Effects of mindfulness training programs delivered by a self-directed mobile app and by telephone compared to an education program for survivors of critical illness: a pilot randomized clinical trial

1. PROTOCOL TITLE

Mobile Mindfulness to Improve Psychological Distress after Critical Illness (LIFT Study)

2. PURPOSE OF THE STUDY

A majority of the >1 million people who require life support in an intensive care unit (ICU) now survive. As survival has improved however, growing numbers suffer not only from subsequent physical disability, but also persistent symptoms of depression, anxiety, and post-traumatic stress disorder (PTSD). Few interventions address ICU survivors' psychological distress. Fewer still address the physical, geographical, and logistical barriers to receiving post-discharge support that medically ill populations encounter. Consequently, this population suffers with an unmet need of great public health importance.

Mindfulness is an adaptable self-regulation practice that alleviates psychological distress symptoms using a variety of meditative techniques, typically taught face-to face over months. As an extension of standard mindfulness practices, we developed a telephone-/web-delivered mobile mindfulness-based training (mMBT) system informed by ICU survivors' input that could address medically ill patients' delivery barriers. Our recent pilot study demonstrated early support for mMBT's feasibility and acceptability, now with enhanced content and electronic patient-reported outcomes capability.

Our early work on mMBT, while promising, identified key knowledge gaps in population targeting, plausible ranges of psychological distress estimates relevant to study design, and assurance of acceptability that must be addressed before a definitive clinical trial is conducted. Therefore, we propose a 2-year pilot study including approximately 25 patients in a usability assessment and 90 in a pilot randomized trial. In the trial, ICU survivors will be randomized to one of three arms: (1) an education control, (2) 4 weekly telephone sessions of mMBT, or (3) a 4-week course of self-directed mMBT. Our specific aims will use quantitative and qualitative methods to: (1) evaluate mMBT and self-directed mMBT feasibility, acceptability, and usability as well as (2) better estimate the effect of both mMBT or self-directed mMBT on psychological distress symptoms

Aim 1: To test the feasibility, acceptability, and usability of a telephone- and web-delivered mobile mindfulness-based training (mMBT) interventions for distressed ICU survivors.

Understanding participants' perceptions about mMBT and self-directed mMBT—and making responsive refinements—is critical to the success of a future RCT. We will assess feasibility by examining observed vs. benchmark rates of enrollment, session completion, and website use. We will assess acceptability and usability using quantitative and qualitative measures of satisfaction, usefulness, and system performance

Aim 2: To provide a plausible range of psychological distress estimates for each treatment group at both post-intervention and long-term follow up.

To improve our understanding of how these outcomes are operationalized and reflect change relevant to the planning of a larger RCT, we will evaluate to what extent mMBT, self-directed mMBT (using electronic patient reported outcomes (ePRO)-based symptom monitoring to efficiently direct therapist calls on an as-needed basis), and the education program reduce symptoms of depression, anxiety, and post-traumatic stress over 3 months post-intervention. We will also explore associations between changes in symptoms and clinical/demographic characteristics to refine inclusion and exclusion criteria for future study.

We propose an exploratory pilot project that represents an important transition from past description of a serious public health issue to an innovative, conceptually strong, patient-centered intervention that addresses the problem. It also represents a paradigm shift from the standard focus on reducing ICU death to improving long-term ICU patient survivorship, described as "the defining challenge of critical care for the 21st century."[1] This proposal addresses key national research priorities in post-discharge critical illness treatment and in the management of persistent psychological distress.[2, 3] Innovative qualities include the new direction in critical illness treatment, its low cost, its ability to be personalized, its adaptability to new delivery formats as technology advances, and its likely future applicability to broader populations. Importantly, this study is both necessary and sufficient to inform a future definitive RCT that could substantially improve and advance our approach to critical care. Overall, data derived from this study will be necessary and sufficient to inform the development of a future definitive RCT that could change the current approach to critical care—and improve ICU survivorship.

3. BACKGROUND & SIGNIFICANCE

Psychological distress after critical illness is common, important, and understudied. Acute respiratory failure requiring mechanical ventilation life support is the most common admission diagnosis for the more than 5 million patients managed annually in intensive care units (ICUs)—a number expected to double by 2020 because of our aging population (*Figure 1*).[4] Because of technological and process advances, the majority of these patients now survive this once fatal condition.[5] However, nearly all experience important emotional and physical symptoms that impair their quality of life, act as barriers to workplace reentry, and strain family units.[6-12] In fact, ICU survivors suffer from psychological distress at rates 5- to 10-fold greater than the US population [13-15] including symptoms of depression (35-62%), anxiety (24-63%), and post-traumatic stress disorder (PTSD) (22-63%).[16-26] A recent study of 1-year ICU survivors found that a third sought psychiatric care and nearly half required psychiatric medications.[27] This distress can persist for >10 years and diminish quality of life.[18, 28-31] However, very few studies have addressed ICU survivors' distress and the numerous physical, financial, and social barriers that limit their access to care.[32] Therefore, we aim to improve the experience of critical care survivorship with a novel telephone-based intervention designed to reduce post-discharge psychological distress and promote quality of life.[2, 33]

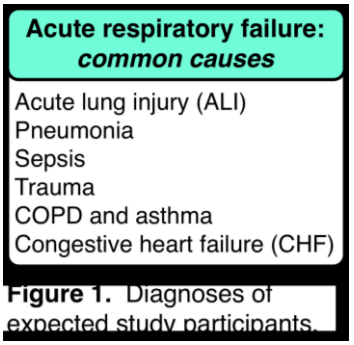


Figure 1. Diagnoses of expected study participants.

Mindfulness is an innovative, promising treatment for ICU survivors' distress. Mindfulness is awareness of one's experience in the present moment.[34] Mindfulness can be honed through a variety of meditative techniques to help patients cope with stress, illness, and pain. Mindfulness works to reduce distress in two primary ways: (1) by developing mindful qualities that help patients change the way they relate to emotional and physical symptoms, and (2) by facilitating mindful coping that helps patients skillfully regulate difficult emotions, thoughts, and memories (*Figure 2*).[35-42] Mindfulness is based in centuries of meditative practices, and over the past 30 years has been shown to reduce depression, anxiety, and stress, as well as

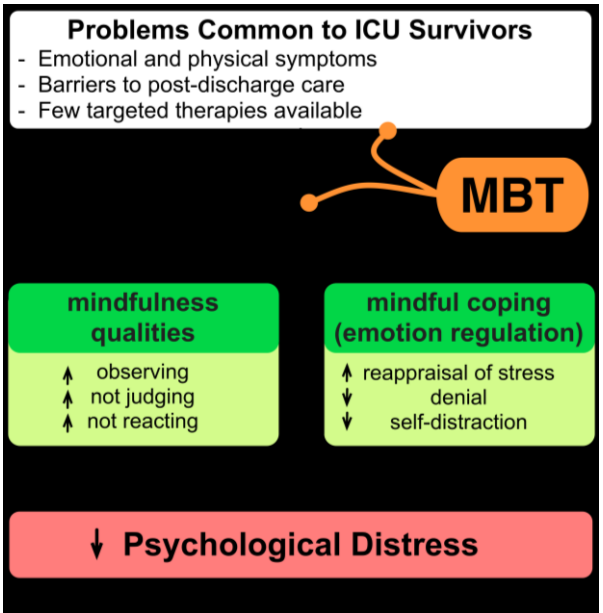


Figure 2. Conceptual model: mindfulness-based training (MBT) is a telephone-based intervention that targets mindfulness qualities & mindful coping (i.e., emotional regulation) to reduce psychological distress.

improve health-related quality of life for patients with diverse medical and mental disorders.[34, 43-47] We have found that although ICU survivors report that coping skills and the ability to manage emotions are important to their overall sense of well being, they use these skills infrequently and ineffectively—a pattern that maintains psychological distress and poor quality of life.[7, 48] MBT could directly target these foundational elements of distress among ICU survivors, including the subjective experience of the ICU and its association with post-traumatic stress.[7, 26, 49, 50] Therefore, we propose to examine an innovative telephone-based MBT intervention designed to reduce psychological distress among ICU survivors.

4. DESIGN & PROCEDURES

Overview of study design. We propose a 2-year pilot study comparing three arms: (1) a 4-session telephone-based, therapist-directed mMBT program, (2) a self-directed mMBT program where both the intervention and data collection are digitally automated (features that could enhance future dissemination to broader populations), and (3) a similar length critical illness education program control. For the therapist-directed mMBT program, ICU survivors will participate in the intervention calls using standard conferencing technology. For all three study arms, we will measure pre- and post-intervention outcomes as the primary effect assessment, as well as at 3 months post-intervention (~4 months post-randomization) to determine the long-term impact.

Settings and participants.

Settings: The setting will be medical and surgical ICUs at Duke University (medical ICU, surgical/trauma ICU, and cardiac ICU) and the University of Washington. These centers have a long history of ICU-based research among diverse populations of critically ill persons, and admit 2,500 patients with acute respiratory failure annually. Assuming conservative rates of ICU death (25%), exclusions (50%), and refusal (25%), over 350 patients would be eligible annually. We will enroll approximately 25 patients during months 1-2 for the purpose of evaluating the usability of our computer interface and intervention. We will enroll 90 patients during months 3-15, aiming for at least 50 to complete the entire study protocol (conservative dropout rate ~30%).[15,63] At each proposed study site, patients will be enrolled into the study. Baseline interviews will be completed in-hospital at each site with subjects. Follow up interviews will be completed by telephone by study staff or online via a secure website. Drs. Cox and Hough will be responsible for supervising all local aspects of enrollment, data collection, and data storage.

Screening, enrollment, study subjects: Clinical research coordinators (CRCs) will review electronic records daily to identify all ICU patients receiving mechanical ventilation using our sites' well-established electronic health record-based daily ICU screening protocol. After identifying a potential subject, the CRC will then obtain permission from the primary physician to approach the patient for informed consent after transfer from the ICU to the ward, but before hospital discharge—a practice that markedly increases the likelihood that patients possess the decisional capacity required for informed consent.[70] Our inclusion criteria, informed by our recent studies and Davydow et al's recent work defining the strong association between in-hospital distress and subsequent long-term psychological disability,[15,37,63] target patients at high risk for long-term psychological distress (see below):

5. SELECTION OF SUBJECTS

We will target patients at high risk for psychological distress.

Patient inclusion / eligibility criteria:

- age ≥18 years
- acute cardiorespiratory failure managed in an intensive care unit ≥24 hrs*

Acute cardiorespiratory failure defined as:

Respiratory failure	**≥1 of these:**

	- mechanical ventilation via endotracheal tube for ≥12 hours - non-invasive ventilation (CPAP, BiPAP) for >4 hours in a 24-hour period provided for acute respiratory failure in an ICU (not for obstructive sleep apnea or other stable use) - high flow nasal cannula or optiflow (≥15L/min) or face mask O2 with FiO2 ≥ 0.5 for ≥4 hours
Circulatory failure	**≥1 of these:** - use of vasopressors for shock of any etiology for > 1 hour - use of inotropes for shock of any etiology for > 1 hour - use of aortic balloon pump for cardiogenic shock

*

- reside at home before hospital admission (i.e., not in a facility)

Other issues relevant to the consent process:
- unable to approach patient for logistical reasons (e.g., off ward in test at time of approach, etc)
- patient discharged before consent could be obtained
- patient dies before consent obtained

Patient exclusion / ineligibility criteria (present before consent): Patients will be excluded if they have characteristics that would prohibit adequate participation including:
- pre-existing significant cognitive impairment (e.g., dementia)
- treated for severe or unstable mental illness within 6 months preceding current admission*
- hospital inpatient within 3 months before current admission
- active substance abuse at the time of admission
- lack decisional capacity**
- current significant cognitive impairment (≥3 errors on the Callahan cognitive status screen; see below)
- need for a translator because of poor English fluency [many study instruments are not validated in other languages]
- expected survival <6 months per attending physician
- ICU length of stay >30 days
- lack of either:
  - reliable or sufficient smartphone with cellular data plan or
  - reliable computer online access plus telephone access
- unable to complete study procedures as determined by study staff
- discharge to a location other than a home setting
- complex medical care expected soon after discharge***

*e.g., depression with psychosis, suicidality, schizophrenia (as per medical record)

**We define "decisional capacity" as the ability to participate in effective decision making and provide informed consent. That is, in the judgment of the examiner, the patient—after reading the IRB approved patient consent document (or having it read to them):
--Can generally <u>understand</u> the terms of participation in the study
- the purpose of the study
- what will be required of study participants
- the potential risks, benefits and alternatives of study participation
- pros & cons of study involvement

--Can <u>communicate a choice</u> in his/her own words (or write on a communication board)

***e.g., multiple planned surgeries, transplantation evaluation (including outpatient daily cardiopulmonary rehabilitation), extensive travel needs for hemodialysis, disruptive chemotherapy/XRT regimen, etc.

Patient exclusion criteria present after consent but before randomization: After providing informed consent, patients will become ineligible if any of the following are present:

- they become too ill to participate (or die)
- they exhibit significant cognitive disability
- they exhibit suicidality
- patient was unexpectedly discharged to location other than a home setting and then did not arrive home within 1 month from hospital discharge

Patient suicidal ideation will be monitored by trained study staff (study coordinators, mindfulness instructors) during study interactions (telephone surveys, mindfulness sessions, etc.) and by monitoring the response to the suicidality question (Item 9 in the PHQ-9 survey). Staff suspecting suicidality will alert the PIs and utilize site based resources as described in **Section 10**.

6. SUBJECT RECRUITMENT AND COMPENSATION

Clinical research coordinators (CRCs) will review daily electronic records daily to determine which ICU patients have acute cardiorespiratory failure. After identifying a potential subject, the CRC will then obtain permission from the primary physician to approach the patient for informed consent *after transfer* from the ICU to the ward, but *before* hospital discharge. By delaying consent until transfer, we will reduce subject distress and enhance enrollment efficiency. We aim to enroll 90 patients overall in the clinical trial and ~25 in the pre-trial usability evaluation, approximately 60 of whom will be enrolled from Duke University Medical Center (the remainder will be from the University of Washington).

We will recruit consecutive patients in the study, and will work to ensure adequate representation of all relevant demographic groups. In our past research, we have enrolled a higher percentage of minority subjects than the average population demographics.

Although studies of families of the critically ill are challenging logistically and emotionally, we have enjoyed low refusal rates (<20%) in past studies and have also achieved 90% follow up with telephone interviews with patients over the course of 6 months. Retention will be enhanced by the use of telephone-based follow up interviews augmented by email, our use of short questionnaires to reduce respondent fatigue, and our experience that participants develop a trusting bond with the research team over time.

We will compensate participants for time spent performing study activities. It is expected that the time required for participants will differ based on the arm to which they are randomized; differential group-based payment reflects this reality. Participants in the education group will receive $25 for each post-discharge interview they complete plus $25 for completing both calls (for a possible total of $100). Participants in the standard mindfulness group can receive up to $150 ($25 for each of the 3 post-discharge interviews and $75 for completing all intervention calls). Participants in the self-directed mindfulness group can receive up to $150 ($25 for each of the 3 post-discharge interviews, $50 for completing the initial intervention call and listening to the weekly audio sessions, and $25 for completing weekly online questionnaires).

For the purpose of testing and evaluating the design and usability of the webapp (essentially a web page viewable as an app), will conduct a small sub-study among patients or family members of ICU patients. We expect that only 20-25 total participants will be needed to identify any errors and concerns about problematic usability issues. We will aim to meet with these participants prior to enrolling in the clinical trial. Participants will be chosen randomly by convenience from ICU waiting rooms or in patient rooms after first clarifying with the treating ICU team that it would be appropriate to approach them (e.g., ensuring that there were no conflicts, serious decisions at hand, etc). The purpose of this study

will be to test the usability of the technological components of the treatment arms (webapp & website). We will ask patients/families/friends to review the webapp and website, and then answer a few brief questions about: what they liked/disliked, recommendations for improvement, how satisfied they were with the program, and how easy it was to understand. We will not record PHI, names, or birthdates. While no PHI will be collected, we will record participants' responses on written questionnaire forms which will be stored in a locked cabinet in Dr. Cox's locked office. We expect this entire process will take 15-20 minutes, depending on the amount of feedback the patient/family wishes to provide. The introductory script for this small substudy is provided below under Point 7, "Consent Process." User testing participants will receive a coffee card with a value of $5 for their time.

7. CONSENT PROCESS

If the ICU physician agrees to allow the team to approach the patient, we will meet them in their private ICU room (or ward room) to discuss the study and obtain signed informed consent. We will do so when no other staff or visitors are present and will close the door. An unlimited time (though this generally requires less than 1-2 hours) will be allowed to describe the study and answer all questions. The full informed consent form will be provided and read by the potential subject. Consent forms will be read to those who are blind or unable to read. Potential subjects will be given 48 hours to decide if they wish to be in the study.

Patients will be assessed for decisional capacity by a medically qualified professional who is also a member of the study staff or by the patient's clinical care provider. In general, this includes assessing the ability to communicate a choice, to understand the study information, to understand the pros and cons of the choice about study participation. Operationally, the potential subject should be able to repeat in his/her own words (or write on an ICU communication board) the purpose of the study, what will be required of study participants, and the potential risks, benefits and alternatives of study participation. The potential subject must also pass the Callahan cognitive screen by responding with no more than 2 errors. Further, if the medical team, family, or study staff believe that approaching the patient would likely provoke serious anxiety or distress we will not do so. All reasons for lacking capacity will be recorded and part of the quarterly DSMB review process. If the patient lacks decisional capacity, study staff will check back periodically to reassess capacity.

After informed consent has been obtained from patients), staff will perform a baseline hospital interview to obtain clinical, socio-demographic, and baseline distress information. A copy of the patient consent form will be placed in the patient's chart, a copy given to the patient, and the original kept in the site PI's locked cabinet in their locked office

For the small usability sub-study described above in Point 6, we will not obtain written consent, as there are no major risks involved and no PHI is collected (see "Waiver of Documentation of Consent" Form uploaded to IRB site separately). The following introductory script however will be used to obtain verbal consent:

Hello! I am _____ from Duke University Hospital. We would like to ask for your help in evaluating a web-based application that is designed to give information to patients who have been in the ICU after they leave the hospital. In fact, this is why we are asking you—because you or your loved one has had firsthand experience with critical illness. Before we start using the web-based application in research studies, we need feedback from patients and families to make the program as clear as it possibly can be.

We would like for you to look at the web application ('webapp'), imagining that you are a patient who will be using it to help you feel better. When you are done, we'll ask you just a few questions about what you liked or disliked about the webapp. The entire process should take 15-20 minutes. After that,

we will not need to contact you again unless you'd like to give us more feedback after you've thought about it some more. We want to assure you that we will not collect your name, data of birth, or any other personal information. Your answers to questions will not be linked you, and they will be used only to improve our program and to show others how to design these computer programs better. There will be no direct benefits to you, although we think your feedback will improve the experience of others who participate in research later. There are no physical risks to you, and your confidentiality will be protected since we are not recording any personal information about your health or otherwise, from you or any other family member. Remember, there are no treatments involved with this study and your involvement is purely voluntary. That means that it is OK if you don't want to answer these questions. If you would be willing to answer questions, your consent is implied by your verbal agreement now and your willingness to give your feedback. You will receive a coffee card with a value of $5 for your time spent with this study activity.

Dr. Christopher Cox from Duke is the main researcher evaluating this webapp. He can answer any questions at (919) 358-6451.

8. SUBJECT'S CAPACITY TO GIVE LEGALLY EFFECTIVE CONSENT

Only participants with legal capacity will be allowed to participate. We will use a three-part capacity assessment procedure. Part one: are they comatose or delirious? That is, if they are delirious (CAM-ICU positive), they will be deemed as incapacitated.[54] If they are not delirious (CAM-ICU negative), study staff will then determine that participants have clinical capacity to provide informed consent. Part two: if patient is not comatose or delirious, study staff must feel confident that the patient has clinical capacity to provide consent. That is, in the judgment of the RA, the potential subject—after reading the IRB approved patient consent document—understands the terms of participation in the study. The potential subject should be able to repeat in his/her own words the purpose of the study (or write on a communication board), what will be required of study participants, and the potential risks, benefits and alternatives of study participation. Further, the subject must complete the Callahan cognitive screen with no more than 2 incorrect responses in order to be considered eligible. Part three: It is possible that the medical team or research staff believes that approaching the patient for consent while they are recovering from life support has a high likelihood of causing the patient serious anxiety or distress. If this is the case, we will not approach the patient for consent. For patient with whom we determine to be incapacitated or psychologically unprepared, we will attempt to re-consent them during the hospitalization as study staff are able.

9. STUDY INTERVENTIONS

Study procedures for usability testing

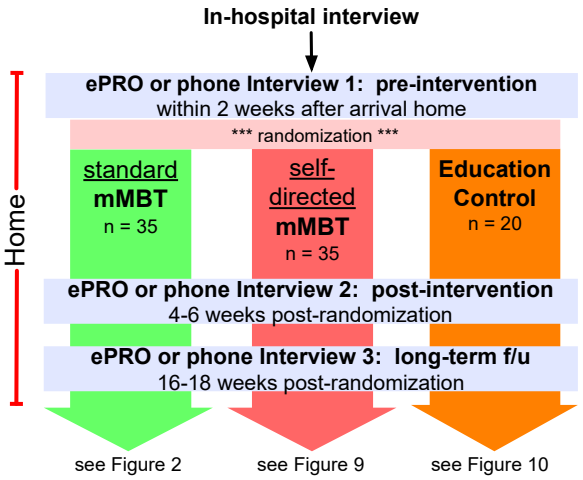
We expect approximately 20-25 participants will be needed to perform adequate usability testing of our website, app, and the intervention itself. After obtaining informed consent, CRCs will observe interactions with the website and app in 'think-aloud' protocols in which users' comments will be recorded in real time. Semi-structured interviews will follow sessions, with usability comments classified as positive, neutral, or negative per Nielsen and Zhang. 'Negative' comments will be categorized into domains and targeted for editing in successive testing cycles. We will use the Systems Usability Scale (SUS), a well-validated industry standard measure with scores ranging from 0 to 100, to measure five critical usability domains: ease of learning, efficiency of use, memorability, error frequency and severity, and subjective satisfaction. We will perform successive testing/revision cycles with repeat user sampling until we observe a mean SUS score >85, representing 'excellent' usability. Based on our past experience, we expect two or three 8-10-user samples to achieve this target—similar to sample sizes needed to reach thematic saturation in qualitative analysis.

Study Procedures for RCT

General aspects of treatment procedures: After obtaining informed consent, the CRC will administer baseline in-hospital questionnaires to each patient, entering data via an encrypted tablet computer

directly into the web-based study electronic clinical research forms that we will manage via RedCap, a password protected, HIPAA-compliant, web-based database system that is built on the RedCap framework, an open-source framework originally designed at Vanderbilt University for clinical research and institutionally supported at Duke. CRCs will track patients thereafter and then perform post-discharge Interview 1 within 2 weeks of arrival to a home setting (and no greater than 1 month from the time of hospital discharge, as dropout escalates thereafter related to persistent medical issues).[15] Such timing also provides higher efficiency compared to an in-hospital approach because of fewer exclusions due to illness acuity and delirium.[84] Next, the study data system will randomize patients into treatment groups in a 1.75:1.75:1 ratio, via the method of minimization to balance the three study aims by the following important prognostic factors: the severity of current psychological distress (Interview 1 PHQ-9 score <15 vs. ≥15; representing a cutoff of 'moderately severe depression symptoms'),[85] severity of current physical symptom distress (Interview 1 PHQ-10 score <10 vs. ≥10; representing a cutoff of 'high somatic severity'), Age (<50 vs. ≥50), ICU service most proximate to enrollment (medical/cardiology vs. trauma/surgical) and study site (**Figure 7**). After randomization and disclosure of group by the CRC, we will mail to participants printed copies of all study materials (e.g., CDs/DVDs of all online content plus instructions on how to access study materials on the study website; each treatment group has a separate password-protected section). Participants will then complete the study interventions, performing makeup sessions as needed. No sessions will be provided during readmissions, though based on our pilot data these are infrequent.[15,63] All sessions must be completed within 6 weeks of randomization. While no specific number of completed sessions is required, we will consider completion rates in analyses. Participants will complete follow up questionnaires as preferred by either telephone (~30 min) or ePRO at post-intervention (Interview 2: 4-6 weeks post-randomization) and long-term follow up (Interview 3: 16-18 weeks post-randomization, or ~3 months post-intervention completion); a short semi-structured interview will conclude Interview 2. As an added feature, after Interview 3 we will allow all participants to access all study features of both arms (education and mindfulness).

Figure 7: Overview of study performed among ICU survivors



Intervention: Mobile Mindfulness-Based Training (mMBT)

- **Therapist-directed mMBT:** mMBT is initiated at the peak incidence of distress—early post-discharge—to maximally attenuate the overall trajectory of distress.[1,20,22,28] mMBT includes 4 weekly telephone sessions, a dose that should be adequate based on our clinical experience and recent piloting.[15] Each ~30-minute mMBT session is composed of four parts: (1) brief discussion about participants' major current stressor(s); (2) rationale and discussion of the didactic focus; (3) practice and review, and (4) discussion about participant's use of mindfulness skills, challenges in applying the skills, and how to maintain progress. As shown in **Figure 4**, the didactic elements of mMBT include: In ***Session 1***, subjects will be provided with a rationale for mindfulness and learn to use awareness of breathing, a core meditation technique that begins to cultivate skills of mindful, non-reactive observation. ***Session 2*** will introduce awareness of body systems that are working well or less well as a way to continue to cultivate skills of observing, describing, and non-judgmental attention.

Figure 4: Distress Targets—and mMBT Session Topics That Could Address These Targets

Distress Targets for ICU Survivors see "Step 2"	**mMBT Session Topics** for Distress Targets see "Step 3"
- Day to day impact of critical illness - Critical illness defines sense of self - Inability to cope - Relationship strain-related stress - Pervasive traumatic memories - Physial and emotional symptoms	1. Awareness of breathing 2. Awareness of body 3. Awareness of emotion *and* Mindful acceptance 4. Awareness of sound

During ***Session 3***, participants will practice awareness of emotion and mindful acceptance, which is designed to acknowledge difficult emotions and cultivate feelings of kindness and compassion towards oneself and others. ***Session 4*** introduces awareness of sound, a practice in which patients will learn to systematically broaden awareness of senses of sound in the context of improving sleeping problems—a common occurrence for ICU survivors. Sensory awareness practice simultaneously builds the skills of attention, concentration, observation, non-judgment, and non-reactivity. Overall, this MBT plan is a blueprint for therapy that can be adapted in the moment to address stress or crises experienced by participants. mMBT recipients will not view the education control content during the time between consent and Interview 3.

- **Self-directed mMBT:** A self-directed mMBT intervention will be the second trial arm. Self-directed mMBT has a goal of focusing therapist time on highly symptomatic or poorly responding patients. Self-directed mMBT (delivered via a web or app version as preferred) will contain all the features of therapist-directed mMBT, with the added features shown in ***Figure 9***. There will also be an introductory video plus an added audio file that addresses maintaining practice. There is an added inclusion of web access or smartphone availability (our past research indicates that <10% would be excluded by this criterion). Also, participants will view a short mMBT video in the hospital that familiarizes them with the study procedures (e.g., they will know to expect a weekly text or email reminder with a link to the relevant web-based information starting within 1 week of arrival home) and provides an introduction and rationale. After CRCs verify that the patient has arrived home, the patient will begin the mMBT program guided by written handouts, the study website, and a brief review by the CRC. Patients will complete the PHQ-9 and GAD-7 weekly survey via a secure password-protected ePRO system after text or email prompting from Redcap.

Figure 9: Added features of **self-directed mMBT** compared to therapist-directed mMBT

Delivery	Telephone calls **if requested** or if suicidal ideation noted on ePROs*
Content	also includes **app version**
Features	ePRO system automates **targeted therapy** based on self-report **patient dashboard** for progress tracking

*ePRO = electronic patient reported outcomes

After an initial introductory call, study staff will manage participant contact using a specific protocol:

1. At the conclusion of each weekly survey or at a timed 1-week interval from randomization, the web app will display a 3-item display with the following responses (see **Figure** opposite): I have technical questions, I need information about the study, and I need help applying the Lift program (mindfulness program). A decision logic interface will then allow the participant to further specify the problem and request a contact. A popup will arise in response to specific questions directing the user to information within the app. For example, a question about 'physical symptoms' will display a popup with a link to the module on this topic. The therapist will contact the participant only if the participant (a) notes physical or emotional symptoms and (b) they request a contact. The therapist will be able to note the weekly PHQ-9 and GAD-7 scores as either 'elevated' or 'not elevated' before they call. We will define 'elevated' symptoms as PHQ-9 score ≥15 or GAD-7 score ≥15 (standard cutoffs for clinically notable distress).

Questions for the study team? Click below to let us know.
☐ **I have technical questions** (app, website, weekly survey, etc)
☐ **I need information about study** (what does study involve, how long does it last, etc)
☐ **I need help applying the Lift program** (for physical symptoms **or** for depression, anxiety, PTSD)

My preferred method of contact is:
☐ phone
☐ email
☐ text

2. If PHQ-9 suicidality item is endorsed on either the weekly survey OR at Interview 1, 2, or 3, the site PI or therapist (a PhD-level clinical psychologist) will call participant.
3. If participant fails to log into the web app within 2 weeks of randomization and each 1 week period thereafter.
4. If participant fails to complete weekly survey within a week of its due date.

We have piloted our ePRO system in an ongoing coping skills RCT as a safety tool (not to direct therapy) and found it to be safe, reliable, and consistent with current recommendations.[74] However, no patient ever needed professional psychiatric support based on questionnaire trigger points (see also Human Subjects for more details). This recent experience suggests that ~15% required calls. By allowing collaboration of CRCs and therapists, as well as the assistance of the app itself, self-directed mMBT has potential to greatly enhance the feasibility of large-scale mind-body intervention trials—a paradigm shift in therapy delivery.

5. We will run a RedCAP-based report weekly that will examine participant use of the web app. Participants will be highlighted who are 'app non-users,' defined as those who do not access the web app's weekly audio file at all. We will send an email or text message (with no PHI, name, identifiers) to the participant (as per their stated preference at Interview 1) with a link to a static web app page. Participants will be expecting such messaging, as the therapist will remind them of this system. On this page, a brief message will be displayed reminding the participant about the study purpose, the timeline, and study tasks. There will be a link for the participant to then securely log in to the app. The information displayed on this 'message' web page will be identical to that displayed elsewhere in the web app. No PHI, names, etc will be displayed.

6. Before making any scheduled or requested telephone call, the therapist will review the participant's RedCAP dashboard that displays their most recent PHQ-9, GAD-7, and physical symptom scores from their weekly survey, as well as their 'active app user' vs. 'app non-user' status. This information will be used to better personalize the experience. The other study staff (with the exception of the study manager) will not be able to access this function.

Control: Education Program: The goal of the control condition, developed and piloted by our group, is to provide subjects with educational information about the nature and treatment of critical illness, but none of the mindfulness training provided to mMBT recipients (***Figure 10***). Control subjects will receive 2 brief, check-in phone calls along with access to educational material. The calls will be targeted 1 week and 3 weeks after randomization to allow time for subjects to receive and review the materials. This scripted conventional educational program has a presentation and discussion format similar to our group's past multi-session protocols (e.g., PCORI PFA 195).[62,86] Participants have rated the credibility of this education protocol highly in focus groups. At the time of randomization, we will give education group patients access to an education website we developed with identical capabilities as the mMBT website, allowing viewing of education handouts and videos we developed. Hard copies of materials will be mailed also. mMBT recipients will not be able to view the education program until after completing Interview 3.

Figure 10: Topics for Education Program Sessions

1. Acute respiratory failure: causes and diagnosis	4. Exercise and critical illness
2. Hospital & post-discharge treatments	5. Internet resources for ICU survivors
3. Neuromuscular weakness	6. Nutrition and critical illness

Role and training of the CRCs: The role of CRCs is to enroll subjects, abstract medical charts, participate in randomization, perform in-hospital and telephone interviews for site-enrolled participants. Also, CRCs will provide the education control intervention for their own site's subjects, a design that will not bias post-discharge questionnaire responses. Drs. Cox and Hough will train CRCs in acute respiratory failure definitions and outcomes, review the education control treatment manual, explain the study web-based data entry and management system (Redcap), and address other topics at an initial 2-day teleconference. Training will be reinforced by biweekly investigator-CRC conference calls and weekly site PI-CRC meetings.

Role and training of the interventionists: The mMBT interventionists, Tina Gremore, PhD and Julie Kosey PhD (both clinical psychologists), has experience in providing MBT and coping skills training for medical populations including ICU survivors. Drs. Porter and Greeson will supervise their training, including review of the treatment manual and roleplay of common scenarios. The CRCs (Brenda

Walton and Anna Ungar), who have experience interviewing ICU survivors, will be the education control interventionists. Drs. Cox and Hough will train them in the use of the education materials. Telephone sessions for all groups will be scheduled either directly by interventionists or by patients using a password-protected, HIPAA-compliant scheduling system (via the study website) and a randomly generated ID code. Interventionist strain is a potential concern, though our pilot work supports the adequacy of the budgeted effort.[15]

Uniformity of treatment and oversight of study staff: As in our previous investigations, we will take steps to ensure that the treatment protocols are uniform and followed consistently throughout the project and across sites: detailed interventionist training, use of treatment manuals, and audio recording of sessions for supervision.[62,66,87] We will develop protocol adherence criteria for each digitally recorded session, with satisfactory adherence defined as 90% or more of the maximum score on the adherence rating scale. Drs. Greeson, Cox, and Porter will rate sessions for adherence prior to the weekly interventionist supervision meetings, thus providing immediate, ongoing feedback. As a safety measure, we will train all staff to immediately refer subjects with any concerning level of emotional distress to a psychiatric expert (using our tested Distress Management System described in Human Subjects) and those with concerning physical symptoms or perceived cognitive decline to their primary physicians after consultation with the site PI.

Recruitment and retention: Although ICU studies are challenging because of patients' residual disability, we have enjoyed low refusal rates (<20%) in our past studies and also achieved 100% follow up with telephone interviews performed over the course of 12 months.[12, 51] Our use of short telephone-based follow up interviews should sustain our success in participant retention and reduce respondent fatigue. In our experience, subjects develop a sense of trust with study staff that enhances retention.

10. RISK/BENEFIT ASSESSMENT

Potential risks: Participants may experience some degree of stress due to the critical illness itself, and it is possible that they could experience anxiety when answering survey questions. In our previous studies using similar self-report batteries (and the mMBT itself), we have encountered little resultant distress. In fact, many participants have reported that they were relieved to be able to discuss such issues. Further, our pilot data demonstrate that mMBT reduces distress. We will, however, continue to utilize interviewers who have been trained to be sensitive to the nature of these issues and who have experience interacting with seriously ill patients and their families. When necessary, subjects who experience psychological distress related to filling out self- report questionnaires will be referred for appropriate psychiatric or psychological care as described below. Each site will have a protocol in place to refer subjects to counseling services appropriate to each setting if significant emotional distress is encountered. These protocols will serve as safety precautions for study participants, though we have not observed significant emotional distress among subjects during our pre-testing of the mMBT program or in previous questionnaire-based studies of similar populations. Finally, there is a theoretical risk of loss of confidentiality of data given known limitations of data systems and human inputs. However, our group has never experienced such issues in the past. Further, we have designed electronic data systems to include the highest level of security possible. Nonetheless, we describe our approach to this potential issue below.

Adequacy of protection against risks

Recruitment and informed consent procedures: First, each research site's Institutional Review Board will review and approve the study protocol before study initiation (as they did for the recent piloting of mMBT). Written informed consent will be required from patients for this study. Second, we will use a standardized screening and enrollment protocol that respects participant privacy and rights. CRCs will first ask each patient's primary ICU physician for permission to approach the patient. If permission is granted, research coordinators will ask the patient in person to read and sign the study consent form at the time of enrollment (day of transfer from intensive care unit to hospital ward). Patients will have up

to 72 hours to consider enrollment, as per Duke policy. We will take great care to present the study group assignment possibilities ("like drawing a number out of a hat") tactfully and with equipoise, noting that assignment to either group is in itself likely an improvement over usual care. A copy of the consent form will be placed in the patient's medical record, a copy given to the patient, and the original kept in the site PI's locked cabinet in their locked office (later delivered by courier to Dr. Cox). A brief electronic health record note will be entered as well, noting enrollment in the study and providing a contact number for the site PI. For patients who lack decisional capacity initially, we will return for a subsequent attempt at consent approximately every 2 days as we do for other ICU-based studies. Our consent procedure is described in detail in the ***Research Plan***.

Protections against risks:

General oversight

There are several ongoing mechanisms for monitoring the occurrence of adverse events. Each Site PI will oversee day-to-day monitoring of the study activities. The Study PI, Dr. Cox, will oversee all study activities at all sites as well. Dr. Cox has demonstrated in past research 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 provided to participants upon entry into the study to report concerns related to study participation, weekly meetings between the CRCs and site investigators to discuss study progress and any adverse events, and direct supervision of the study by the PI.

Specific longitudinal participant oversight plans—interventionists, CRCs, and the data system

Although this study does not meet criteria for a biomedical intervention, we recognize that there is a slight risk that some patients may become distressed when discussing issues in the treatment sessions, as mentioned above. We will take the following measures to prevent negative reactions as well as deal with any that do occur:

(1) All of the intervention sessions will be conducted by highly trained professionals who have experience with patients with serious medical illness and are sensitive to the issues that arise during mMBT or education sessions (e.g., Dr. Cox's ongoing studies).

(2) The interventionists and CRCs will emphasize to subjects that the sessions are patient-controlled. Thus, patients will be instructed that they are in control over what they share and generally how long they discuss any topic that is addressed.

(3) Patients will be told that they can discontinue the discussion at any time and that they are also free to discontinue the session at any time.

(4) The study staff, including the trained CRCs providing the education condition telephone sessions, will monitor participants closely during interviews and will refer those with any concerning level of emotional distress and/or relationship distress to psychiatric evaluation/support at the study site nearest the participant based on previous arrangement by each site PI. This is a successful protocol that is currently in place in Dr. Cox's ongoing studies.

Duke

Call emergency psychiatry at [redacted] or [redacted]. Or call [redacted] ([redacted]) [redacted], who directs these services and can provide weekend or afterhours support.

University of Washington

[redacted]. ([redacted]) [redacted]-[redacted] or the 24 hour crisis line: [redacted], or [redacted].

All sites as a backup

The National Suicide Prevention Lifeline - 1-800-273-TALK (8255) is a free, 24-hour hotline available to anyone in suicidal crisis or emotional distress.

(5) As an additional safety measure, we will electronically monitor RedCAP daily for a positive response to the PHQ-9's suicidality assessment item. CRCs performing interviews will also flag this. Any positive response to this item will result in a call, text message, or email from the site PI. In the past we have used automated depression, PTSD, and anxiety scale scores to appreciate 'alert values.' Of the approximately 15% of patients who we called in a similar past psychobehavioral study, none required referral to an outside psychiatric professional and none endorsed suicidality. Additionally, there are no validated cutpoints of these questionnaires that reliably can be used to direct care. We are very sensitive to the common and pervasive nature of psychological distress among ICU survivors and our study staff are experienced in discussing these issues with patients.

(6) Finally, interventionists and CRCs will be trained to monitor participants closely and discuss with them a possible referral to their primary physician if the staff perceives a significant decline in cognitive or physical function. Generally, these are clinical judgments that the experienced CRCs are well prepared to make. Some may be mentioned by participants themselves and referred to the site PI to navigate, as in our other studies. All such referrals will be discussed with the main PI and a resolution (and follow up) documented in the 'contact log' section of the study data system. The PI will review the recorded session to better target follow up triage to the appropriate physician. In our past studies such referral needs have been uncommon. More common has been specific requests for assistance requiring timely referral (e.g., a likely infected catheter), which we have worked quickly with participants and patients to facilitate without incident.

As mentioned before, we recognize that there is a slight risk that some patients may become distressed when completing self-report measures. In our previous studies using similar self-report batteries, we have encountered little resultant distress. In fact, many participants have reported that they were relieved to be able to discuss such issues. We will, however, continue to utilize interviewers who have been trained to be sensitive to the nature of these issues. When necessary, participants who experience psychological distress related to completing questionnaires will be referred for appropriate psychiatric or psychological care. For those completing ePRO questionnaires, contact numbers for our staff are provided on each page—including the PI's mobile phone number available 24 hours a day.

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 database subsystem patient names and medical record numbers. Further, names, birthdates, telephone numbers, addresses, and medical record numbers are only viewable by the head Duke CRC after entry of multiple passwords. The master list of study ID linkage to this personal data will be deleted after study completion. Screening logs will be kept in a password protected folder on a secure Duke server. Similarly, electronic audio-recordings will be labeled with a study ID number linked to a master list of names kept in a secure, password protected file on a secure Duke server. All personal identifiers will be removed from the audio-recordings at the time of transcription. All audio-recordings will be stored securely on a password protected computer file on a secure Duke server. The audio-recordings will be destroyed at the completion of the study. All printed data (interviews completed by paper and consent forms) will be kept in locked, private storage cabinets in the site PI's office.

Potential benefits of the proposed research to human subjects and others

Although the proposed project is an exploratory pilot study, it involves a randomized design with a control condition. The mMBT intervention may reduce psychological distress. This could in fact hold great promise for helping many others in similar situations in the future. However, this is not certain. Additionally, subjects in the education control condition may experience similar or even greater benefits to those described for mMBT. Then again, they may receive no particular benefit. These facts will be stated clearly in informed consent documents. Nonetheless, study involvement puts subjects at low

risk for any adverse physical or psychological risk. Therefore, the potential benefits justify the minimal risk to those enrolled in the proposed study.

Importance of knowledge to be gained
To our knowledge, this is the first study proposed to address the psychological distress of both ICU survivors using a telephone-based or mobile platform-based behavioral intervention. These persons face enormous but common disability as a result of critical illness and its sequelae. Therefore, the implications of this research, designed to mitigate this stress and suffering, are significant for the approximately one million such patients and their families treated each year in the US. We hypothesize that our intervention could greatly improve participants' well being in the future, and we therefore believe that important knowledge could come of this proposed study. Overall, we believe that the potential risks are reasonable in comparison to the potential important knowledge to be gained.

11. COSTS TO THE SUBJECT
None.

12. DATA ANALYSIS & STATISTICAL CONSIDERATIONS
Measures and Data Collection. We will gather data from charts and interviews with patients identical in content for both treatment groups with the timing shown in **Figure 7**. All patients will complete the measures shown in **Table 1** (**see also Appendix Figure 1**). We chose measures based on psychometric properties (validity, responsiveness, reliability), population relevance, performance in pilot studies, and brevity. We have used all measures in past and pilot research. We expect the total questionnaire burden to be approximately 30 minutes per interview.

Primary outcomes: feasibility, acceptability, usability
Feasibility will be measured as by comparison of observed frequencies to pragmatic benchmarks of enrollment (percent of patients who provide consent among all who either consent or refuse; target 70%) and randomization success (60% of those who provide informed consent), post-randomization dropout at the time of Interview 2 (20% target among those who are alive and did not drop out), completeness of responses to telephone interviews (75% target among those neither dropped out nor died), completeness of weekly surveys among self-directed MBT participants (60% target among those who did not die), and participant session attendance (75% target among those who neither dropped out nor died). We will record the rate of post-enrollment exclusions, noting dropout due to cognitive disability—a factor we expect to be uncommon given our pilot-driven protocol changes.[15] We will note our success in retaining patients who were discharged to a post-acute care facility before arrival home, as we have done previously.[20]

Acceptability will be measured with the Client Satisfaction Questionnaire (CSQ), which assesses credibility as well as perceived effectiveness of/satisfaction with services (target mean >15),[88] and with a 100-point visual analog satisfaction scale (target rating 80%). Open-ended feedback will also be incorporated in our assessments.

Usability testing of the web interface and intervention components will be guided by Usability.gov recommendations, comparing to benchmarks (>90%) such as speed (<2 minutes to find session), search accuracy (<2 false clicks), success in accessing the relevant information (yes/no), and with the well-validated 10-item System Usability Scale (SUS).[72] Website use and video/audio views will be quantified with URL and video/audio "hit numbers." We will also conduct a semi-structured interview at the end of Interview 2, using open-ended probe questions to assess feelings about acceptability, usefulness, and application of both programs. Responses will be digitally recorded, transcribed, and analyzed.

Table 1: Study outcomes measures and timing

Outcomes for all study aims	Timing
Feasibility: Enrollment, randomization, retention, adherence to telephone sessions	Interview 1, 2, 3
Acceptability and **usability:** Client Satisfaction Questionnaire,[88] Systems Usability Scale,[72] semi-structured open-ended exit interview	Interview 2
Depression and **anxiety symptoms:** PHQ-9 and GAD-7 [a]	Interview 1, 2, 3
Post-traumatic stress disorder symptoms: The Post-Traumatic Stress Scale (PTSS)	Interview 1, 2, 3
Physical symptoms: The PHQ-10	Interview 1, 2, 3
Mindfulness Measures (Mechanistic Factors)	
Mindfulness: Cognitive and Affective Mindfulness Scale- Revised	Interview 1, 2, 3
Mindful coping: Brief COPE avoidance domain	
Sociodemographic and Clinical Variables	
Sociodemographics: Age, gender, race/ethnicity, employment, insurance, education level, marital status	Hospital
Clinical characteristics at enrollment: prior functional status,[89, 90] comorbidities,[91] psychiatric medication use, illness severity,[92] ICU delirium (CAM-ICU),[93] Callahan cognitive screen,[82] diagnosis, duration of ventilation, ICU & hospital LOS, disposition.	Hospital
Post-discharge factors: quality of life (Global health scale),[94] functional status, use of psychiatric medications, cognitive function (TICSm),[95] frequency of mindfulness skills use, social support,[35] hospitalizations/clinic visits/days at home, daily caregiving requirement	Interview 1, 2, 3
Electronic patient-reported outcomes: PHQ-9, GAD-7, PTSS, numerical quality of life visual scale[96]	Interview 1, 2, 3
Objective physical measures: functional status,[89, 90] key physical symptoms[97]	Interview 1, 2, 3

[a] *also in hospital*

Secondary outcomes

Psychological distress symptoms will be measured using the PHQ-9 depression scale, the GAD-7 anxiety scale, and the PTSS PTSD scale. The PHQ-9 is a 9-item scale with scores ranging from 0 to 27. Symptom interpretations are as follows: 5 or less 'normal,' 6-10 'mild,' 11-15 'moderate,' 16-20 'moderately severe,' and >20 'severe.' The GAD-7 is a 7-item scale with scores ranging from 0 to 21. Symptom interpretations are as follows: 5 or less 'normal,' 6-10 'mild,' 11-15 'moderate,' 16-21 'severe.' The PTSS is a 10-item PTSD scale (score range 10-70; >35 likely PTSD) used frequently among ICU survivors that assesses ICU-related traumas by anchoring memory recall to hospitalization.[101] The PTSS has excellent internal consistency and reliability, evidence of concurrent validity, good responsiveness in RCTs, is highly specific and sensitive compared to DSM-IV PTSD criteria among ICU survivors.[102-104] We successfully tested both scales in our IRB-approved, web-based ePRO system.

Physical symptoms will be assessed using an adapted version of the PHQ-15 symptom scale that has 10 items (and is thus termed the PHQ-10 for clarity). We will measure generalized stress with the 4-item Perceived Stress Scale (PSS-4).

Mindfulness and mindful coping measures

We will measure mindfulness qualities using two primary questionnaires. First, the Cognitive and Affective Mindfulness Scale-Revised (CAMS-R) is a 12-item scale that assesses awareness, attention, and reactions. We will measure mindful coping using the avoidance domain of the Brief COPE,[109] a scale that has excellent psychometric properties [108] and high correlations with distress in ICU populations.[15,63]

Statistical analysis & power considerations

We will use a mixed methods approach to address key knowledge gaps and subsequently use the results to refine the mMBT program in an iterative, consensus-driven revision process as done

previously.[15,63,73] Descriptive statistics, including graphical displays, will be used to summarize all study variables. We will examine both the distributional properties (e.g., ceiling and floor effects) of the continuous outcome variables and the stratification variables to determine the appropriateness of our a priori cutoffs. We will construct individual and mean trajectory plots of the outcome variables to understand their general longitudinal trends as well as their variability and correlation structure. In these analyses, we will focus on 95% confidence intervals (CIs) to contextualize point estimates of treatment groups given the potential imprecision of these pilot data.

Aim 1: To test the **feasibility**, **acceptability**, and **usability** of both a telephone-delivered, mobile mindfulness-based training (mMBT) intervention for distressed ICU survivors as well as a self-directed mMBT intervention.

Feasibility will be examined by calculating overall rates of eligibility and enrollment. Rates of attrition, adherence to telephone sessions, and interview completion will be compared by treatment group using tests for differences in proportions, means, or medians as appropriate. Clinical and personal characteristics associated with feasibility will be explored as well via contingency tables and regression analyses. ***Acceptability*** and ***usability*** will be evaluated similarly, using between-treatment group differences in quantitative measures of perceived satisfaction (CSQ) and usability (SUS). Feasibility and acceptability will be the key outcomes of focus in comparing mMBT and self-directed mMBT. Also, we will use qualitative analysis to understand participants' attitudes about the intervention, perceived effectiveness (or lack of it), and application to their daily lives in their own words. We will use a grounded theory approach to develop a systematic open coding scheme.[110] Starting with the first five participants, the investigators will independently identify major emerging themes related to intervention attitudes from de-identified transcriptions. Axial coding, the process of relating codes to themes using both inductive and deductive thinking, will be used to achieve a more robust coding table.[111] Codes may evolve based on further experience with these data and will be finalized only after reaching investigator consensus. We will use MAXQDA in coding and data management. Dr. Cox has experience in qualitative analysis.[1]

Aim 2: To provide a plausible range of psychological distress estimates for each treatment group (mMBT, self-directed mMBT, and control) at both post-intervention and long-term follow up.

Psychological distress (PHQ-9, GAD-7, and PTSS scores) will be measured at times 1, 2, and 3. A general linear model will be used to estimate mean changes and corresponding 95% CIs in psychological distress between mMBT and control as well as for self-directed mMBT and control over the 3 months of post-intervention follow up using SAS PROC MIXED (SAS Institute, Cary NC). We will fit the models with an unstructured covariance matrix to better understand and represent the correlation between patients' repeated measures. We will also use similar modeling strategies to explore how the key clinical (e.g., history of ICU delirium, illness severity, diagnosis grouping), objective physical (e.g. functional status), sociodemographic, and mechanistic (e.g. mindfulness qualities) factors are associated with changes in psychological distress, both within and between treatment groups.[5,26,28,68,101,112,113] This part of the analysis aims to refine inclusion/exclusion criteria for a future study.

Sample size considerations. This exploratory pilot study is not intended to test mMBT's efficacy. While the sample size chosen must reflect the pragmatics of recruitment during a short enrollment period, we will have adequate sample size to provide meaningful CIs for our estimates.[54,114-116] Additionally, because our primary aim focuses on feasibility and acceptability comparisons between mMBT and self-directed mMBT, we plan to enroll more patients in these two groups (1.75:1.75:1 allocation ratio). Previous work has consistently shown that the standard deviation of PHQ-9 scores in this population is ~9.0 and the minimal clinically important difference is 5 units.[6,63,85] With 20-35 patients per treatment group, we will be able to estimate CIs for the PHQ-9 with 6.0-7.6 points of

prevision (the total width of the CI); note that a minimal clinically important difference is generally considered to be ~3 points.[117,118] For the PTSS, a common standard deviation is 14.0.[15,63] We will be able to estimate 95% CIs with a precision of 4.8-6.0—a width smaller than standard change scores seen among ICU survivors.[15,63] PASS software was used for precision estimates (NCSS, Kaysville UT).

DATA & SAFETY MONITORING

Plans for assurance of compliance regarding adverse event reporting. All study sites require investigators to report adverse events to the Institutional Review Board (IRB) on both a per case and an annual basis. Additionally, every research project conducted at each study site is required to have a yearly Departmental and IRB review. Also, all adverse events are reported as part of the progress reports in the non-competitive and competitive renewals. Dr. Cox 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 this study at all times but will be in close and frequent contact with other investigators, including the University of Washington site PI (Dr. Hough). Dr. Cox and Dr. Olsen, the study biostatistician and Dr. Cox's current collaborator, will be the chief data managers and will adhere to established federal and institutional patient safety and protection guidelines. To assure data accuracy, Drs. Cox and Olsen will review the computer data files on a monthly basis. Additionally, CRC staff will process the RedCap database biweekly to search for errors and generate basic reports for dissemination at regular meetings. Protocol compliance will be reviewed during weekly meetings between site clinical research coordinators and Dr. Cox as well as bi-weekly meetings (more frequent if required) between Drs. Cox, Hough, Porter, and Greeson. Also, Drs. Porter and Greeson will closely review protocol adherence with the psychologist interventionists regularly as described in the Research Strategy above.

Data safety monitoring board (DSMB). Although this is an exploratory pilot study, it will be supervised by a single independent central DSMB due to its interventional nature. Dr. Cox has successfully developed 2 independent DSMBs for his recent multicenter RCTs (NIH and PCORI). The DSMB will include professionals with significant experience in clinical trials, mind-body interventions, and biostatistics who are not directly involved in the study, its interpretation, or any study institution. [redacted] will serve as the DSMB chair, with other members including [redacted], [redacted], and [redacted]. [redacted] has served on other DSMBs and has experience in conducting clinical trials among the critically ill and their families. The main responsibilities of the DSMB will be to (a) assess for the presence of potential harms and unintended consequences of the intervention, (b) ensure the validity and integrity of the data, and (c) make recommendations 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, and establishing the review methodology and procedures. The first DSMB data review will then occur either after the first 10 patients (5 per treatment group) have been enrolled or enrollment has occurred for 3 months, whichever is observed first. Thereafter, the DSMB will review cleaned data pulled from the RedCap database system every six months during enrollment and will prepare a report with any recommendations within the following month. While this is an intensive DSMB engagement schedule, the short enrollment period will demand greater oversight.

The specific study functions and outcomes that the DSMB will review at each meeting include: dropout rate, randomization rate, PHQ-9, GAD-7, and Post-Traumatic Stress Scale (PTSS) scores. The primary safety measures will be Adverse Events reports and post-intervention PHQ-9 scores. Other

items reviewed by the DSMB at each meeting will include: (a) data quality, completeness, and timeliness; (b) performance of the Duke and University of Washington centers; (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.

During the review process, formal statistical tests for examining the differences in Adverse Event or outcome rates between study groups may be performed under DSMB supervision if requested. However, this is unlikely given the exploratory pilot study design. For differences in study dropout rates, appropriate changes to the protocol will be made by investigator consensus after DSMB member input. Additionally, the DSMB may request a formal statistical assessment if a suspicious increase in PHQ-9 score is observed in either group. If the intervention group is found to have either a statistically significant increase in PHQ-9 score, the DSMB scope of action will include recommendation for cessation of the trial. Dr. Olsen, the biostatistician, will oversee any DSMB statistical requests and interpretations. Any protocol changes, as well as any adverse events, will also be reported to the Institutional Review Boards of all study sites, as well as to the NIH.

13. PRIVACY, DATA STORAGE & CONFIDENTIALITY

We have a number of strategies to ensure the quality of the data. RedCap will be the unique web-based data collection and recording system that will be used for the proposed study. RedCap is a web-based application built to support clinical research studies at universities across the United States. RedCap gives us the capability to set up a shared workspace for the study to collect data, as well as managing its participants and study activities. RedCap has been implemented successfully in multi-site studies across the United States and is institutionally supported by Duke. RedCap can “force” responses to most questionnaire items before allowing progression through the particular interview’s template, thereby avoiding problems with missing data. After enrollment of the first 10 participants at each site, the study investigators will examine electronic summary CRFs to ensure adequacy and accuracy of data collection. Agreement between centers will be reviewed and discrepancies will be discussed.

During the analysis phase, experienced RedCap support staff at Duke work with the project staff to shape the application design. For example, during this phase, the typical study participant's timeline is worked out. After frequent incremental meetings to review system design, the system is customized to the study needs and design. A benefit to the current proposed study is that RedCap staff can easily revise platforms built for previous studies with similar database and data collection needs. This reduces overall programming costs significantly.

Tablet computers (iPads) will be used by study staff to input and manage data in the RedCap system. All tablet computers used are password protected and encrypted.

Reports that are needed on a day to day study management basis are built into the system as real-time tables, graphs, or data downloads. The study staff can log in to the study website at any time and download current study data for analysis. RedCap will also allow timely data preparation for DSMB review, as well.

Confidentiality will be safeguarded by a number of strategies. Subjects will not be identified on any study reports. We will keep all paper study materials (i.e. consents, paper interviews, etc.) including participant names, contact information, and personal identifiers linked to study IDs in a locked filing cabinet in the site PI’s office. Screening logs will be kept in a password protected folder on a secure Duke server. Duke firewalls, multiple passwords, and encryption programs protect the security of the electronic data entry system.

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