID study.

15. Risk-benefit assessment

Potential risks

It is possible that participants could experience a breach of privacy should their records be accessed unlawfully by an outside party. Also, it is possible that participants may experience mild anxiety when answering survey questions, though we have not observed this in similar interventions such as LIFT or CSTEP. However, we believe that involvement in this study will present no significant physical, psychological, financial, legal, or other risks. Additionally, there is always the potential of a breach of data security, as is noted in any IRB-approved consent form. However, we have a number of security features to protect these data that will be described below in Section 2.

Adequacy of protection against risks

Recruitment and informed consent procedures

First, the Duke Institutional Review Board (IRB) will review and approve the study protocol before study initiation (as they did for our preliminary work conducted under Duke IRB Protocols #00062340, #00069031, and #00071161). Informed consent (verbal, e-consent, or written) will be required from all participants. Second, we will use a standardized screening and enrollment protocol that respects participant privacy and rights. Clinical research coordinators will approach patients to discuss the study at the time the BLUE CORAL participant is on the phone completing a BLUE CORAL survey. This will be possibly be aided by a short IRB-approved recruitment video we have produced and piloted for LIFT, similar to other highly rated videos our group has made for similar purposes in other clinical trials. After following the verbal consent script, the clinical research coordinator will then obtain verbal informed consent from the participant. If a patient wishes to do e-consent, this procedure will be followed as described above in Section 6.B. Potential subjects will have up to 72 hours to consider enrollment. For the clinical trial, we will take great care to present the treatment group

assignment possibilities ("like drawing a number out of a hat") tactfully and with clearly stated equipoise in person, as we have done successfully in past ICU-based clinical trials. A copy of the consent form will be emailed or mailed to participant (as they prefer) and the original maintained in the study data system (e-consent) or in a secure location at the study site (mailed consent). The study team will provide contact information for the PI.

Protections against risk

General oversight

There are several ongoing mechanisms for monitoring the occurrence of adverse events. The University of Michigan, Duke, Colorado, and Oregon investigators will perform day-to-day monitoring of the study activities at their sites as they have done in many other trials and studies involving similar participants. The Principal Study Investigator, Dr. Cox, has demonstrated in research to date involving nearly 1,500 participants that he keeps careful records of patients' whereabouts and health status. Careful monitoring of all persons entering the study will minimize attrition and will ensure the clinical safety of these patients. This monitoring is facilitated by a telephone number (PI's cell phone) and email address (LIFTCOVID@duke.edu) provided to participants upon entry into the study to report concerns related to study participation, weekly meetings between the clinical research coordinators and co-investigators to discuss study progress and any adverse events, and direct supervision of the study by the PIs.

Plans to prevent coercion of patients and to ensure voluntary participation

We will strive to create an environment free of any coercive practices for patients. We will stress that study involvement is absolutely voluntary and that choosing to participate or not participate will not affect their care in anyway. In addition, we will utilize the standardized 2-minute informational video (lift.duke.edu/COVID), which has been used successfully in the LIFT trial to describe treatment groups and ensure a similar approach across sites.

Specific longitudinal participant oversight plans for severe psychological distress (including suicidal ideation)—research coordinators and the study data system

Given the difficult situations faced by COVID patients, we recognize that there is a slight risk that some participants may become distressed completing questionnaires or viewing study materials, as mentioned above. Additionally, given the extreme stresses of the critical illness experience, participants may even endorse suicidal ideation. We will take the following measures to prevent any negative reactions as well as effectively manage any serious distress that occurs:

(1) All of the in-person and telephone-based data collection sessions will be conducted by highly trained research coordinator professionals who are sensitive to the issues that arise.

(2) Clinical research coordinators will emphasize to participants that any interviews or other study interactions are participant-controlled. Thus, participants will be instructed that they are in control over what they share and generally how long they discuss any topic that is addressed.

(3) Participants will be told that they can discontinue an interview at any time and that they are also free to reschedule an interview or treatment session at any time within the week.

(4) Overall, we are very sensitive to the common and pervasive nature of psychological distress among COVID survivors and are experienced in discussing these issues with them. There is also a potential risk for identifying underlying mental health issues through the LIFT sessions, telephone calls, and survey responses. For issues such as passive suicidal ideation or symptoms of depression, anxiety, or PTSD, an informational sheet will be provided with contact numbers for additional mental health services. Additionally, at the beginning of the program, all subjects will be informed that the training program may uncover unresolved and distressing thoughts or feelings; and a list of resources will also be provided at that time.

(5) As a safety measure that we have used in past/current clinical research, the study team will be trained to monitor participants closely beyond just the parameters of questionnaire scores. The study staff, including the trained clinical research coordinators and the therapist, will monitor participants closely during any interviews performed and will refer those with any concerning level of emotional distress and/or relationship distress to the PI to evaluate by phone. This will be done immediately, particularly if there is staff concern about a participant who indicates suicidality. Point #6 below describes PI actions that will follow.

(6) We have developed a specific protocol to manage any study participant who expresses suicidal thoughts in person, by telephone, or via the app at any point during the study. All study participants will be informed of this suicidality response plan prior to signing the informed consent for their participation in the study. The PI or trained CRC will complete the online Columbia Suicide Severity Rating Scale (C-SSRS) training, a 30-minute interactive slide presentation followed by a question-answer session. The C-SSRS is scale that can delineate high, moderate, and low-risk levels.

Our Suicidality Response Plan can be activated in two main ways.
First, study staff (coordinators, therapists, investigators, PI) may have in-person or telephone interactions that concern them.

Second, the study app system will automatically detect any endorsement of active suicidal intent in a 2-step process that is contingent on the PHQ-9's item #9 (which evaluates suicidal thoughts) and the C-SSRS item #4 (which evaluates intent by asking: *Have you had these thoughts and had some intention of acting on them?*) as shown here:

PHQ-9 item 9 response	Suicidal intent item response	Action by app system	Action by team
0	n/a	n/a	n/a
1, 2, or 3 (i.e., $\neq 0$)	NO	n/a	n/a
1, 2, or 3 (i.e., $\neq 0$)	YES	Alert to study manager, therapist, and PI	Immediately contact participant

If the participant is deemed to be at high risk for active suicidality based on direct interaction or the PHQ-9 item plus the C-SSRS item response, the app system will send an alert email and/or text message in real time to the study manager, the study therapist, and relevant site PI (no PHI included, only study ID). One of these study staff will then immediately contact the participant. Using the full C-SSRS, the trained staff will then help to assess the participant to determine if they endorse active suicidal ideation. The trained staff will also determine if the participant is currently being treated by a mental health professional.

If the participant is considered to be actively suicidal then at least one of the following plans will be followed depending on the location of the participant for each of the following situations:

Situation 1. If the participant is with one of the study personnel [not expected to occur in the RCT]:

a. The study personnel will notify the PI immediately

b. The study personnel will either physically walk the subject to the emergency department, or call a Psychiatric Emergency services number relevant to the site as described above.

Situation 2. If the participant is on the telephone:

a. The study personnel will notify the PI immediately.

b. The study personnel will stay on the telephone with the subject participant.

c. The study personnel will immediately contact 911 to initiate an on-site rescue if such action is clinically indicated.

d. The study personnel will stay on the telephone with the subject until EMS services have contacted the participant.

Situation 3. If there are any active suicidal concerns in any of the surveys (e.g., PHQ-9 above):

a. The study data system will notify the PI and Study Manager immediately.

b. The study personnel will then contact the honest broker to de-identify the participant information.

c. Next, the study personnel will contact the participant by telephone.

d. The study personnel will stay on the telephone with the subject participant.

e. The study personnel will use a different telephone line to immediately contact 911 to initiate an on-site rescue if action is clinically indicated.

f. The study personnel will stay on the telephone with the subject until EMS services have contacted the participant.

If the participant if determined to be actively suicidal and require immediate medical therapy, they will be withdrawn from the study.

If the patient is deemed not to be actively suicidal, they will be given contact information for the National Suicide Prevention Lifeline (1-800-273-TALK), a free, 24-hour hotline available to anyone in suicidal crisis or emotional distress. This will occur via the app for the intervention group and via email for control participants.

(7) As described in above, all concerns about participant safety will be discussed immediately with the PI including concerning, severe distress that does not involve suicidality. For these situations, once an "alert situation" is known, the PI will refer the participant if needed (based on a PI-led phone call) to local psychological resources as we have done previously with this well-tested Distress Management Protocol used successfully by Dr. Cox in 3 past clinical trials involving family members that used psychological distress outcomes. We will also make urgent and emergency referrals as needed based on information learned by any site PI on a site-by-site basis (see contact information above). It is important to note that this system has been developed in full partnership with the Duke IRB, who approve it in its entirety and have described it as a model for future patient safety in Duke-based clinical research. To date based on these studies that have included over 400 participants, we have found that <5% of participants will require a call from the PI during some point in the study period. Of those, none have required referral to acute psychiatric care after a detailed interview from the PI. After a disposition / solution has been made, both the resolution (and follow up) will be documented in the 'contact log' section of the data system for reporting to the DSMB.

(8) Finally, though there were no patient deaths during the LIFT COVID RCT follow-up period, we recognize that we are working with a seriously ill population that is at risk for death during follow up due to their underlying illness. We are very sensitive to issues surrounding patient death in relation to study procedures and interviews. We have dealt with this respectfully for years in our studies involving in-person, telephone, and app-based interviews and surveys. On phoning any participant, we will initiate a conversation in a sensitively scripted manner to tactfully ascertain the patient's vital status should a family member answer first. If the patient has died, we will provide brief support. If a patient states that they wish to drop out, we will respect that as well.

Vulnerable populations. We will not enroll patients from vulnerable populations (e.g., imprisoned persons, minors).

Adverse events (AEs), serious adverse events, (SAEs) and unanticipated problems (UPs). Our plan for AEs, SAEs, and UPs has been reviewed and accepted by the NIH. As mentioned before, we recognize that there is a slight risk that some participants may become distressed when completing self-report measures or participating in interviews. In our previous studies using similar self-report surveys (telephone, in person, or ePRO), we have encountered little resultant distress. In fact, many participants have reported that they were relieved to be able to have a platform through which to reflect on such issues. When necessary, participants who experience psychological distress related to completing questionnaires will be referred for appropriate

psychiatric or psychological care. All participants will have access to a PI's mobile phone number available 24 hours a day (shown in the consent form). If a telephone interview is required, it will be conducted by an experienced interviewer who has been trained to be sensitive to the nature of these issues.

In this trial, we expect AEs to be extremely uncommon because it is a behavioral trial. However, it is possible that participants could become distressed in an ICU setting in the event that their loved one dies or becomes more ill. One particular symptom of note that will be considered an AE and reported to the IMC will be suicidal ideation as operationalized by responding to PHQ-9 item #9 (Thoughts that you would be better off dead or of hurting yourself in some way) with either 'more than half the days' or 'nearly every day' out of the preceding 2 weeks. In this trial, we do not anticipate any SAEs because it is a behavioral trial. A SAE in this trial would include a suicide attempt, a hospitalization, or death. All serious adverse events will be reported within the standard timelines required to these bodies as well as to the OHRP and the NIH/NCCIH. AEs and SAEs will be reported to these agencies per their standard guidelines.

While we do not anticipate any UPs because it is a behavioral trial that focuses on ICU patients, critical illness and its recovery process are unpredictable. Unanticipated problems will be identified, discussed by the PIs, and resolved by group consensus. Therefore, should there be unanticipated problems observed we propose the following reporting process—itself framed by NIH guidelines. First, the PIs and Duke University will include a written report that will be submitted to the NCCIH, the study DSMB, and the Central IRB that will describe the UP, the context, and the proposed corrective plan. This written report will be provided within 1 week (unless it/they is/are also an SAE, in which case the timeline for SAE reporting will be followed). The UP will also be forwarded OHRP using ohrp@osophs.dhhs.gov within two weeks of the event.

Period and Frequency for Event Assessment and Follow-Up
Unanticipated problems will be recorded in the data collection system throughout the study.
The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

Characteristics of an Adverse Event
Relationship to Study Intervention
To assess relationship of an event to study intervention, the following guidelines are used:

1. Related (Possible, Probable, Definite)
    a. The event is known to occur with the study intervention.
    b. There is a temporal relationship between the intervention and event onset.
    c. The event abates when the intervention is discontinued.
    d. The event reappears upon a re-challenge with the intervention.
2. Not Related (Unlikely, Not Related)
    a. There is no temporal relationship between the intervention and event onset.
    b. An alternate etiology has been established.
    c.

Expectedness of SAEs
The Study PI and Independent Monitoring Committee will be responsible for determining whether an SAE is expected or unexpected. An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention.

Severity of Event
The following scale will be used to grade adverse events:

1. Mild: no intervention required; no impact on activities of daily living (ADL)
2. Moderate: minimal, local, or non-invasive intervention indicated; moderate impact on ADL
3. Severe: significant symptoms requiring invasive intervention; subject seeks medical attention, needs major assistance with ADL

Reporting Procedures

We have a strong plan for AE reporting and follow up. First, we have a very robust monitoring system for psychiatric and emotional symptoms. For all groups, we will know 'alert' values of depression, anxiety, and PTSD symptoms the second a questionnaire is completed. For the mobile mindfulness study arm, we will also know depression / anxiety symptoms weekly as well. For symptoms that are either great in total burden (i.e., total score is high), we will call the participant to check in. For specific symptoms such as the suicidal ideation item in the PHQ-9 depression questionnaire, we will also call the participant and assess the severity of the situation, triaging them as appropriate to psychiatric support. For other matters, the study interventionist will also have frequent telephone contact with most participants, and can also refer those with concerning symptoms. Last, we have broadly placed our email addresses and phone numbers in all study materials and will encourage people to contact us regarding any issues.

Since this is a psychosocial intervention, we do not expect study related physical issues to occur. Furthermore, there is no labwork involved.

All deaths will be reported to NIH Program Officer and to the DSMB Chair within 72 hours of study's knowledge of death. For each patient who dies, a brief report containing the following variables will be provided:

Age
Principal diagnosis
Number of comorbidities
Admission APACHE II score
Days since enrollment
Brief description of circumstances surrounding death including expected or unexpected.

Serious (fatal or life-threatening) SAEs that are unanticipated (i.e., not listed in the Data and Safety Monitoring Plan) and that are related to the intervention will be reported to the NIH Program Officer and to the DSMB Chair within 7 days of study staff's knowledge of the SAE. The summary of all other SAEs will be reported to NIH Program Officer and to the DSMB quarterly, unless otherwise requested by the DSMB. Additionally, for SAEs, we will hold an all-investigator teleconference within 7 days. The PIs will draft a description of the SAE and an action plan. This will be passed on to the IRB, the NIH, and DSMB within 72 hours of the teleconference.

Reporting for Multi-Center Trials

The site PI must immediately report to the coordinating center PI (Dr. Cox) any serious adverse event, whether or not considered study related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study caused the event within 48 hours of PI awareness of the event.

They must also report any unanticipated problems within the same timeframe. The Site PI must also report any protocol deviations or violations to the coordinating center PI within 7 days of PI awareness. Participating centers must also submit all reports to their local IRB in accordance with their institutional policies.

Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for unanticipated problems require the creation and completion of an unanticipated problem report form. OHRP recommends that investigators include the following information when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB:

- Appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number;
- A detailed description of the adverse event, incident, experience, or outcome;
- An explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:

- Unanticipated problems that are serious adverse events will be reported to the IRB, Independent Safety Monitor(s), and NCCIH within 7 days of the investigator becoming aware of the event.
- Any other unanticipated problem will be reported to the IRB, Independent Safety Monitor(s), and NCCIH within 14 days of the investigator becoming aware of the problem.

All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB's receipt of the report of the problem from the investigator.

Adverse Event Reporting of Non-IND Studies

SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the Independent Safety Monitor(s), IRB, and NCCIH in accordance with requirements.

- Unexpected fatal or life-threatening AEs related to the intervention will be reported to the NCCIH Program Officer, and Independent Safety Monitor(s) within 3 days of the investigator becoming aware of the event. Other serious and unexpected AEs related to the intervention will be reported within 7 days.
- Anticipated or unrelated SAEs will be handled in a less urgent manner but will be reported to the Independent Safety Monitor(s), IRB, and other oversight organizations in accordance with their requirements. and will be reported to NCCIH on an annual basis.
- All other AEs documented during the course of the trial will be reported to NCCIH on an annual basis by way of inclusion in the annual report and in the annual AE summary which will be provided to NCCIH and to the Independent Monitors. The Independent Safety Monitor(s) Report will state that all AEs have been reviewed.

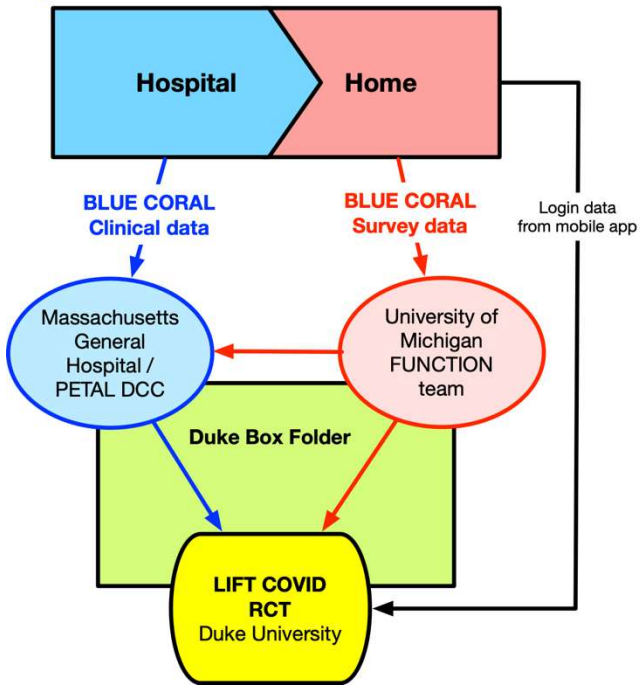
Privacy. We will closely safeguard participant privacy regarding protected health and personal information. Study ID numbers, generated randomly at the time of enrollment, are linked in a separate app subsystem that contains patient names and medical record numbers. Further, names, birthdates, telephone numbers, addresses, and medical record numbers will be stored securely as described in the RDSP and only accessible by trained staff listed on the delegation log. The PIs will be unable to view data in the database because they will lack passwords to do so. Data will be delivered to the Duke site from the University of Michigan and PETAL REDCap databases in a scheduled manner and with data use agreements in place with both the University of Michigan and the Massachusetts General Hospital (i.e., PETAL DCC; Figure 2). Data will be transferred via a Duke Box password protected folder system. These data will be delivered as CSV files for subsequent upload by the statistical team as analytical files (e.g., SAS). No PHI is visible in any user interface, with the exception of the initial survey in which the participant will enter this identifying information. Study participants cannot view data via the app system, only enter data (a 'one-way view'). Patients access this one-way view app system via secure, PHI-free email or text links sent from our study RedCAP data system.

Language specifying the way we use and release data will be shown in the informed consent form as required by the IRB.

Digital security. The study digital infrastructure consists of a mobile (i.e., native) app and a separate RedCAP digital study database. We take digital security very seriously and will follow institutional guidelines for safeguarding data, health information, and study results.

All technology will be managed by the PIs in a collaborative manner.

Figure 2



- ***LIFT app:*** The LIFT app is a native app. Our programming service providers, Pattern Health, endeavor to build technological solutions that preserve the privacy, confidentiality, and security of protected health information that may be part of health records or research datasets. Protected Health Information (PHI) is handled according to appropriate Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy and Security Regulations. All staff who work with sensitive data are required to complete appropriate HIPAA training with periodic updates, complete human subjects and data privacy training, comply with site IT Security Policies, and agree to the provisions of the University Rules of Behavior and Sanction Policy. All sites strive to implement reasonable security controls in its product builds guided by FISMA, HIPAA, and OMB Circular A-130, Appendix III.

Data security is of the upmost importance for our study, particularly in providing a digital, online intervention for our participants. Beyond the robust security that RedCAP provides, Pattern Health has implemented and maintains several security protocols and controls for apps as well. Pattern Health has developed a formal information security program, with a named individual responsible for its overall execution. Pattern Health also periodically conducts an information technology (IT) security risk assessment on its projects, maintains formal documented protocols for reporting security breaches, assesses and manages security risks associated with vendors and subcontractors, maintains employee on-boarding and off-boarding policies that protect study data and integrity, and ensures continuing employee awareness of and education on security policies, standards, and procedures. In terms of development approaches to security, Pattern Health evaluates and installs security patches in a timely fashion, protects systems against self-propagating malware, maintains secure coding policies and practices, and utilizes standardized secure build processes to protect Pattern Health hardware that accesses customer networks, protecting confidential data against attack. Any and all storage of confidential participant data on Pattern Health hardware is strictly prohibited, and the use of off-shore service providers and/or data center facilities is prohibited unless approved by client. For our study, the native app application and supporting backend system that Pattern Health develops will be hosted securely per DHTS regulations.

16. Data management.

16.a. BLUE CORAL data management

Data collected by study staff will contain identifiers. For transmission of data to the PETAL DCC, 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 DCC 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 use agreements will be put in place between Duke and both the University of Michigan (BLUE CORAL) and the Massachusetts General Hospital (PETAL DCC).

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.

16.b. LIFT COVID data management

For all non-PETAL gathered data, LIFT study staff will complete electronic case report forms (eCRFs) securely integrated within the LIFT platform that includes an electronic database. We will use a parallel study operations workflow tracking application to manage participants' contact history log, survey schedule, and recorded adverse events. Study personnel will utilize these data systems to create scheduled reports on the trials' conduct (e.g., study milestones) to enhance the study's quality. We will monitor the quality and consistency of data in a number of ways. Monthly data cleaning will be done by the Study Manager and statistical team using customized group-blinded reports that will identify missing, outlier, or nonsensical data at time points when remedying them is feasible.

17. Data & safety monitoring plan for LIFT COVID RCT

Plans for assurance of compliance regarding adverse event reporting. All sites require investigators to report adverse events (including serious adverse events) to the central Institutional Review Board (IRB) at Duke, their own site IRB, and the study Data Safety Monitoring Board (DSMB) on both a per case and an annual basis. Also, all adverse events are reported as part of NIH Progress Reports in the non-competitive and competitive renewals. The co-PIs will be responsible for contacting the NIH grant Program Officer in the event that any action resulting in temporary or permanent suspension of the study occurs. The proposed research will adhere to all monitoring requirements imposed by 45 CFR Part 46.

Plans for assuring data accuracy and protocol compliance. Dr. Cox will supervise the study, including data management, data accuracy, and protocol compliance. The study biostatistician and Study Manager will be the chief data managers and will adhere to established federal and institutional patient safety and protection guidelines. To assure data accuracy, the Study Manager will review data system reports on a routine basis for the first 2 months followed by monthly thereafter. These reports will show enrollment, missing data, and other values that are neither study ID- nor outcome-based. The Study Manager will also be in charge of monitoring the safety system linked to weekly PHQ-9 surveys completed by active LIFT users—human oversight intended

to provide a redundant process given the importance of this safety feature. Additionally, the Study Manager will process detailed routine reports to search for errors and generate basic reports for dissemination for regular staff meetings.

Data safety monitoring board (DSMB). This RCT trial will be supervised by a single independent DSMB composed of professionals with significant experience in clinical trials, mind and body interventions, epidemiology, and biostatistics who are not directly involved in the study, its interpretation, or any study institution and have no active research relationship with a study team member—the same individuals who are overseeing the parent U01 factorial trial.

The main responsibilities of the DSMB will be to (a) assess for the presence of potential harms and unintended consequences of the LIFT intervention, (b) ensure the validity and integrity of the data, and (c) make recommendations to the investigators and to the NIH about whether the study should be continued without modification, continued with modification, or terminated.

The initial DSMB meeting will occur before the initiation of subject enrollment for the purpose of updating members on the study, ensuring agreement on the review process, establishing the review methodology and procedures, ensuring all conflicts of interest are disclosed (to be reviewed by NCCIH staff), reviewing the protocol, and codifying a written charter. The NCCIH's Data Safety Monitoring Plan (DSMP) Template will be used to guide the drafting of the charter. This document will specify procedures for protocol amendments, ensuring participant confidentiality and privacy, ensuring database protection, coordinating center responsibilities, creating adverse outcome definitions (adverse events, unanticipated problems, and serious adverse events), protocol for reporting and responding to adverse events while also maintaining subject confidentiality, justifying sample size, assessing accrual and compliance, halting and stopping rules (drafted with the assistance of the DSMB chair and the DSMB lead statistician), approving informed consent documents, and guidelines for quality control and quality assurance. Before enrollment begins, the DSMB charter will be approved by both the DSMB and the NCCIH; additionally, ClinicalTrials.gov registration will be finalized as per the Milestone Plan shown in the Research Strategy document.

The first DSMB data review will occur either after the first 50 participants have been enrolled—representing approximately 20% of randomization target—or enrollment has occurred for 6 months, whichever is observed first. Thereafter, the DSMB will review cleaned data reports (provided by the Study Manager 2 weeks before the DSMB meeting) every 6 months during enrollment and follow up, and will prepare a report with any recommendations within 2 weeks following their review. The specific study metrics that the DSMB will review at each meeting include: enrollment rate, dropout rate, PHQ-9 scores, GAD-7 scores, PTSS scores, and Adverse Events. The primary safety measures will be Adverse Events reports and PHQ-9 scores. Other items reviewed by the DSMB at each meeting will include: (a) data quality, completeness, and timeliness; (b) performance of the individual sites; (c) adequacy of compliance with goals for recruitment and retention, including women and minorities; (d) protocol adherence; and (e) presence of factors that could adversely affect study outcome or compromise data confidentiality. Study participants will be recovering from life-threatening illnesses managed in intensive care units which increase the likelihood of death over time in comparison to healthy individuals. As such, any patient deaths and their cause during the follow up period will be recorded, discussed, and highly scrutinized.

The study biostatistician, will oversee any DSMB statistical requests and interpretations. During the review process, formal statistical tests may be performed under DSMB supervision if requested (e.g., examining the differences in Adverse Event or outcome rates between factor-based groups). Additionally, the DSMB may request a formal statistical assessment if a suspicious increase in PHQ-9 score is observed in any factor-based group. If a specific factor group is found to have a statistically significant increase in PHQ-9 score, the DSMB scope of action may include recommendation for stopping the trial. For differences in study dropout rates, appropriate changes to the protocol will be made by PI consensus after DSMB member input. Any

protocol changes, as well as any adverse events, will also be immediately reported to the relevant site IRB, the Central Institutional Review Board (located at Duke University), as well as to the NIH Program Officer.

Quality assurance and confidentiality: We have a number of strategies to ensure the quality of the data. First, the RedCAP electronic data entry system "forces" responses to key questionnaire items (e.g., primary outcomes surveys) before allowing progression through the particular interview's template, thereby minimizing missing data. For less critical items, delayed data entry is possible (though these data elements are non-essential to primary aims analyses). However, each time the clinical research coordinator logs into the secure data entry system, prompts appear on the welcome screen that show what data elements remain incomplete (as well as the time frame within which they must be entered) for all site participants.

The study investigators will ensure the validity of the data system in a number of ways. First, they will input data from 5-10 'dummy' forms and cross-check it with the source data for accuracy, including the scoring of all study instruments. Second, the investigators will examine electronic summary case report forms within the RedCAP system to ensure adequacy and accuracy of data collection as well as transcription to the database itself after enrollment of the first 5 participants. Agreement will be reviewed and discrepancies will be discussed.

Confidentiality will be safeguarded by a number of strategies. Subjects will not be identified on any study reports. University firewalls, multiple passwords, and encryption programs protect the security of the electronic data entry system, which will be housed on a highly secure Duke University server. All personal computers are located in lockable offices and are accessible only by frequently changed passwords. The server room is accessible only to designated University Systems Administrators.

18. Privacy, Data Storage & Confidentiality

18.a. BLUE CORAL

Data will be collected from the Michigan FUNCTION group and entered into the HIPAA compliant BLUE CORAL REDCap database. Only study personnel will have access to the REDCap database. Data from PETAL sites will remain in the PETAL central BLUE CORAL REDCap database overseen by the DCC 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.

18.b. LIFT COVID RCT

As noted above, data use agreements will be put in place to clarify data transferred from both the University of Michigan and the Massachusetts General Hospital and Duke University. Non-BLUE CORAL data will be entered into a LIFT COVID database. Data will be transmitted to Duke in CSV format from PETAL via secure, Duke University-approved, password protected, cloud systems (i.e., Box). These data will be uploaded to a secure, password protected REDCap database housed on a Duke server.

19. DUHS IRB as Single IRB (sIRB)

The Duke IRB will act as the single IRB for the LIFT COVID RCT and include Duke, Oregon Health & Sciences University, University of Colorado, and PETAL sites within its oversight. We believe this is reasonable because of the low risk nature of the proposed trial, the good working relationships the Co-PIs from each site have demonstrated in current and past work, and the expressed preferences of the NIH PETAL network.

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