Protocol
Optimizing a Mobile Mindfulness Intervention for ICU Survivors (LIFT2)
NCT04038567
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Study Title: Optimizing a self-directed mobile mindfulness intervention for improving cardiorespiratory failure survivors' psychological distress

Short Title: LIFT2

Study Design: A multi-phase optimization strategy (MOST) Framework

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Abbreviations and Definitions

- Activities of Daily Living (ADLs)
  - An assessment designed to assess one's ability to complete basic self-care skills.
- Adverse Event (AE)
  - Any untoward medical occurrence associated with or observed in the context of a study procedure. For this study and patient population, an AE will be considered any suicidal ideation. No other events will be considered AEs as this patient population is ill and it is expected that other untoward medical occurrences will occur.
- Clinical Trial Management System (CTMS)
  - For this study, a CTMS known as OnCore will be utilized to manage the study's administrative responsibilities and subject level documentation.
- Duke Regional Hospital (DRH)
  - Study site in which eligible patients will be enrolled.
- Duke University Hospital (DUH)
  - Study site in which eligible patients will be enrolled.
- Oregon Health & Science University (OHSU)
  - Study site in which eligible patients will be enrolled.
- University of Colorado-Denver (COL)
  - Study site in which eligible patients will be enrolled.
- University of Washington-Seattle (UW)
  - Study site in which eligible patients will be enrolled.
- Electronic Data Capture (EDC)
  - For this study, the EDC will be supported and secured by Duke University via REDCap in which relevant study data, such as screening, enrollment, and clinical variables both from research participants' medical records and app will be documented.
- Electronic Health Record (EHR)
  - Used interchangeably with EMR; the EHR is the patient-specific medical record located in the secure MaestroCare (aka: EPIC) or other electronic medical record platform.
- Electronic Medical Record (EMR)
  - Used interchangeably with EHR; the EMR is the patient-specific medical record located in the secure MaestroCare (aka: EPIC) or other electronic medical record platform.
- Electronic Patient Reported Outcomes (ePRO)
  - ePRO can be used to describe study source, such as the patient-completed questionnaires (e.g.,PHQ-9, GAD-7, PTSS, PHQ-10), or can refer to the system that houses patient-derived data. For this study, ePRO may refer to the patient-questionnaires for psychological distress OR it may refer to the system, which houses the patient-derived data, which is the mMT app known as "LIFT."
- General Anxiety Disorder (GAD-7)
  - An assessment designed to assess anxiety and depression symptoms
- Institutional Review Board (IRB)
  - Ethical and regulatory committee who provides approval and oversight of clinical trial at study site.
- Instrumental Activities of Daily Living (IADL)
  - An assessment designed to assess one's ability to complete complex self-care skills.
- Intensive Care Unit (ICU)
  - Defined as any medical, surgical, trauma, neurological, cardiac, or cardio-thoracic unit in which a patient is receiving cardiac or respiratory support for survival means.
- Mindful Attention Awareness Scale (MAAS)

    - 15-item scale designed to assess a core characteristic of mindfulness.
- Mobile Mindfulness Training app (mMT, also known as 'LIFT')
    - A native mobile app that uses a self-contained program and is subject to the device operating system. The mMT created for this study known as "LIFT", was developed, and is maintained by Pattern Health (212 W Main St Suite 213, Durham, NC 27701).
- Patient Health Questionnaire-9 and Patient Health Questionnaire-10 (PHQ-9 and PHQ-10)
    - Physical and emotional symptoms assessment, including suicidal ideations with intent to act.
- Post-Traumatic Stress Scale survey (PTSS)
    - Scale designed to assess Post Traumatic Stress Disorder (PTSD) symptoms
- Protocol Deviation (PD)
    - An inadvertent event or event this is out of the control of the study team and/or the subject that occurs outside of the study protocol design and/or procedures.
- Protocol Violation
    - An act of intentionality that is committed by the study team and/or the subject that occurs outside of the study protocol design and/or procedures.
- Serious Adverse Event (SAE)
    - Defined as an adverse event that is both serious and expected in nature; the event may have a reasonable possibility that it is related to a study. SAEs for this study are defined as a suicide attempt, a hospitalization, or death.
- Suicide Ideation (SI)
    - The idea of committing self-harm and/or the intent to act on the idea of committing self-harm.
- Unanticipated Problem (UP)
    - Any other event, not meeting the definition of PD, UP, AE or SAE that, in the opinion of the principal investigator, merits documentation as it occurred outside the expected design of the study and/or study procedures. These events, like PDs, UPs, AEs, or SAEs, may be reported to the IRB and/or the study sponsor, as applicable.

Clinical Protocol Synopsis

1. Title

Optimizing a self-directed mobile mindfulness intervention for improving cardiorespiratory failure survivors' psychological distress (a.k.a., 'LIFT2')

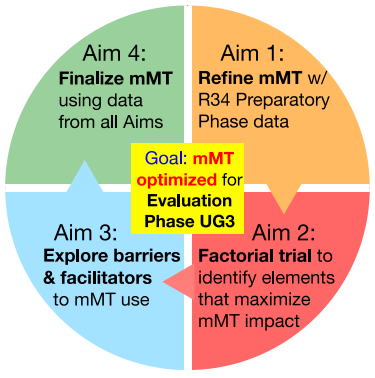
2. Background & Rationale

As survival has improved for the 2 million people with cardiorespiratory failure managed annually in the US intensive care units (ICUs), it has become apparent that these patients suffer from severe and persistent post-discharge symptoms of psychological distress including depression, anxiety, and post-traumatic stress disorder (PTSD). However, few targeted interventions exist that are relevant to patients' experiences and that accommodate their many physical, and social barriers to personalized care. To fill this gap, we developed an innovative app-based mobile mindfulness training program that promotes automated care delivery and self-management of symptom-related distress.

Previously, a pilot randomized clinical trial (RCT) called LIFT (R34 AT00819) in which this project is built on, compared mobile mindfulness to both a standard telephone mindfulness program and an ICU education control among survivors of cardiorespiratory failure. LIFT demonstrated that mobile mindfulness was feasibly delivered, acceptable, usable, and had a greater clinical impact on psychological distress than either comparator. This trial also highlighted opportunities to improve the intervention's impact related to its targeted population, content delivery, and system technology.

Therefore, we propose a 5-year, multi-site project titled "LIFT2" that is conceptualized as the Optimization Phase of a multiphase optimization strategy (MOST) framework. The project will be conducted at Duke University, Oregon Health & Sciences University (OHSU), and University of Colorado (COL). Mobile mindfulness will be optimized via four specific aims (Figure 1):

- Aim 1: Optimize the usability of the mMT intervention's key technological features.
- Aim 2: Using a factorial experimental trial, identify mMT intervention components that contribute most meaningfully to feasibility, usability, and impact on psychological distress.
- Aim 3: Explore barriers and facilitators to mMT implementation and dissemination.
- Aim 4: Using lessons learned from Aims 2 & 3, operationalize the final optimized mMT system.



atory failure survivors through quantitative & qualitative investigation and strong partnerships.

3. Study Design

This is a 5-year, multi-site project that is conceptualized as the Optimization Phase of a multiphase optimization strategy (MOST) framework. As mentioned in section 2, this project consists of four distinct aims:

Aim 1: Optimize the usability of the mMT intervention's key technological features

Informed by lessons learned from the R34, we will add and refine the mMT app user interface features to improve interaction and engagement of participants, and thus dose, adherence, and retention. Participants eligible for Aim 1 will be an uncontrolled sample of 10-15 individuals which may consist of patients, caregivers of patients, and other volunteers. Each participant will be asked to sign and date informed consent and then complete one 30-60 minute visit in which they will complete usability testing. Usability testing involves the following: 1) registration of user in app, 2) completion of baseline survey, and 3) randomization via completion of T1 survey. Additionally, participants will be asked to test certain scenarios, such as chat room functionality, suicide ideation, and moving from task to task on a given study day. Tasks completed by the participants during this study visit are intended to achieve the following goals: 1) enable a "recommender system" which will permit sophisticated logic-driven personalized app-user interaction, which includes guidance to specific app content based on response to the weekly ePRO survey; 2) update the mMT user interface to ensure that the app is in compliance with the Americans with Disability Act (ADA) standards; and 3) automate post-discharge distress screening. During the study visit, participants and delegated study team members will be asked to provide their feedback, input and note any errors (e.g., typographical or technical) that occur during the usability visit. At the completion of the study visit, participants will be asked to complete a standardized usability survey to assess their overall opinion and feedback related to the app and its accessibility and usability. All feedback, input, and errors, as well as survey results, will be provided to the study PI, study manager, and Pattern Health for review. The study PI, study manager and Pattern Health will implement necessary changes and updates to ensure excellent usability (mean Systems Usability Scale > 85) and ensure 100% success rate of post-randomization distress and randomization. The completion of Aim 1 will ready the mMT for Aim 2.

Aim 2: Using a factorial experimental trial, identify mMT intervention components that contribute most meaningfully to feasibility, usability, and impact on psychological distress.

Aim 2, which is the focal point of this project is to determine which mMT factors optimize MOST constraints (i.e., outcomes). The primary objective of Aim 2's is to determine which mMT factors optimize MOST constraints (i.e., outcomes). The main effects of each factor will be tested as well as the conditional effects of factor combinations on a priori-defined operational targets (feasibility, acceptability, usability) as well as improvements in psychological distress symptoms (depression, anxiety, PTSD) at 3 months.

To do so, we will conduct a 3-factorial experimental trial with a 3 month follow-up in which 240 patients, meeting eligibility criteria as outlined in section 5, will be consented, enrolled and randomized to 1 of 8 combination of mMT factors:

- Group 1: Team Introduction, High Dose and Team Help
- Group 2: App Introduction, High Dose and Team Help
- Group 3: Team Introduction, High Dose and App Help
- Group 4: App Introduction, High Dose and App Help
- Group 5: Team Introduction, Regular Dose and Team Help
- Group 6: App Introduction, Regular Dose and Team Help
- Group 7: Team Introduction, Regular Dose and App Help
- Group 8: App Introduction, Regular Dose and App Help

Each randomized group will allocate a combination of 3 factors to each participant:

1. Dose (standard [4 weeks] versus high [the standard 4-week program with the addition of extra audio meditation sessions and the use of a voluntary, anonymous, study interventionist-proctored in-app support function]),
2. Stepped approach to intervening for worsening or persistent symptoms (therapist vs. app), and
3. Method of initiating mMT (therapist call versus app).

Prior to randomization, each patient will be asked to review, sign, and date the informed consent; register the Pattern Health LIFT app using their own personal device (i.e., cell phone, laptop), and complete a baseline survey. The participant will then be asked to complete a randomization survey (T1) that will ultimately assess psychological distress for enrollment into the trial. If the patient is eligible for randomization, he/she will be assigned to 1 of 8 intervention combinations and asked to complete the following over a period of 3 months:

- 4 weeks of daily mMT
- Four (4) weekly check-ins to assess distress and anxiety
- 1 month (T2) survey
- 3 month (T3) follow-up survey

The weekly check-ins and surveys completed at baseline, hospital discharge (T1), 1 (T2) and 3 (T3) months will be used to assess changes in distress and anxiety levels. Each survey includes a combination of the following assessments: PHQ-9, PHQ-10, GAD-7, PTSS, MAAS, as well as medical services, sociodemographic, financial and social support, quality of life questions, and ADL/IADL assessments.

Adherence to the mMT plan will be assessed throughout the patient's participant. Depending on randomization group, patients may receive therapist intervention introducing them to the concept of mindfulness and then receive frequent follow-ups from the study therapist to provide training, education and support. The mMT app provides a built-in safety mechanism that detects increased levels of distress and may alert the study team (i.e., site PI, study manager, and study therapist) of the increased distress levels. In doing so, a delegated member of the study team will follow-up with the patient and assess their safety and overall well-being, as outlined in section 12.

Aim 3: Explore barriers and facilitators to mMT implementation and dissemination.
Using qualitative analysis of semi-structured interviews in up to 40 participants enrolled from Aim 2's trial, we will explore perceived barriers to accessing, using, and applying mMT effectively. Purposive sampling informed by symptom trajectories and mMT app use pattern analytics will allow inclusion of responders and non-responders, as well as infrequent and frequent app users. Patients who participate in this Aim will be asked a series of questions to determine app access, use and content during a single study visit lasting 30-60 minutes.

Aim 4: Using lessons learned from Aims 2 & 3, operationalize the final optimized mMT system.
Consistent with NIH guidelines on mixed methods research[1] we will integrate quantitative (Aim 2) and qualitative (Aim 3) data from Years 2-4 to finalize the mMT app build that optimizes MOST outcomes of feasibility, usability, and clinical impact. After updating app software to current standards, we will ensure mMT reaches 'excellent' usability (mean SUS score ≥85) among a diverse purposive sample of up to 25 individuals—and is ready for off-the-shelf use in a next-step RCT.

4. Study Objectives, Hypotheses, and Outcomes

The overall objective is to optimize the mobile mindfulness training intervention (i.e., mMT) by identifying which components contribute most meaningfully to feasibility, usability, and clinical impact on symptoms of psychological distress assessed over a 3-month follow up period.

We hypothesize that the optimal mMT use case will include the following factor components: high dose, app-based approach to responders, and app-initiated study introduction.

Feasibility will be evaluated by comparing observed to targeted benchmark rates of consent (70%), completion of weekly surveys (75%), and 3-month retention (75%). We will use server analytics to quantify participants' app adherence (e.g., frequency of daily use, average session duration). More specifically, adherence will be monitored closely using the app-integrated data system and automated web analytics. In particular, mobile web app analytics will allow real-time monitoring of each participant's frequency of app use, average duration of app use per session, completion of weekly components, and other behaviors. Weekly reports generated by the study data system will allow the study team to make proactive interventions (e.g., reminder emails and calls) if needed to either get the participant back on schedule or to address a logistical need. Acceptability will be measured with the Client Satisfaction Questionnaire (CSQ; target mean ≥10) and by analysis of Aim 3's semi-structured interviews. Usability will be assessed with the Systems Usability Scale (SUS; target mean ≥85).

Secondary outcomes will be assessed to ascertain information on the multidimensional effects of the intervention.

- Anxiety symptoms: Generalized Anxiety Disorder 7-item scale (GAD-7).
- Post-traumatic distress disorder (PTSD) symptoms: Post-Traumatic Stress Syndrome Inventory (PTSS).
- Quality of life: The EuroQOL-5D (EQ-5D) and its 100-unit visual analog scale (VAS).
- Physical symptoms: Patient Health Questionnaire 10-item symptoms scale (PHQ-10).

5. Study Population

LIFT2 is centered around Aim 2 of the project. As such, the primary characteristics of the targeted study population will be those individuals who have experienced an ICU admission and meet eligibility criteria as outlined below. For Aim 1, we intend to enroll 2-5 patients who meet eligibility criteria for the clinical trial, 2-5 caregivers of patients admitted at the enrolling ICU, and up to 5-10 other individuals, if necessary, to ensure an adequate sampling of usability. These "other individuals" could include members of our patient and caregiver stakeholder cohort whom we have called on in past projects to give feedback on apps and websites. For Aim 3, patients previously enrolled in Aim 2 will be purposively sampled and will include both responders and non-responders, as well as frequent versus non-frequent app users. For Aim 4, the targeted population will be new patients, not previously enrolled in Aim 2 or 3, that meet the criteria outlined below or healthy volunteers.

Eligibility Criteria: Patients who are deemed eligible for study participation will ultimately be those individuals who experience high levels of psychological distress (i.e., PHQ-9 $\geq$ 5).

Specifically, patients enrolled into this pilot, RCT will meet the following criteria:

Inclusion Criteria (at the time of hospital admission)

1. Adult patient $\geq$18 years of age.
2. Acute cardiorespiratory failure, defined as $\geq$ 1 of the following *:
    a. Mechanical ventilation via endotracheal tube for $\geq$ 12 hours
    b. Non-invasive ventilation (CPAP, BiPAP) for $\geq$ 4 hours in a 24-hour period provided for acute respiratory failure in an ICU (not for obstructive sleep apnea or other stable use)
    c. High flow nasal cannula or face mask for $\geq$ 4 hours in a 24-hour period

And/or

Acute cardiac/circulatory failure, defined as ≥ 1 of the following:

d. Use of vasopressors for shock of any etiology for ≥ 1 hour
e. Use of inotropes for shock of any etiology for ≥ 1 hour
f. Use of aortic balloon pump for cardiogenic shock for ≥ 1 hour

*In an ICU setting, NOT including the operating room or emergency department

3. Managed in an adult medical, cardiac, trauma, surgical, or neurological ICU for ≥24 hours during the time inclusion criterion #2 is met.
4. Cognitive status intact, defined as:
    a. No history of significant cognitive impairment (e.g., dementia) per electronic medical records
    b. Absence of current, significant cognitive impairment (≥ 3 errors on the Callahan cognitive status screen)
    c. Decisional capacity present
5. Absence of severe and/or persistent serious mental illness that could disrupt study participation, as noted in the electronic medical record (EMR) or affirmed by clinical staff at the time of screening and approach for consent.
   Defined as any of the following:
    a. Treatment for severe or unstable mental illness (e.g., psychosis, bipolar affective disorder, schizoaffective disorder, schizoid personality disorder, schizophrenia [as per medical record], hospitalization for any psychiatric disorder) within the 6 months preceding the current hospital admission
    b. No endorsement of active suicidality at time of admission or informed consent
    c. No active substance abuse at a severity that impairs ability to participate
6. English fluency

Exclusion Criteria (at the time of hospital admission)

1. Hospitalized within the preceding 3 months with life-threatening illness or injury.
    a. Patients may be enrolled into the study if they had a hospitalization within the preceding 3 months that is determined to be non-serious. Non-serious admissions are defined as those admissions that are non-life threatening and/or potentially impacting patient's well-being long-term or likely to precipitate additional future admission. Examples of non-serious, non-life threatening hospitalizations could be, but may not be limited to, admission for a bronchoscopy, admission for deep vein thrombosis, or admission to ED resulting in overnight stay for cardiac work-up.
2. Admitted from a location other than home (e.g., nursing home, long-term acute care facility, inpatient rehabilitation facility).
3. Anticipated or actual discharge to a location other than an independent in home setting (e.g., nursing home, long-term acute care facility, inpatient rehabilitation facility, home hospice).
4. Complex medical care expected soon after discharge (e.g., planned surgeries, transplantation evaluation, extensive travel needs for hemodialysis, disruptive chemotherapy/radiation regimen)
5. Unable to complete study procedures as determined by staff.
6. Lack of reliable smartphone with cellular data plan or Wi-Fi.

Exclusion Criteria (at the time of arrival home)

1. Low baseline psychological distress symptoms, defined as the absence of the following at T1:
    a. PHQ-9 score < 5
2. Failure to randomize within 2 months (60 days) post-discharge.

7. Study Procedures

Screening, Recruitment and Consent

For aim 1, eligible patients will be recruited from a pool of diverse individuals willing to participate in the study. Prior to approaching individuals for aim 1 consent, the study team will obtain the applicable research introduction from the clinical team and ensure approach is acceptable by the eligible individual. If the individual is willing to speak with the study team, the study team will approach the individual, provide an overview of the study and review the informed consent with the individual. Should the individual opt to participate in Aim 1, they will sign and date the informed consent, and then complete a singular 30-60 minute study visit in which they will complete usability testing. Usability testing involves the following: 1) registration of user in app, 2) completion of baseline survey, and 3) randomization via completion of T1 survey. Additionally, participants will be asked to test certain scenarios, such as chat room functionality, suicide ideation, and moving from task to task on a given study day. Tasks completed by the participants during this study visit are intended to achieve the following goals: 1) enable a "recommender system" which will permit sophisticated logic-driven personalized app-user interaction, which includes guidance to specific app content based on response to the weekly ePRO survey; 2) update the mMT user interface to ensure that the app is in compliance with the Americans with Disability Act (ADA) standards; and 3) automate post-discharge distress screening. During the study visit, participants and delegated study team members will be asked to provide their feedback, input and note any errors (e.g., typographical or technical) that occur during the usability visit. At the completion of the study visit, participants will be asked to complete a standardized usability survey to assess their overall opinion and feedback related to the app and its accessibility and usability. All feedback, input, and errors, as well as survey results, will be provided to the study PI, study manager, and Pattern Health for review. The study PI, study manager and Pattern Health will implement necessary changes and updates to ensure excellent usability (mean Systems Usability Scale > 85).

For aim 2, screening for eligible patients will occur daily via MaestroCare by delegated study team members. The study team will maintain a robust screening log of all individuals reviewed and will document whether or not each individual was eligible for the study. Additionally, they will document if each individual was approached for consent and the outcome of consent. It will be essential, for the future projects that it is understood why individuals are or are not eligible for approach and/or subsequent consent, therefore the screening log will track reason for ineligibility and reason for non-consent.

For those individuals who are eligible to consent, the study team will recruit the individual in-person or remotely. Patients for aim 2 will be approached, ideally at the time of their hospital admission, just prior to their discharge to an in home setting, if possible. Should the study team be unable to successfully present the study to the patient during the hospitalization, the study team will contact them once they have been discharged home. Patients can be approached earlier in their admission, if well enough, or within a week of returning to their home for participation in the study. All patients will be informed at the time of recruitment that research is voluntary and they do not have to participate if they do not want to. Furthermore, they will be informed that participation will not affect their care in any way. If a patient chooses to not participate, he/she will be documented as a ‘declined’ patient and the date of decline, as well as reason for decline (if available) will be documented. Should a patient be approached while in the hospital and opt to consent, they will be asked to complete the app registration and baseline survey, and then a study team member will contact them, once home, to remind them to login to the app to complete T1 for randomization. Should a patient be approached post-hospital discharge, he/she will be asked to complete app registration, baseline survey and T1 on the same day for study enrollment and randomization purposes. As with screening, the study team will be required to maintain a robust

enrollment log that documents the patient's consent status, version of informed consent with reference date of IRB approval, and then ultimate study status with associated visit milestones.

It is important to note that for this study, there are several statuses an individual can have. They are listed below:

- **Screened (in screening or screened):** defined as any individual who's EMR or other general data that has been reviewed against protocol for eligibility purposes. Individuals who are assigned this status must be noted on the screening log.
- **Consented**: defined as any individual who is approached for consent and voluntarily chooses to consent to the study, the procedures, risks and benefits with the understanding that they may withdraw at any time. A signed/dated informed consent must be on record to account for this individual. Patients, enrolled in the aim 2, who reach this status will be required to complete T1 at the time of hospital discharge within 1 week but no more than 1 month from returning to home. Individuals who are assigned this status must be noted on the enrollment log.
- **Declined**: defined as any individual who was approached for consent, but opted to NOT consent and therefore to NOT participate in the study. Individuals who are assigned this status must be noted on the screening log.
- **Randomized:** defined as any patient who was consented to the study, is discharged from hospital to home, completes T1 survey, and continues to meet all eligibility criteria (see Eligibility Criteria, section 5). Patients who reach this status will be required to interact with the app on a daily basis for 1 month and then complete T2 and T3. Patients who are assigned this status must be maintained on the enrollment log.
- **Screen Failed:** defined as any patient who
    - consents to the study and completes the initial study visit, but prior to discharge is determined by the clinical care team to require support and services of a long-term acute care facility (LTAC), skilled nursing facility (SNF), acute rehab facility (ARF), or other in-patient rehabilitation center, the patient's study participation will be terminated and the study team will replace the patient.

      OR
    - consents to the study, completes the initial study visit, is discharged to an independent home setting, but is subsequently re-admitted to the hospital prior to randomization (i.e., completion of survey T1), the patient's study participation will be terminated.
        - *Note: the study team may re-approach the individual in this scenario, re-consent, and repeat all study visit procedures.*
- **Post Randomization Failure:** defined as any patient who consents to the study, completes the initial study visit, is discharged to an independent home setting, completes survey T1 and is randomized to the study, and anytime during the first month study participation is re-admitted to the hospital. Should this occur, the patient may be terminated if the hospitalization lasts $\geq$ 7 days and/or the patient is unwilling or unable to continue study procedures.
    - *Note: If the participant is terminated, he/she will be included in the analyses up to the point that they were excluded.*
- **Withdraw by PI or Self:** defined as any individual who voluntarily consents to participate in the study, but is then withdrawn from the study.
    - The PI may withdraw a participate at any time without their consent if the PI deems it is in their best interest to no longer participate OR the patient demonstrates continuous lack of compliance with study protocol and study procedures.
    - The patient may withdraw themselves at any time; the study team will be asked to document the reason for withdraw for study records.

Patients who reach this status will have no additional follow-ups or study requirements. Patients who are assigned this status must be maintained on the enrollment log. A reason for withdraw should be recorded in the study records.

- **Lost to Follow-Up (LTF):** defined as any individual who voluntarily consents to participate in the study but after non-compliance and at least 3 documented, attempted contacts appropriately spaced 1-5 days apart, the individual will be considered LTF.
    - For aim 2 only:
        - Patients who reach this status will have no additional follow-ups or study requirements. Patients who are assigned this status must be maintained on the enrollment log.
        - A patient who returns the study team's contacts within 1 week of last attempted contact may resume study participation.
- **Completed:** defined as any individual who both consented and randomized to the study and completed T1-T3 (aim 2 only) or any individual who completed assigned study visit (aims 1, 3 and 4). Individuals who reach this status have no additional follow-up or study requirements. Individuals who are assigned this status must be maintained on the enrollment log.

Study Visits

For aims 1, 3 and 4 each participant will be asked to complete a singular study visit that will last approximately 30-60 minutes. During this study visit, post consent, the individual may be asked to do the following:

- Find and install the Pattern Health app (aim 1 and aim 4)
- Register to the LIFT2 study (aim 1 and aim 4)
- Complete baseline survey (aim 1 and aim 4)
- Randomize to 1 of 3 groups or screen fail purposely (aim 1 and aim 4)
- Audio-recording for interview using qualitative analyses (aim 3)
- Provide feedback on app content and usability (aim 1, 3, and 4)

For aim 2, each consented patient will be asked to complete up to four individual study visits.

- **Baseline:** this visit is to occur post-consent (same day, ideally) at the time of hospital admission just prior to discharge. However, this visit may occur at the time of hospital discharge within 7 days of returning to home. At this visit, the following will occur:
    - App Registration
    - Baseline Survey Completion
- **T1 (Day 0) (+30 days):** this visit is to occur at the time of hospital discharge to home, ideally within the first week (7 days) of returning to home; however, it can occur up to 1 month (30 days) from the time of hospital discharge to home. At this visit, the patient will complete the T1 survey via the app, which includes the PHQ-9, PTSS, PHQ-10, and MAAS surveys. Score dependent, the patient will be randomized to 1 of 8 intervention combinations. If the patient's psychological distress score is too low; he/she will receive an automated alert via the app describing they are not eligible and their study participation is complete.
- **T2 (Day 30) (+60 days):** this visit is to occur post 1 month randomization for those patients who remain eligible to participate in the study. PHQ-9, PTSS, PHQ-10, and MAAS surveys will be administered again. If the patient's survey scores indicate high levels of distress, as defined by a triggered SI alert or increased distress score from T1, a delegated study team member will contact the patient for safety precautions.
- **T3 (Day 90) (+30 days):** this visit is to occur post 3 months randomization for those patients who remain eligible to participate in the study. PHQ-9, PTSS, PHQ-10, and MAAS surveys will

be administered again. If the patient's survey scores indicate high levels of distress, as defined by a triggered SI alert or increased distress score from T1, a delegated study team member will contact the patient for safety precautions. At the completion of this survey and assuming no additional follow-up is required due to high levels of distress, the patient's participation in the study is complete.

Additionally, each patient who is randomized will be asked to complete:

- **Weekly Check-In**: for those patients who are eligible for randomization, a weekly check-in will be completed via the app. This weekly check in will be available beginning day 4 of the week until day 7 of the week.

Compensation

Compensation for study participation will be provided. Participates in aim 1 will receive $20 for study participation and completion of the singular study visit. Participants in aim 2 may receive up to a total of $60 for study completion, $20 for each survey (T1, T2 and T3) to be paid after the participant has completed the trial. Participants in aims 3 and 4 will receive $20 for each completed study visit.

8. Enrollment Sites

This study will be conducted at 3 health systems: Duke University in Durham, NC (includes Duke Medical Center [Clinical Coordinating Center] and Duke Regional Community Hospital); Oregon Health & Sciences University (OHSU) in Portland, Oregon; and the University of Colorado-Denver in Denver, Colorado.

Each of the 3 sites is expected to randomize approximately 80 patients over 36 months for Aim 2's factorial trial for a total of 240 patients across the network, with the aim of 192 patients completing assessments and mindfulness through T2 (1 month study participation post-randomization).

Sites, PIs, Targets, and Available Patients*

Site	PI	Available	Randomization Target
Duke University & Duke Regional Hospital	Christopher Cox	826 (23/mo)	80
Univ. of Washington†	Catherine Hough	590 (16/mo)	10
OHSU†	Catherine Hough	630 (18/mo)	70
University of Colorado	Marc Moss	630 (18/mo)	80

**Total for 36 months of screening*

† *University of Washington was an enrolling site from the inception of the study project to 07/31/2020, when Dr. Hough moved to Oregon Health & Sciences University (OHSU). OHSU is anticipated to begin screening and enrollment in October, 2020.*

9. Statistical Design, Analyses Plan, and Sample Size and Power

Statistical Design and Analyses Plan

Analyses for Aim 1: After inclusion of Table 7's features in the mMT system, we will employ a user testing analytic approach guided by Usability.gov guidelines and our past studies. [3,4,26] We will conduct in-person interviews among enrolled individuals identified by stratified purposive sampling with characteristics that could impact usability (~25% ≥age 65, ~25% <high school education, ~25% with low technology confidence). [27,29] Participants will complete: (1) a 'think aloud' protocol in which coordinators record patient comments as they use mMT; [30] (2) Systems Usability Scale (SUS); [28] (3) all system tasks, and (4) a semi-structured interview. In a parallel approach, staff will test the screening and randomization system using a series of 100 simulations, aiming for 100% success in correct and equal randomization to Aim 2's factor conditions. We will organize any identified problems with Nielsen usability heuristics to guide subsequent revisions.31 Based on our past work, [3-5,14,15] we anticipate 2-5 cycles of 2-5 participants each will be sufficient to reach a target of 'excellent' usability (i.e., mean SUS score ≥85) [26,32] as well as to ensure confidence in the screening system's feasibility.

Table 7

	Limitations identified in R34 pilot trial	**Features planned** for the mMT system in Aim 1
Engagement & personalization	- Limited dynamic engagement (data display, notifications, reminders) - Limited interactivity and personalization of experience - Not ADA compliant	**1. Recommender system for:** - Sophisticated logic enabling stepped care - Robust symptom-responsive feedback - Visualization of use data **2. ADA compliant features**
Study mechanics	- No screening system for post-discharge distress - Manual initiation of randomization	**3. Automated post-discharge screening & randomization system**

Analyses for the trial (Aim 2): The main goal of our intention-to-treat analyses is to estimate main effects and interactions of combined experimental conditions to be able to determine which LIFT use case is best. That is, would LIFT impact be greater by accepting the "high" level of a factor instead of the simpler default "low" level of the factor. Our overall analytic approach will be guided by frameworks presented by Collins and Collins & Kugler. [33,34] To understand general patterns in the data, we will first calculate raw means, medians, and measures of variability at each time point for the primary and secondary outcomes. These will be grouped by the main effect of each factor (e.g. standard versus high-dose), collapsed over the other factors. We will also examine these descriptive statistics by groups as defined by the two-way and three-way interactions of the factors.

A constrained longitudinal general linear model with unstructured covariance to take into account repeated measures on individuals over time will be used to estimate changes in the primary and secondary outcomes from T1 to T2 and from T1 to T3. [35] Often for trial analyses, intervention group and time are dummy coded indicator variables (i.e., levels 0 and 1) in model specification. Instead, given our factorial design, the main effects and interactions will be represented with effect coding (i.e., levels -1 and 1). In the scenario of balanced sample sizes across the factors, effect coding results in a model with independent coefficients.

Using the estimated model coefficients, we will first determine if any of the main effects indicate improvement of at least 2 points on the PHQ-9 at T2. Candidate components not reaching these benchmarks will be set to the "low" level of the component. We will then carefully examine the interactions, starting with those that include the largest main effect factor. Estimated means and plots will be used to explore the impact of the interactions and whether they are "synergistic" or "antagonistic." The final "screened in" set of combinations (i.e., main effects and synergistic interactions indicating improvement of at least 2 points on the PHQ-9) will provide evidence of possible optimized intervention components.

As a next step in the decision-making process, we will examine the secondary outcomes and the sustained intervention effects at T3, potentially reconsidering decisions made in the previous step. As an additional part of this step of the decision-making process, we will examine feasibility and adherence metrics for all components, as well as open-ended study participant study staff feedback.

Analyses for Aim 3: We will use modified grounded theory methods [24,26] to inductively and iteratively develop frameworks to describe patients' experiences with the mMT app. [37-39] This approach will avoid making incorrect assumptions and also maximize the chance of effectively refining the intervention. To develop the preliminary coding frameworks, we will independently perform line by line open coding of the first 5 interviews (1) to identify themes and concepts relating to perceived barriers and facilitators to mMT use and application of content, (2) to assign codes to each, and (3) to group similar concepts into categories. Categories will be developed further by comparison between transcripts (axial coding). In a series of meetings, all investigators will review these preliminary coding frameworks and arrive at consensus on the coding framework. [24,25] Thereafter, coordinators will code each new interview using ATLAS.ti, an approach that provides the opportunity to modify the interview guide iteratively and, through constant comparison, to collect data that will further enhance an understanding of barriers and facilitators. We will ensure validity by (1) maintaining an audit trial that captures the research design, decisions made about data collection, and analyses;[40] (2) minimizing bias by using a multidisciplinary team to develop the coding framework; and (b) using member checking to present results to 15 study patients for confirmation or modification. [22,41]

Analyses for Aim 4: After reviewing transcribed interviews, investigators will organize any usability concerns with Nielsen heuristics and then perform revisions. [31] We anticipate 1-2 cycles of iterative revisions involving 5-10 participants per cycle to reach a target of 'excellent' usability (defined by a Systems Usability Scale [SUS] mean score ≥85). [26,32] Aim 4 will conclude with a full updating of all mMT software and hardware components.

Sample Size and Power

As the project centers around Aim 2 (RCT), we calculated power for the test of a main effect or factor interaction in a constrained longitudinal general linear model with unstructured covariance matrix via simulation. Based on LIFT pilot data, the baseline standard deviation of PHQ-9 was assumed to be 5.3 and the covariance between time points ranged from 3.9 to 11.5. We examined a range of sample sizes at T2, from 120 to 200 participants. 500 simulated datasets were simulated under the alternative model, with power calculated as the proportion of times the estimated coefficient was found to be statistically significant at $p<0.05$. Results indicated that with 192 total patients at T2 (24 per experimental condition; 240 total at T1 [randomization] assuming 20% dropout by T2), we will have >90% power to detect a factor main effect or factor interaction effect of 2 units on the PHQ-9 scale.

By targeting 240 randomized participants, we will have ample power to detect factor main and interaction effects even with deviations from our assumptions (e.g., higher dropout rate, misspecified covariance matrix, etc.). For Aims 3 and 4, these samples should be adequate for theme saturation.

10. Subject Participation Duration

Participating subjects in aims 1, 3 and 4 will be asked to participate in a singular study visit lasting 30-60 minutes. Participating subjects in aim 2 will be asked to participate for up to a total of 3 months. Participating in the factorial trial (aim 2) will require 1 month of daily, active participation in which the patient is practicing mMT daily and completing weekly check-ins. At the end of the 1 month (post T1 completion), the patient will be asked to complete T2 survey. Once the patient has completed the T2 survey, he/she is finished with active study participation for an additional 2 months at which time they will be asked to complete T3 survey.

11. Study Duration

We estimate that from the time the factorial experiment trial opens to enrollment during Month 9 of Year 1, it will require approximately 41 months to complete data collection (approximately 36 months for cumulative enrollment with 4-5 months to complete all long-term follow up; this time does not include start up and analyses) and 4-6 months to perform all final data analyses for all Aims.

12. Risk-Benefit Assessment

Potential risks

It is possible that participating patients could experience a breach of confidentiality should their records be accessed unlawfully by an outside party or general, inadvertent error. 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.

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. Informed consent (e-consent or written) will be required from all participants, including content experts. Second, we will use a standardized screening and enrollment protocol that respects participant privacy and rights. The study team will only approach those patients that are deemed appropriate for the study, which will be determined by EMR review, other data, and/or conversations with the clinical team and/or PI. The approach of patients may be aided by a short IRB-approved recruitment video. The study team will then ask the patient to read and sign the study consent form at the time of enrollment. Potential subjects will be given as much time as they need to consider study participation. For Aim 2, 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, as we have done successfully in past clinical trials. A copy of the consent form will be given to participant and the original maintained in a secure location at.
the study site

Protections against risk

General oversight

There are several ongoing mechanisms for monitoring the occurrence of adverse events. The PI or delegated study team member will perform day-to-day monitoring of the study activities. Careful monitoring of all persons entering the study will minimize attrition and will ensure the clinical safety of these patients. A telephone

number for the study team facilitates this monitoring and an email address (liftstudy@duke.edu) provided to participants upon entry into the study to report concerns related to study participation.

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 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, which has been used successfully in past trials describe treatment groups and ensure a similar approach across sites.

Specific longitudinal participant oversight plans for severe psychological distress (including suicidal ideation)
Given the difficult situations faced by patients, we recognize that there is a slight risk that some participants may become distressed completing questionnaires or viewing study materials, as mentioned above.

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 study team members who are sensitive to the issues that arise.

(2) Study team members 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 or telephone session at any time and that they are 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 ICU survivors and are experienced in discussing these issues with them. There is also a potential risk for identifying underlying mental health issues through the mMT 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 be provided at that time.

Suicidality Response Plan

First, delegated study team members 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 below:

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 PIs	Immediately contact participant

Should a patient indicate to a study team member or via the app, thoughts of suicidality or ideation of suicidality, the Suicidality Response Plan could be activated.

If the participant is deemed to be at high risk based on direct interaction plus the C-SSRS item response, the delegated study team member will administer the C-SSRS 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 patient is deemed not to be actively suicidal, they will be given a list of local mental health resources as follows:

- Duke University: Call Emergency Psychiatry at (919) 681-4410 or (919) 681-1316, available 24 hours a day, 7 days a week.
- Oregon Health & Sciences University: National Suicide Prevention Lifeline - 1-800-273-TALK (8255)
- University of Colorado: Call Psychiatric Emergency services at (303)-602-7221, a 24-hour resource line

All sites, may use, 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.

If the participant is considered 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, the study personnel will notify the site PI one of the other PIs immediately.
    - 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:
        - The study personnel will notify the site PI one of the other PIs immediately
        - The study personnel will stay on the telephone with the subject participant.
        - The study personnel will immediately contact 911 to initiate an on-site rescue if such action is clinically indicated.
    - The study personnel will stay on the telephone with the subject until EMS services have contacted the participant.

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

As described 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. The study team will also make urgent and emergency referrals as needed based on information learned.

To date based on some 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 has 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.

Patient Death While in Study

Finally, we recognize that we are working with a critically ill population that is at risk for death during follow up due to their underlying illness. Before T2 and T3 data collection, the study team will review the EMR to look for records of death, halting all study procedures if death has occurred and noting the date. On phoning any participant, the study team will initiate a conversation to tactfully ascertain the patient's vital status should a family member answer first. If the patient has died, the study team will provide brief support and their condolences.

Withdraw While in Study

If an individual states that they wish to drop out, the study team will respect that as well. A follow-up question may be asked to ascertain the reason for withdraw; however, this is for documentation purposes only. Additionally, the study and/or site PI retain the right with withdraw the participant from the study if they feel that participation is no longer in the participant's best interest and/or the participant is non-compliant despite numerous attempts to contact by the study team.

Vulnerable Populations

This project will not enroll individuals from vulnerable populations (e.g., imprisoned persons, minors).

Adverse events (AEs), serious adverse events, (SAEs) and unanticipated problems (UPs).

It is recognized that there is a slight risk that some participants may become distressed when completing self-report measures or participating in interviews. 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 the PI's contact information 24 hours a day (shown in the consent form). If a telephone interview is required, a trained study team member who has been trained to be sensitive to the nature of these issues will conduct it.

It is anticipated, in this study, for AEs to be extremely rare as it is a behavioral study. However, it is possible that participants could become distressed in a hospital setting or post-discharge due to increased illness and/or limitations. As such, participants could exhibit signs of and/or experience suicidal ideations or be admitted for mental health symptoms. Therefore, for this study, only increased levels of distress related to completing the questionnaires or completing the coping skills practice and/or suicidal ideations will be considered AEs.

Like, AEs, it is not anticipated that SAEs will occur. However, for this study, an SAE would be defined as a suicide attempt, a hospitalization (post hospitalization that initiated the patient's eligibility for study participation), or death. All serious adverse events will be reported within the standard timelines required to the IRB, study sponsor, and/or DSMB, as appropriate and when applicable.

Given the nature of this study, it is anticipated that most enrolled patients will not complete their study visits within the assigned protocol window. Additionally, it is expected that visits and/or mMTpractices will be missed. As such, these will not be considered protocol deviations. Should other protocol deviations or unanticipated problems occur, they will be discussed with the PI, documented, and reported to the IRB, study sponsor, and/or DSMB, as appropriate and when applicable.

Period and Frequency for Event Assessment and Follow-Up

Protocol deviations and other unanticipated problems, as well as AEs and SAEs, will be recorded in the data collection system throughout the study and reported, as appropriate, to the IRB, study sponsor, and/or DSMB, when applicable.

The study team 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 study team will inquire by way of verbal or written request and/or EMR review, of the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

Characteristics of an Adverse or Serious 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.

Expectedness
The Study PI will be responsible for determining whether an event is expected or unexpected. An 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
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

Adverse and Serious Adverse Events
For symptoms that are either great in total burden (i.e., total score is high), a delegated study team member (e.g., therapist) will call the participant to check in. For specific symptoms such as the suicidal ideation, a delegated study team member will also call the participant and assess the severity of the situation, triaging them as appropriate to psychiatric support.

For other matters, the study team will maintain frequent telephone contact with most participants, and can refer those with concerning symptoms.

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 and that are related to the intervention will be reported to the NHLBI 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.

Protocol Deviations and Other Unanticipated Problem Reporting

Incidents or events that meet the reporting criteria, as outlined by the Duke IRB, will be reported to the Duke IRB as needed.

The following will be included, at a minimum:

- A detailed description of the event, incident, experience, or outcome;
- 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.

Reporting for Multi-Center Trials

The study site must immediately report to the coordinating center and study manager any serious adverse event, whether or not considered study related, including those listed in the protocol 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 study site must also report any protocol deviations or violations to the coordinating center and study manager within 7 days of study team awareness.

Privacy

The study team will closely safeguard participant privacy regarding protected health and personal information. A study ID number will be generated at the time of consent and will be maintained in a secure file (e.g., linker file) which will contain the patient name and medical record number. Further, names, birthdates, telephone numbers, addresses, and medical record numbers will be stored securely as described in the RDSP and only accessible by delegated study team members. The RedCAP system will store all data on a secure Duke University server with a sophisticated dual backup system. Study participants cannot view data via the ePRO system, supported by Pattern Health or the electronic data capture (EDC) system, supported by Duke University RedCap. Patients will only have access to the ePRO system and will access the one-way view ePRO system via secure, PHI-free email or text links sent from the app.

Digital security

The study digital infrastructure consists of a mobile (i.e., native) app with a built-in electronic patient reported outcomes (ePRO) function and an electronic data capture (EDC) system, RedCAP digital study database.

- ***mMT app:*** The mMT app will be a native app. The 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. 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. 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.

- ***ePRO:*** This password protected, HIPAA-compliant, IRB-approved ePRO system is similar to those we have successfully used among hundreds of ICU survivors and family members. Strong passwords randomly generated by our study group will be provided for patient participant access of the ePRO system.
- ***REDCap:*** The project will utilize a REDCap database system customized for our data needs and EDC. For data validation, a series of project-defined data checks and conditional constraints can be required to ensure the highest quality data collection. All system login procedures and data submissions will be transported and encrypted via the Transport Layer Security (TLS) protocol to the secure central database at Duke University. The study team will use login/password (reset every 6 months) credentialing for authentication of all study staff. User-level permissions will be based on user roles and defined within the project system to limit a user's access to only those records an individual is authorized to see. Duke Health Technology Solutions staff to verify that security measures are operational will review audit logs routinely. The servers are scanned twice weekly for vulnerabilities and are currently maintained at the highest level of vendor and CERT security recommendations. Data will never be shared outside the project unless authorized by the project leader and the Duke IRB. User authentication is based on user passwords as described earlier. Password creation requirements are in place to guarantee "strong passwords" as defined by the CERT security recommendations. The lead systems administrator is GIAC Security Essentials certified through May 2018.

13. Data management

Most data entry will be self-completed by participants using the validated ePRO system accessed via the mMT app. The study team will complete electronic case report forms (eCRFs) securely integrated within the EDC by abstracting relevant clinical data from each patient's EMR. RedCap will be utilized to maintain study screening and enrollment logs and house the eCRFs. The mMT app dashboard, developed by Pattern Health for administrative use only, will be accessed and used by delegated study team members to create scheduled reports on the trials' conduct (e.g., study milestones) to enhance the study's quality. Through this dashboard, quality and consistency of data, will be monitored. The Project Manager will do routine data cleaning and statistical team using customized group-blinded reports that will identify missing, outlier, or nonsensical data at time points when remedying them is feasible.

14. Data & Safety Monitoring Plan

Plans for Assurance of Compliance regarding Adverse Event Reporting.

The study team will be required to document and report adverse events (including serious adverse events) to the Institutional Review Board (IRB), as appropriate and in line with institutional reporting criteria. In addition, all adverse events are reported as part of NIH Progress Reports in the non-competitive and competitive renewals.

Plans for Assuring Data Accuracy and Protocol Compliance.

The PI will supervise the study, including data management, data accuracy, and protocol compliance. The study biostatistician and Project 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 Project Manager will review data system reports on a routine basis. These reports will show enrollment, missing data, and other values that are neither study ID- nor outcome-based. The Project Manager will process detailed reports to search for errors and generate basic reports for dissemination for regular staff meetings.

Data Safety Monitoring Board (DSMB).

Aim 2's factorial 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 main responsibilities of the DSMB will be to (a) assess for the presence of potential harms and unintended consequences of the mMT 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 NHLBI staff), reviewing the protocol, and codifying a written charter. The NHLBI'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 NHLBI; 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 60 participants have been enrolled or enrollment has occurred for 6 months, whichever is observed first. Thereafter, the DSMB will review cleaned data reports (provided by the Project Manager 2 weeks before the DSMB meeting) every 3 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, HADS scores, PTSS scores, and Adverse Events. The primary safety measures will be Adverse Events reports and HADS 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 overtime 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 HADS score is observed in any factor-based group. If a specific factor group is found to have a statistically significant increase in HADS 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 NHLBI Program Officer.

Quality Assurance and Confidentiality

First, the 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 study team 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 PI will ensure the validity of the data system by examining electronic summary case report forms within the EDC 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

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 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.

15. Privacy, Data Storage & Confidentiality – see Research Data Security Plan.

16. IRB of Record

Duke University Health System (DUHS) IRB will be utilized as the central IRB of record.

A copy of the most recent DUHS IRB Federal Wide Assurance (FWA) statement may be found at: https://irb.duhs.duke.edu/about-us/federal-wide-assurance

DUHS IRB current and historical rosters may be found at: https://irb.duhs.duke.edu/irb-review-process/rosters

DUHS IRB meeting dates may be found at: https://irb.duhs.duke.edu/irb-review-process/irb-meetings

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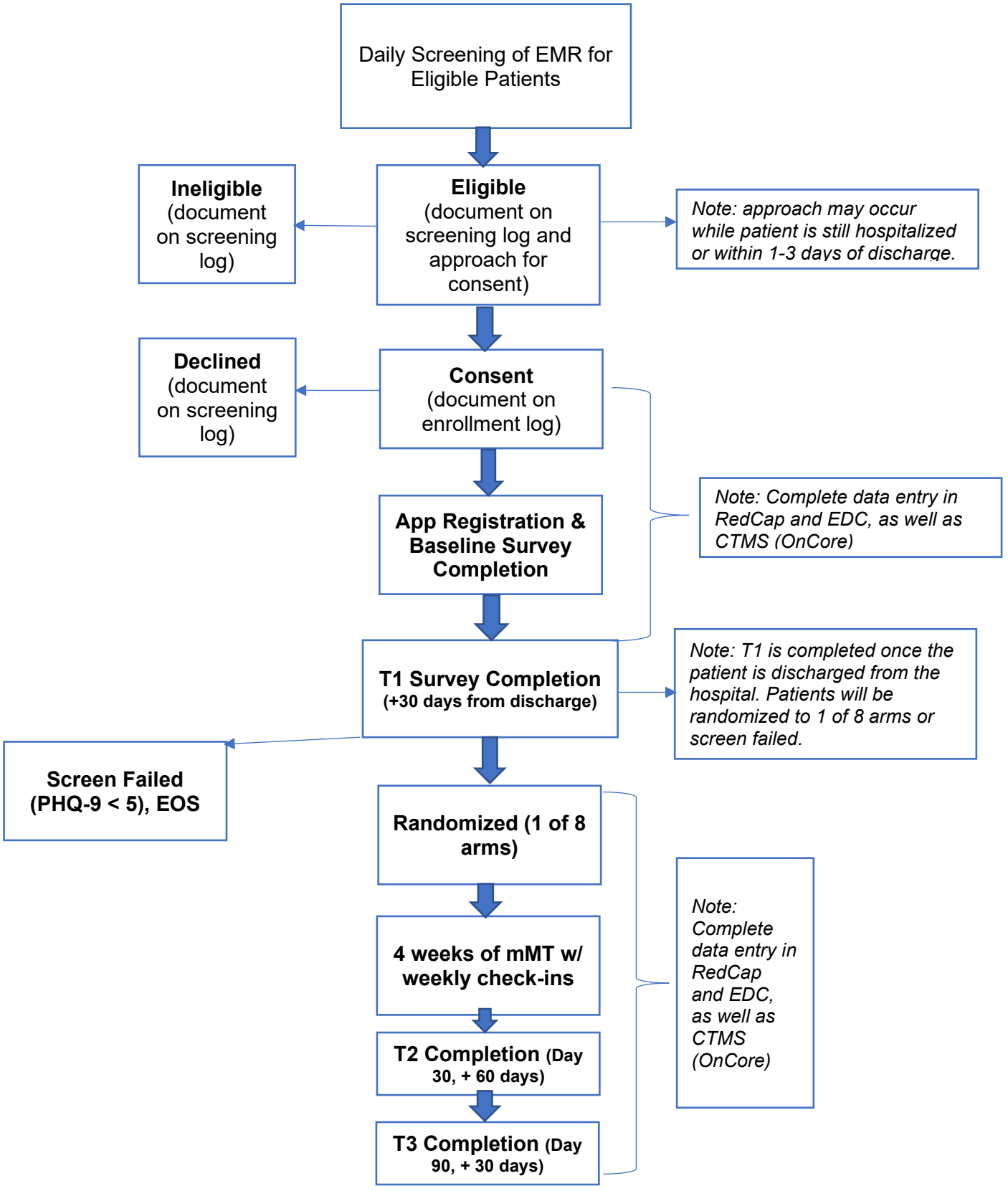
Appendix 1: Schedule of Events

	Day 0 (In-Hospital, Baseline)	Day 1 , T1 (Discharge) (+30 days)	Week 1	Week 2	Week 3	Week 4 Day 30, T2 (+60 days)	Day 90 (+30 days), T3
Screening*	X						
Consent (a)*	X						
App Registration*	X						
Baseline Survey (b)*	X						
Usability Survey*							
T1 Survey (c)		X					
T2 Survey (c)						X	
T3 Survey (c)							X
Weekly Check-In (d)			X	X	X		
Data Entry (e)	X	X				X	X
AE/SAE assessment (f)	X	X				X	X
Survival Status (f)		X				X	X
End of Study (g)							X

a) Patients may be approached and consented during their admission, if well enough; their hospitalization (e.g., while in step-down), or within 7 days of returning to their home for participation in the study.
b) Completion of the baseline survey includes the patient providing self-reported information such as social and demographic information and general health status.
c) Surveys 1, 2 and 3 will be completed via the app by all study participants, regardless of intervention combination assignments.
d) For those participants randomized to 1 of the 8 intervention combinations, they will complete a weekly check-in to ascertain overall safety of the patient and usefulness of coping skills practice.
e) AE/SAE assessment and survival status will be completed via EMR review and/or telephone interview.
f) Study completion for patients enrolled in the study is considered to occur at the completion of T3. However, participants may undergo EOS if they are withdrawn from the study by the PI or opt to withdraw from the study voluntarily at any time. Should withdraw of a patient occur, the reason for withdraw and date of withdraw will be documented. AE/SAEs and survival status will be noted, as applicable.

*For aim 1 only.

Appendix 2: Study Workflow



Appendix 3: Randomization Arms