Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Optimizing a self-directed mobile mindfulness intervention for improving cardiorespiratory failure survivors' psychological distress (LIFT2): Design and rationale of a randomized factorial experimental clinical trial

Christopher E. Cox, Maren K. Olsen, John A. Gallis, Laura S. Porter, Jeffrey M. Greeson, Tina Gremore, Allie Frear, Anna Ungar, Jeffrey McKeegan, Brittany McDowell, Hannah McDaniel, Marc Moss, Catherine L. Hough

* Department of Medicine, Division of Pulmonary & Critical Care Medicine and the Program to Support People and Enhance Recovery (ProSPER), Duke University, Durham, NC, United States of America
† Department of Biostatistics and Bioinformatics, Duke University Center of Innovation to Accelerate Discovery and Practice Transformation, Durham VA Medical Center, Durham, NC, United States of America
‡ Department of Biostatistics & Bioinformatics, Duke Global Health Institute, Duke University, Durham, NC, United States of America
§ Department of Psychiatry & Behavioral Sciences, Duke University, Durham, NC, United States of America
© Department of Psychology, College of Science and Mathematics, Rowan University, Glassboro, NJ, United States of America
∥ Department of Medicine, Division of Pulmonary & Critical Care Medicine, University of Washington, Seattle, WA, United States of America
¶ Department of Medicine, Division of Pulmonary & Critical Care Medicine, University of Colorado, Denver, CO, United States of America

ARTICLE INFO

Keywords:
Critical illness
Intensive care units
Psychological distress
Depression
Anxiety
Post-traumatic stress disorder
Mindfulness
Multiphase optimization strategy
MOST
Optimization
Factorial experimental trial

ABSTRACT

Introduction: Although as many as 75% of the > 2 million annual intensive care unit (ICU) survivors experience symptoms of psychological distress that persist for months to years, few therapies exist that target their symptoms and accommodate their unique needs. In response, we developed LIFT, a mobile app-based mindfulness intervention. LIFT reduced distress symptoms more than either a telephone-based mindfulness program or education control in a pilot randomized clinical trial (LIFT1).

Objective: To describe the methods of a factorial experimental clinical trial (LIFT2) being conducted to aid in the development and implementation of the version of the LIFT mobile mindfulness program for ICU survivors that is optimized across domains of effect, feasibility, scalability, and costs.

Methods and analysis: The LIFT2 study is an optimization trial conceptualized as a component of a larger multiphase optimization strategy (MOST) project. The goal of LIFT2 is to use a 2 × 2 × 2 factorial experimental trial involving 152 patients to determine the ideal components of the LIFT mobile mindfulness program for ICU survivors across factors including (1) study introduction by call from a therapist vs. app only, (2) response to persistent or worsening symptoms over time by therapist vs. app only, and (3) high dose vs. low dose. The primary trial outcome is change in depression symptoms 1 month from randomization measured by the PHQ-9 instrument. Secondary outcomes include anxiety, post-traumatic stress disorder, and physical symptoms; measures of feasibility, acceptability, and usability; as well as themes assessed through qualitative analysis of semi-structured interviews with study participants conducted after follow up completion. We will use general linear models to compare outcomes across the main effects and interactions of the factors.

https://doi.org/10.1016/j.cct.2020.106119

Received 3 April 2020; Received in revised form 5 August 2020; Accepted 11 August 2020

Abbreviations: ICU, intensive care unit; MOST, multiphase optimization strategy; PTSD, post-traumatic stress disorder; RCT, randomized clinical trial

E-mail addresses: christopher.cox@duke.edu (C.E. Cox), maren.olsen@duke.edu (M.K. Olsen), john.gallis@duke.edu (J.A. Gallis), laura.porter@duke.edu (L.S. Porter), greeson@rowan.edu (J.M. Greeson), tina.gremore@duke.edu (T. Gremore), allie.frear@duke.edu (A. Frear), amu@uw.edu (A. Ungar), jeffrey.mckeegan@cuanschutz.edu (J. McKeegan), brittany.mc.dowell@duke.edu (B. McDowell), hannah.mcdaniel@cuanschutz.edu (H. McDaniel), marc.moss@cuanschutz.edu (M. Moss), houghc@ohsu.edu (C.L. Hough).

© 2020 Elsevier Inc. All rights reserved.
1. Introduction

As survival has improved for the 2 million people with cardiorespiratory failure managed annually in 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, social, and financial barriers to personalized care.

Mindfulness is a practice of non-judgmental awareness that can alleviate distress by uncoupling emotional reactions and habitual behavior from unpleasant symptoms, thoughts, and emotions [1,2]. Standard mindfulness training, typically provided face to face in group settings, has proven efficacious in improving psychological distress in various patient populations [3,4]. However, in-person therapy is infeasible for the many ICU survivors with new disabilities, financial distress, and great distance from referral centers [5].

Therefore, we developed a telephone-delivered mindfulness-based training program for ICU survivors called LIFT and found that it was associated with improved symptoms of depression, anxiety, and PTSD in an uncontrolled pilot evaluation [6]. Next, we adapted the LIFT program to a self-directed mobile mindfulness training app to overcome the inconvenience of scheduled weekly telephone sessions, and then compared it to telephone-based mindfulness and an education control in a pilot randomized controlled trial (LIFT1) [7]. This trial provided compelling evidence for the mobile mindfulness app's feasibility, adherence, retention, and clinically meaningful and comparatively greater impact on depression, anxiety, and physical symptoms compared to both telephone-based Lift content as well as a critical illness-themed education control. It also showed how the LIFT program could be improved further by better targeting a population more likely to respond (and less likely to drop out), improving the app's delivery of content through a variety of media formats (video, audio, text, interactive exercises), and automating features to improve user engagement such as individualizing content in response to participant symptoms over time.

Having addressed these gaps, we are now initiating a $2 \times 2 \times 2$ factorial clinical trial (LIFT2) that is conceptualized as the Optimization Phase within the multiphase optimization strategy (MOST) framework. Through this trial, we will optimize mobile mindfulness by assessing three intervention components and their interactions among 152 cardiorespiratory failure survivors with high levels of psychological distress just after hospital discharge. At the conclusion of this trial, we will deliver a mobile mindfulness system fully optimized for usability, efficiency, scalability, and clinical impact that will be off-the-shelf ready for a next-step definitive RCT (LIFT3)—and can serve as a model for distance-based mind and body interventions.

In this manuscript, we describe the factorial clinical trial’s design, methods, and planned analyses.

2. Materials and methods

2.1. Study objective

The overall objective of the LIFT2 trial is to optimize the mobile mindfulness training intervention (i.e., LIFT) 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. Fig. 1 demonstrates an overview of past, current, and proposed future work on the LIFT intervention.

2.2. Study design

This is a prospective 3-factor factorial experimental trial with 3-month follow up conducted among survivors of cardiorespiratory failure managed in adult intensive care units (ICUs) at three health systems across the United States. The trial uses the MOST methodological framework [8]. Specifically, as part of the optimization phase of MOST, are employing a factorial randomized trial to optimize constraints of feasibility, usability, and impact [9]. In this trial, all participants will receive some version of LIFT; there will be no control comparator. Table 1 and Fig. 2 demonstrate the 8 conditions tested in this $2 \times 2 \times 2$ trial. Data are collected at the time participants return home from the hospital (Time 1 [T1]; also the time of randomization), 1 month post-randomization (Time 2 [T2]), and 3 months post-randomization (Time 3 [T3]).

2.3. Study sites

This study is being conducted at 3 health systems including Duke University (includes the Duke Medical Center [Clinical and Data Coordinating Center] and Duke Regional Community Hospital) in Durham, NC; the University of Washington / Harborview Medical Center in Seattle; and the University of Colorado in Denver.

2.4. Participant eligibility

We aim to randomize 152 participants to ensure that 120 complete the 1-month follow up. Given their recent critical illness, patients’ expected physical health status will initially be moderately poor, though the expectation for recovery will be relatively favorable. Cognition must be intact for participation, however, and will be expected to be normal at the time we approach patients for informed consent.

2.4.1. Inclusion criteria

The inclusion criteria shown in Table 2 are designed to identify adults treated in an ICU for cardiorespiratory failure who are at high risk of having persistent psychological distress after hospital discharge.

2.4.2. Exclusion criteria

The criteria shown in Table 2 are designed to exclude those likely to
drop out or display non-adherence due to medical illness that is unstable or likely to worsen, a high likelihood of needing multiple disruptive post-discharge medical procedures, or a non-supportive social situation. The majority of these exclusion criteria were applied successfully in the LIFT1 trial as well as a coping skills training intervention trial [7,10]. Revised criteria have been informed by these same trials as well as data defining ICU survivor poor outcome phenotypes more likely to be non-adherent or drop out due to unstable medical illness [11].

2.5. Recruitment

This study involves a two-step screening strategy:

Step 1—hospital-based screening to identify cardiorespiratory failure survivors

Clinical research coordinators at each site screen adult medical, cardiac, surgical / trauma ICUs daily for potentially eligible patients (i.e., those who meet the definition of ‘cardiorespiratory failure’ in Table 2) using an EHR-based algorithm. Patients are approached for informed consent in the hospital around the time of planned transfer from the ICU to the hospital ward to increase the likelihood they have recovered sufficiently to possess decisional capacity. Prospective participants are shown a 2-min study informational video (available at lift.duke.edu) at the time of the approach as well. Given the current concerns of coronavirus transmission, potential participants are often approached by distance as well using a combination of calls, emails, and texts. After obtaining informed consent, a research coordinator assists each participant in downloading the LIFT mobile app from the relevant app store onto their device and establishing a login. This process creates an individual user profile in the app platform.

Step 2—home-based screening at T1 to identify and then randomize those with elevated distress

After obtaining informed consent, site coordinators monitor the participant's hospital course and update the app study staff dashboard with the date of discharge. Two days later, the app platform sends an alert within the Lift app that prompts the participant to complete the PHQ-9, GAD-7, and PTSS scales within the app. The coordinator monitors the participant's progress in completing the scales; failure to complete the initial survey within a week of discharge, will prompt the coordinator to call the participant for the screening interview. Based on real-time within-app survey scoring, patients with elevated symptoms of psychological distress (i.e., PHQ-9 score > 5) are auto-randomized to one of 8 intervention conditions described below and shown in Fig. 2. The ~25–30% who lack elevated distress are not randomized, and their session will end with an explanatory message displayed in the app. After three 48-h cycles of auto-prompts without randomization or survey completion post-randomization, the coordinator calls the participant for the screening interview.

2.6. Experimental condition allocation

The combination of the three factors each at two levels results in 8 experimental conditions. Allocation of the patients into one of the 8 experimental conditions (152 patients randomized with 19 in each condition) occurs at the time of T1 data collection completion (i.e., the first data collection after arrival home from the hospital). To ensure balance between the conditions on these important confounders, allocation is stratified by site (Duke, Colorado, Washington), medical vs. surgical ICU, depression symptom score at T1 (PHQ-9 < 15, ≥15), physical symptom score at T1 (PHQ-10 < 10, ≥10), and age (< 50, ≥50). Because of the large number of stratification variables relative to the experimental condition size, treatment assignment is conducted via a dynamic allocation minimization method [12]. This algorithm is programmed directly within the LIFT mobile app platform; details of the algorithm are in Appendix A. Because of the automated allocation procedure and the fact that our data system gives restricted views based on user login password, no study staff is able to ascertain treatment assignment in the data system except for the study manager. Therefore, all other study staff remain masked to patients’ experimental conditions throughout.

2.7. Duration of subject participation and study

It requires 3 months for participants to complete the entire study from the time of randomization, including the intervention and all the follow up surveys. Based on our past similar studies, we anticipate a time period of approximately 2 weeks between the time of in-hospital informed consent (generally performed just after transfer from ICU to the ward) and randomization. During this period, the remaining medical issues are managed in the hospital and the study coordinators will

---

**Table 1**

| Condition | Dose | Approach to non-responders | Method to initiate intervention |
|-----------|------|-----------------------------|-------------------------------|
| 1         | High (High) | Therapist (High) | Therapist (High) |
| 2         | High (High) | Therapist (High) | App (Low) |
| 3         | High (High) | App (Low) | Therapist (High) |
| 4         | High (High) | App (Low) | Therapist (High) |
| 5         | Standard (Low) | Therapist (High) | Therapist (High) |
| 6         | Standard (Low) | Therapist (High) | App (Low) |
| 7         | Standard (Low) | App (Low) | Therapist (High) |
| 8         | Standard (Low) | App (Low) | App (Low) |

---

*a* Dose quantified as high (twice daily meditation) and standard (once daily meditation).

*b* Approach to participants whose weekly PHQ-9 score is either > 20 or higher than prior week’s score.

*c* Method to initiation intervention is the initial method of introducing the LIFT mobile app to participants.
### Inclusion and Exclusion Criteria

| Inclusion Criteria                              | Definition                                                                 |
|------------------------------------------------|-----------------------------------------------------------------------------|
| **Adult**                                      | Age $\geq$ 18 years                                                       |
| Acute cardiorespiratory failure                | Acute respiratory failure, defined as $\geq 1$ of the following:           |
|                                                | - mechanical ventilation via endotracheal tube for $\geq 12$ h               |
|                                                | - non-invasive ventilation (CPAP, BiPAP) for $\geq 4$ h in a 24-h period provided for |
|                                                | - acute respiratory failure in an ICU (not for obstructive sleep apnea or other stable use) |
|                                                | - high flow nasal cannula or face mask for $\geq 4$ h in a 24-h period      |
| and/or                                         | Acute cardiac / circulatory failure, defined as $\geq 1$ of the following:  |
|                                                | - use of vasopressors for shock of any etiology for $\geq 1$ h              |
|                                                | - use of inotropes for shock of any etiology for $\geq 1$ h                 |
|                                                | - use of vasodilators for cardiogenic failure of any etiology for $\geq 1$ h |
| ICU setting                                    | Managed in an adult medical, cardiac, trauma, surgical, or neurological ICU for $\geq 24$ h during the time of meeting Inclusion Criteria #2 |
| Cognitive status intact                        | • No history of pre-existing significant cognitive impairment (e.g., dementia) as per medical chart |
|                                                | • Absence of current significant cognitive impairment (impairment defined as $\geq 3$ errors on the Callahan cognitive status screen) |
|                                                | • Decisional capacity present (per Appelbaum [NEJM 2007], generally that the participant is able to understand the relevant information, to appreciate the medical consequences of the situation, to reason about treatment choices, and to communicate a choice) |
| Absence of severe and/or persistent mental illness | • Treatment for severe and/or persistent 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 |
| English fluency                                | • No endorsement of suicidality at time of admission or informed consent |

| Exclusion Criteria, in-hospital | Description/rationale                                                                 |
|--------------------------------|--------------------------------------------------------------------------------------|
| Hospitalized within the preceding 3 months with life-threatening illness or injury. | Patients may be enrolled into the study if they had a hospitalization within the preceding 3 months that is determined to be non-serious admissions that are non-life threatening and/or potentially impacting patient's well-being long-term or likely to precipitate additional future admissions. 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. |
| Complex medical care expected soon after discharge (e.g., planned surgeries, transplantation evaluation, extensive travel needs for hemodialysis, disruptive chemotherapy/radiation regimen) | These poor prognosis phenotype factors identify those with unstable medical or psychological illnesses that are expected to result in rapid readmission, death, or care in a facility for weeks to months that would disrupt both intervention delivery and outcomes ascertainment. As such, these factors would be a distraction for participants to comply with the intervention. We believe that different interventions than LIFT would likely be needed to better assist these patients. |
| Admitted from a location other than home (e.g., nursing home, long-term acute care facility, inpatient rehabilitation facility) | Without smartphone access, participants cannot access the intervention, complete surveys required to gauge symptoms, and other activities. In LIFT1 using this criterion and identical inclusion criteria, only 6% of otherwise eligible participants were excluded based on this factor. |
| Unable to complete study procedures as determined by staff | |
| Admitted from a location other than home (e.g., nursing home, long-term acute care facility, inpatient rehabilitation facility) | |
| Lack of reliable smartphone with cellular data plan or Wi-Fi | |
intermittently check on each patient’s progress both in-person and via the medical record, being careful to note if there is a change of plans and the patient requires transfer to a care facility (in which case they become ineligible).

We estimate that from the time the factorial experiment trial opens to enrollment, it will require 40–45 months to complete data collection (~36 months for cumulative enrollment with 4–5 months to complete all long-term follow up; this time does not include start up) and 4–6 months to perform all final data analyses.

2.8. Retention plan

Having performed 2 multi-center RCTs testing psychobehavioral interventions for ICU survivors that included long follow-up periods, we have fine-tuned strategies to optimize adherence and retention. First, the stringent eligibility criteria are designed to exclude those most likely to drop out due to medical illness, substance abuse, and other issues. Second, the LIFT mobile app itself was designed to be a convenient and flexible self-management tool that allows participants to complete all study outcomes surveys. Third, the study manager will prepare weekly reports using LIFT app analytics that identify randomized participants who are not logging into the LIFT app (or doing so infrequently). This will allow proactively delivered reminder emails/ texts, followed by telephone calls if necessary, to encourage more consistent participation with LIFT in a timely manner. Fourth, we compensate participants for their effort each time they complete a study procedure. Last, to we will attempt to attenuate loss to follow up using the guidance of recent guidelines from clinical research experts [13].

2.9. Intervention

LIFT intervention and core content

LIFT is initiated early after discharge to maximally attenuate the overall trajectory of distress [5,14]. Those randomized to the intervention will receive a separate alert linking them to one of 8 study webpages that explains the study arm to which they belong. Thereafter, the LIFT app guides the user through each week’s activities using text and visual prompts as relevant to the factor-based condition to which they are randomized. At the end of each week, the LIFT app prompts completion of the PHQ-9 within its user interface; the app platform will generate real-time alerts to PIs prompting calls to patients who endorse the PHQ-9’s suicidal ideation item plus a branching logic item about intent.

LIFT content for all factor conditions includes 4 weekly app-based sessions as tested in the original LIFT study [7]. Each session is composed of three parts: 1. Video presentation describing rationale (3–5 min.), 2. Audio guided meditation (8–10 min.), and 3. Other relevant in-app exercises (e.g., tips to help apply mindfulness to daily life; 1–3 min.). Table 3 and eFig. 1 (eFigs. and eTables are found in Appendix B) show the didactic elements of LIFT by week and how they map to distress triggers in our conceptual model. Appendix C demonstrates detailed elements of the LIFT mobile app and its content.

LIFT factors—description, rationale, operationalization

This trial will evaluate three LIFT factors, chosen based on patient feedback and staff experience from the LIFT study, that represent potentially important tradeoffs in convenience, personalization, effort, cost, scalability, and possibly effect (Fig. 3, eFig. 2).

- Factor 1—Method of intervention initiation

We will compare therapist-based initiation of the LIFT program to app-based initiation. The therapist-based approach will follow a specific protocol: Following randomization, the therapist will call the patient to
explain the rationale for LIFT, discuss the study timelines and milestones, lead the participant through an awareness of breathing exercise, and answer all questions (total time ~ 15–30 min). Patients randomized to the app-based approach will receive similar content through a short explanatory video that explains the rationale for the study, a quick ‘how to’ overview of the app and study, and a review of key LIFT elements likely to enhance success. The app approach is initiated by an email or text (per participant preference) with links to study materials and the LIFT website (lift.duke.edu). The method to initiate LIFT is important to study because app-based automation is more convenient, cheaper, and efficient at reducing startup delays than scheduling a therapist call—a factor associated with dropout in other psychosocial interventions delivered to ICU survivors [10]. However, some LIFT1 patients felt the ability to personalize an initial guided exercise and to ask questions about using the app were valuable. Altogether, understanding the comparative and combined effects of these LIFT factors is a critical step in building an intervention optimized for a successful RCT.

• Factor 2—Dose

We will compare standard dose vs. high-dose LIFT. Standard-dose LIFT is similar to the 4-week program tested in the LIFT pilot RCT, with the expectation that participants listen to one guided meditation per day. High-dose LIFT includes the expectation of two mindfulness sessions a day. The rationale for testing the dose factor is that a standard dose was convenient and effective in LIFT1, though more practice time was strongly correlated with effect. Although a higher dose would provide greater practice time and recapitulate the dose used in recent successful mindfulness trials including the initial uncontrolled LIFT pilot [6,15,16], it may be less convenient and lead to non-adherence.

• Factor 3—Response to symptoms

We will compare a therapist-based approach to an app-based approach to those with persistent or worsening symptoms, defined as a participant who each week has either a PHQ-9 > 20 or an increase in PHQ-9 > 5 units compared to the prior week. The therapist-based approach involves contacting the non-responder patient via their preferred method of communication (email, text, phone) to arrange a telephone call. In the 15–30-min call, a protocol similar to that tested in each therapist-delivered session in the LIFT study’s telephone-based mindfulness arm will be followed: the rationale for call is given, patient identifies current stressors, and the therapist explains a rationale for how mindfulness could address the stressor-associated distress. At the conclusion of the call, the therapist uses her judgement regarding the need for further attention for severe symptoms per our Distress Management Protocol. All therapist calls (as well as their date, time, length, and key content) are logged into the LIFT study staff platform for subsequent export to a study REDCap database. The app-based approach to non-responders uses the app’s logic to display hovering messages and notifications within the app that may be applicable to the user. Depending on whether emotional or somatic depression symptoms are dominating the PHQ-9 score for the individual, a unique video is shown within the app that features the study interventionists leading a brief exercise in which the participant is coached by the interventionist in the application of mindfulness for the symptoms the participant has endorsed. The app-based approach to non-responders has 8 unique videos, 2 for each week (i.e., one tailored to emotional symptoms, one to somatic symptoms).
tailored to somatic symptoms). We believe the stepped approach to non-responders (i.e., persistent or increasing PHQ-9 score from week to week) is the most exciting opportunity to enhance LIFT’s impact. A LIFT app-based approach guiding users to symptom-relevant content using sophisticated algorithms applied to patient-reported data is a highly scalable way to automate precision medicine with dynamic engagement. Yet while therapist input is time-intensive, this added personalization may yield a greater impact than an app-only approach.

2.10. Outcomes measures

Survey-based data collection occurs three times as shown in Table 4: at T1 (week of arrival home; pre-randomization), T2 (1 month post-randomization), and T3 (3 months post-randomization). We allow T2 data collection to be completed up to 6 weeks post-randomization and T3 up to 4 months post-randomization if absolutely necessary, though all efforts are made to obtain data per the timeline. The default strategy for data collection is through the LIFT mobile app itself, which is linked to the secured cloud-based study data system. Study staff blinded to experimental condition will conduct a telephone interview for those participants who are non-compliant with the LIFT mobile app-assisted surveys (~5% in our experience).

2.10.1. Primary outcome

The Patient Health Questionnaire-9 (PHQ-9) assessed at T2 is the primary outcome of the trial. It is a 9-item depression scale (range 0–27; scores ≥ 10 are elevated) [17–19] that is short and highly responsive to psychosocial interventions [20].

2.10.2. Secondary outcomes

We also measure psychological distress using the Generalized Anxiety Disorder-7 (GAD-7) and the Post-Traumatic Stress Syndrome inventory (PTSS)—scales used successfully in the LIFT pilot trial. The 7-item GAD (range 0 to 21; scores ≥ 7 are elevated) has response choices that mirror the PHQ-9 [21]. The PTSS is a 10-item post-traumatic stress disorder (PTSD) symptom scale (range 10–70; ≥ 20 is notably elevated) used frequently to assess ICU-related traumas by anchoring memory recall to hospitalization [22]. It has excellent reliability, responsiveness, and is highly specific and sensitive compared to DSM-IV criteria [23]. Quality of life is assessed with a 100-point visual analog scale used successfully in numerous ICU survivor studies [24]. Distress associated with physical symptoms is measured using a 10-item survey adapted from the PHQ-15 (range 0–30; higher scores denote greater distress) by collapsing all pain-themed items into a single item [25].

Feasibility is evaluated by comparing observed to target rates of consent (target: 75%), completion of weekly surveys (target: 75%), 3-month retention (target: 70%), and number of therapist calls (target: < 3 per participant). We will use app analytics to quantify participants’ LIFT mobile app adherence (e.g., frequency and duration of use). Acceptability is measured with the Client Satisfaction Questionnaire (CSQ; target mean ≥ 10) [26] and by analysis of semi-structured interviews conducted 3 months post-randomization. Usability is assessed with the industry standard Systems Usability Scale (SUS) [27].

2.11. Data collection and management

All non-clinical data entry is done by participants via the LIFT mobile app as prompted by alerts within the app. Coordinators abstract medical charts for hospital-based data (e.g., illness severity, ICU and hospital length of stay, diagnosis), entering data directly into the digital data system via password-protected linkage. All clinical values and measurements is abstracted from site EHR systems and derived from processes of normal hospital (and ICU) care; no post-discharge laboratory or clinical testing will be done. Study staff complete electronic case report forms securely integrated within the REDCap data system. Using tested password-based customization strategies, the LIFT platform allows each site’s study team to view their site’s own patient-level data including experimental condition. Only the study manager is able to view all patient-level data and experimental conditions. We are using a parallel study operations workflow tracking application to record participant contacts survey completion, and adverse events. Study personnel utilize these data systems to create scheduled reports on the trial’s conduct (e.g., study milestones) to enhance the study’s quality. We monitor the quality and consistency of data in a number of ways. Monthly data cleaning is done by the study manager and statistical personnel utilize these data systems to create scheduled reports on the trial’s conduct (e.g., study milestones) to enhance the study’s quality. We monitor the quality and consistency of data in a number of ways. Monthly data cleaning is done by the study manager and statistical personnel utilize these data systems to create scheduled reports on the trial’s conduct (e.g., study milestones) to enhance the study’s quality.
Management Protocol used successfully in the LIFT study, safety monitoring by an independent DSMB and a central IRB, and distress monitoring within the LIFT app itself. We do not enroll from vulnerable populations.

This study includes redundant technological and human processes designed to protect the safety of participants. Each week the LIFT app uses a series of messages as needed (hovering box on screen, email with link, text with link—all strategies we have used successfully) to prompt the user to complete the PHQ-9 survey within the app interface. The PHQ-9 includes a single item addressing suicidality, to which we added branching logic about intent and plan for clarity (see Appendix C section ‘LIFT2 Popup Messages & Logic Statements’ for details). By virtue of the LIFT mobile app’s integration with the study data system, real-time alerts will be sent to the PIs and the study manager to notify them of the presence of two situations representing extreme distress that will prompt activation of either our Distress Management Protocol or the Suicidal Ideation Protocol—each of which involves immediate contact from study staff:

- Endorsement of both suicidal ideation (a response other than ‘none’) via the PHQ-9’s relevant item as well as an active plan for self-harm based on branching logic item prompted by a ‘positive’ PHQ-9 response (action: site PI calls the participant within 24 h; note only 9 such calls were prompted over 15 months in the LIFT1 trial).
- Participant requests a call for severe symptoms or unmanageable distress via the app, email, text, or phone call (action: therapist will call participant within 48 h; content of call will be tailored to participant’s stressors though will emphasize selected content within the LIFT app)

Based on an internal algorithm, the LIFT app displays a message to the participant after entering the survey that they should expect a call from study staff to check in on their progress (a benign message worded to minimize concern).

2.13. Statistical analysis

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 (Table 1). Our overall analytic approach will be guided by frameworks presented by Collins and Collins & Kugler [28,29]. 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 vs 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. More details on the statistical analysis plan and power calculations are shown in Appendix D.

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 [30]. 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 uncorrelated 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. We will also consider the timing of participant randomization relevant to the COVID pandemic, as well as whether participants were admitted with COVID-related illnesses.

We recognize that the experience of study participants and study staff alike may be valuable considerations when determining the optimized intervention case [31]. Therefore we will use a stratified purposive design to sample 75 participants (~2 / mo.) across sites, a number sufficient for theme saturation [32], at the time of T3 (3 months post-randomization). These 30-min semi-structured one-on-one telephone interviews conducted by study staff will explore app access, use, and satisfaction with content [33,34]. Theoretical sampling will ensure sufficient variability in characteristics that may influence experiences, stratifying cases by response (high vs. low), app use (high vs. low), demographics (age, gender), baseline distress (moderate vs. high), and factor group. We will use modified grounded theory methods [35,36] to inductively and iteratively develop frameworks to describe patients’ experiences with the LIFT2 intervention [37–39]. These qualitative data may be particularly helpful in understanding important negative or positive qualities of intervention factors not otherwise captured by surveys. They will also be useful in identifying user experience issues that could prove to be barriers to future feasibility of certain intervention approaches.

2.14. Sample size and power considerations

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 (eTable 1). 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 120 total patients at T2 (15 per experimental condition; 152 total at T1 assuming 20% dropout by T2), we will have ~89% power to detect a factor main effect or factor interaction effect of 2 units on the PHQ-9 scale (eTable 2).

3. Results

Thus far, we have enrolled 37 participants in 5 months in the factorial trial (registered at: NCT04038567). Lessons learned to date have included balancing eligibility factors with individual sites’ unique patient population characteristics and practice patterns (e.g., removing the exclusion for discharge to nursing home given common practice of brief post-discharge nursing home stays in Colorado); standard challenges deploying mobile apps to a population that is diverse in age, geography, and technological confidence; and the completely new challenges of attempting to conduct clinical research during a pandemic in which direct patient contact is impossible due to infection control concerns.
4. Discussion

4.1. The LIFT program fills an important clinical care gap

For years, thought leaders have stressed the need to improve post-discharge outcomes for ICU survivors ‘beyond 28-day mortality,’ a time when patients often feel forgotten [40–42]. Prior to the LIFT1 pilot trials, there were only a handful of trials that targeted patients’ distress—none of which had positive results. The LIFT mobile mindfulness program has evidence of impact, fills a treatment gap, addresses research priorities in distress symptoms and self-management, and can provide a model for the scalable web-based delivery of mind-body interventions. It also represents a paradigmatic shift from hospital-based, mortality-focused interventions to home-based, patient-centered self-management.

The LIFT program’s key innovation is its real-time personalization of therapy as a component of self-management [43,44]. LIFT prompts patient self-report of symptoms within the app itself, translates symptom severity and trajectory into risk profiles, and then can automatically step care up or down—all in weekly cycles [45]. This approach contrasts with less efficient standard protocols in which all participants receive telephone calls or clinic visits regardless of symptom status, likely worsening retention. Because LIFT can be disseminated through the web and can automate every step from distress screening to long-term follow-up, it is ideal for a low-cost pragmatic trial. If later found to be efficacious, health systems could implement LIFT via the web for their thousands of annual ICU survivors. Such an automated, symptom-responsive, population-scalable approach that could also be personalized and self-managed would represent an evolution in the delivery of mind-body therapy.

4.2. Key knowledge gap relevant to LIFT—and how this trial will address it

There is also a key knowledge gap for the LIFT program—just how much human contact, if any, is required. The LIFT pilot RCT demonstrated that the clinical effect on depression, anxiety, and physical symptoms of the app-delivered intervention was more powerful than the therapist-delivered version [7]. However, the therapist-delivered version had slightly better adherence and retention. Furthermore, participants reported that they particularly enjoyed speaking with the study interventionist. These observations underscore a debate that has existed for years unresolved about just what exactly constitutes the ‘ideal contact’ between patient and clinician and what is a sufficient minimal and optimal dose of therapy [46]. Beyond clinical impact, clinicians and researchers have concerns about scalability, feasibility, and cost—all of which are moderated by the amount of study staff involvement in the delivery and oversight of the intervention.

For these reasons the optimization phase of the MOST methodology is ideal. MOST will use engineering principles and randomized experimentation to determine which factors of LIFT, a complex intervention, optimize constraints of clinical impact, acceptability, and feasibility. As such, this trial will determine which LIFT build is most sustainable, streamlined, and efficient for a future RCT. Factorial experiments are ideal because they require far fewer participants than would a standard RCT with multiple arms [47], yet are able to provide a substantial amount of information on individual intervention components.

4.3. Limitations and alternative approaches

First, while we have considered hospital-based interventions, no in-hospital intervention has improved depression, and ICU patients’ illnesses and delirium would make LIFT infeasible. Second, while we recognize that some participants may have psychiatric distress symptoms that precede their hospitalization, our RCT experience demonstrates that this population is just as likely to respond to therapy. However, those with severe psychiatric illness (e.g., psychosis) will be excluded. Third, we will use the PHQ-9 and the PTSS instead of the Hospital Anxiety and Depression Scale (HADS) and the revised Impact of Events Scale (IES-R) as recommended by a recent Delphi consensus of critical care researchers [48]. However, the PTSS is also commonly used among ICU patients [49] and past participant feedback has consistently indicated that the PHQ-9 is easier to understand than the longer HADS. The PHQ-9 and GAD-7 also share an identical response structure, which improves usability for those completing surveys on mobile devices. Last, we considered other designs such as stepped-wedge or cluster RCTs, though these designs were less advantageous because of our post-discharge focus and the absence of other care processes or contamination risks. An adaptive trial design was also considered, though the LIFT intervention itself is capable of auto-stepped care that adapts to symptom trajectories.

4.4. Conducting clinical research in a pandemic

Currently acute infection with the severe acute respiratory syndrome novel coronavirus 2 which leads to coronavirus disease 2019 (COVID-19) is causing the largest pandemic of pneumonia, a key LIFT trial inclusion criterion, in over 100 years [50,51]. It is expected that COVID-19 infection will likely place patients at even higher risk of distress than other forms of cardiorespiratory illness given the global state of emergency and economic stress [52,53]. The COVID-19 pandemic represents a unique threat to patient-centered care given new norms of ‘social distancing,’ limited healthcare resources that serve as barriers to distress assessment and timely treatment, and economic devastation of those impacted by it [49,54,55]. Additionally, most research institutions have banned study staff from conducting clinical research that includes direct patient contact. These barriers require a novel approach that we believe can be effectively provided by LIFT. LIFT’s ‘touchless deployment’ allows automated screening, consenting, intervention activation, and data collection without direct patient contact—critical for successful enrollment of patients with and without COVID in this trial. Additionally, LIFT is a self-guided mobile app that works on any device, giving it the flexibility and scalability required in a pandemic. That said, reshaping our teams’ focus on conducting clinical research that begins in a hospital setting presents numerous logistical, regulatory, and methodological challenges.

4.5. Other potential implementation challenges and how to address them

There may be other challenges as well. Should technological challenges arise, our past experience has provided numerous lessons learned about how to develop creative, cost-conscious solutions with our app programming consultants. We recognize that patients will occasionally have questions about the app or surveys, though study staff solved these within 24 h by email or phone in LIFT. LIFT’s web app build allows use on any operating system and any digital device via cellular or Wi-Fi or internet connections. This approach is highly accessible, as only 6% of otherwise eligible patients were excluded from LIFT1 because of no smartphone or computer [7].

5. Conclusions

We developed a self-directed mobile mindfulness training mobile app called LIFT to meet the unique needs of patients who are recovering from serious cardiorespiratory illness. We are now conducting a 2 × 2 × 2 factorial clinical trial that is conceptualized as the Optimization Phase within the multiphase optimization strategy (MOST) framework in which we will assess three intervention components and their interactions with the goal of optimizing LIFT across outcomes of usability, efficiency, scalability, and clinical impact. At the conclusion of this factorial trial, LIFT will be off-the-shelf ready for a next-step definitive RCT that can serve as a model for distance-based
mind and body interventions. Supplementary data to this article can be found online at https://doi.org/10.1016/j.cct.2020.106119.

Funding

This work was supported by the National Institutes of Health (grant numbers R34 AT008819 and U01 AT009974). The funder had no involvement in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

CRediT statement

Conceptualization: CEC, LP, JG, TG, CH, MM.
Methodology: MKO, JAG, CEC, CH, MM.
Formal analysis: MKO, JAG.
Investigation: CEC, CH, MM, MKO, LP, JAG, AF, AU, HM, BM, JM.
Data Curation: MKO, JAG, CEC, CH, MM.
Writing - Original Draft: CEC, CH, MM, MKO, LP, JG, JAG, AF, TG, AU, HM, BM, JM.
Writing - Review & Editing: CEC, CH, MM, MKO, LP, JG, JAG, AF, TG, AU, HM, BM, JM.
Project administration: CEC, AF.
Funding acquisition: CEC, CH, MM, MKO, LP, JAG.

Suggested peer reviewers

Ann Long, University of Washington.
Erin Kross, University of Washington.
Ann Parker, Johns Hopkins University.
Ramona Hopkins, University of Utah.
Samuel Brown, University of Utah / Intermountain Health.

Acknowledgements

Andrew Corcoran (Duke Health Technology Systems); Edward Barber and Jennifer McLaughlin (Pattern Health); Derek Jones, MDiv; Wen Reagan, PhD.

References

[1] J. Kabat-Zinn, Full Catastrophe Living, Delta Publishing, New York, NY, 1990.
[2] D.S. Ludwig, J. Kabat-Zinn, Mindfulness in medicine, JAMA 300 (2008) 1350–1352.
[3] L.O. Fjorback, M. Arendt, E. Ornbol, P. Fink, H. Walach, Mindfulness-based stress reduction and mindfulness-based cognitive therapy: a systematic review of randomized controlled trials, Acta Psychiatr. Scand. 124 (2011) 102–119.
[4] R.A. Gotink, P. Chu, J.J. Rutschbach, H. Benson, G.L. Frischione, M.G. Hunink, Standardized mindfulness-based interventions in healthcare: an overview of systematic reviews and meta-analyses of RCTs, PLoS One 10 (2015) e0124344.
[5] C.E. Cox, S.L. Docherty, D.H. Brandon, C. Whaley, D.K. Attix, A.S. Clay, D.V. Dore, C.L. Hough, D.B. White, J.A. Tulsia, Surviving critical illness: acute respiratory distress syndrome as experienced by patients and their caregivers, Crit. Care Med. 37 (2009) 2702–2708.
[6] C.E. Cox, L.S. Porter, J.P. Buck, M. Hoffa, D. Jones, B. Walton, C.L. Hough, D. Brooks, P. Murphy, V. Strecher, The multiphase optimization strategy (MOST) and the sequential multiple assignment randomized trial (SMART): new methods for more potent eHealth interventions, Am. J. Prev. Med. 32 (2007) 173–181.
[7] C.E. Cox, C.L. Hough, D.M. Jones, J. Ungar, W. Reagan, M.D. Key, T. Gremore, M.K. Olsen, L. Sanders, J.M. Greason, L.S. Porter, Effects of mindfulness training programmes delivered by a self-directed mobile app and by telephone compared with an education programme for survivors of critical illness, Ann. Am. Thor. Soc. 11 (2014) 173–181.
[8] C.E. Cox, C.L. Hough, D.M. Jones, A. Ungar, W. Reagan, M.D. Key, T. Gremore, M.K. Olsen, L. Sanders, J.M. Greason, L.S. Porter, Effects of mindfulness training program delivered by a self-directed mobile app and by telephone compared with an education programme for survivors of critical illness: a pilot randomised clinical trial, Thorax 74 (2019) 33–42.
[9] L.M. Collins, S.A. Murphy, V. Strecher, The multiphase optimization strategy (MOST) and the sequential multiple assignment randomized trial (SMART): new methods for more potent eHealth interventions, Am. J. Prev. Med. 32 (2007) S112–S118.
[10] L.M. Collins, J.B. Trail, K.C. Kugler, T.B. Baker, M.E. Piper, R.J. Mermelstein, Evaluating individual intervention components: making decisions based on the results of a factorial screening experiment, Transl. Behav. Med. 4 (2014) 238–251.
[11] C.E. Cox, C.L. Hough, S.S. Carson, D.B. White, J.M. Kahn, M.K. Olsen, D.M. Jones, T.J. Somers, S.A. Kelleher, L.S. Porter, Effects of a telephone- and web-based coping skills training program compared with an education program for survivors of critical illness and their family members. A randomized clinical trial, Am. J. Respir. Crit. Care Med. 197 (2018) 66–78.
[12] A. Martin, W. Rief, A. Klappert, S. Biebl, Effectiveness of the Brief Patient Health Questionnaire Mood Scale (PHQ-9) in the general population, Gen. Hosp. Psychiatry 28 (2006) 71–77.
[13] L.M. Collins, J.B. Trail, K.C. Kugler, T.B. Baker, M.E. Piper, R.J. Mermelstein, Evaluating individual intervention components: making decisions based on the results of a factorial screening experiment, Transl. Behav. Med. 4 (2014) 238–251.
[14] T.J. Somers, S.A. Kelleher, L.S. Porter, Effects of a telephone- and web-based coping skills training program compared with an education program for survivors of critical illness and their family members. A randomized clinical trial, Am. J. Respir. Crit. Care Med. 197 (2018) 66–78.
[15] C.E. Cox, C.L. Hough, S.S. Carson, D.B. White, J.M. Kahn, M.K. Olsen, D.M. Jones, T.J. Somers, S.A. Kelleher, L.S. Porter, Effects of a telephone- and web-based coping skills training program compared with an education program for survivors of critical illness and their family members. A randomized clinical trial, Am. J. Respir. Crit. Care Med. 197 (2018) 66–78.
[16] M.A. Polusny, C.R. Erbes, P. Thuras, et al., Mindfulness-based stress reduction for posttraumatic stress disorder among veterans: a randomized clinical trial, JAMA 314 (2015) 456–465.
[17] D.S. Ludwig, J. Kabat-Zinn, Mindfulness in medicine, JAMA 300 (2008) 62–67.
[18] J. Kabat-Zinn, Full Catastrophe Living, Delta Publishing, New York, NY, 1990.
[19] A. Martin, W. Rief, A. Klappert, S. Biebl, Effectiveness of the Brief Patient Health Questionnaire Mood Scale (PHQ-9) in the general population, Gen. Hosp. Psychiatry 28 (2006) 71–77.
[20] L.M. Collins, J.B. Trail, K.C. Kugler, T.B. Baker, M.E. Piper, R.J. Mermelstein, Evaluating individual intervention components: making decisions based on the results of a factorial screening experiment, Transl. Behav. Med. 4 (2014) 238–251.
[21] C.E. Cox, L.S. Porter, Effects of a telephone- and web-based coping skills training program compared with an education program for survivors of critical illness and their family members. A randomized clinical trial, Am. J. Respir. Crit. Care Med. 197 (2018) 66–78.
[22] O.J. Bienvenu, E. Colantuoni, P.A. Mendez-Tellez, V.D. Dinglas, C. Shanholz, N. Hussein, C.R. Dennison, M.S. Herridge, P.J. Pronovost, D.M. Needham, Depressive symptoms and impaired physiologic function after acute injury: a 2-year longitudinal study, Am. J. Respir. Crit. Care Med. 185 (2012) 517–524.
[23] C.E. Cox, L.S. Porter, Effects of a telephone- and web-based coping skills training program compared with an education program for survivors of critical illness and their family members. A randomized clinical trial, Am. J. Respir. Crit. Care Med. 197 (2018) 66–78.
[24] C.E. Cox, C.L. Hough, S.S. Carson, D.B. White, J.M. Kahn, M.K. Olsen, D.M. Jones, T.J. Somers, S.A. Kelleher, L.S. Porter, Effects of a telephone- and web-based coping skills training program compared with an education program for survivors of critical illness and their family members. A randomized clinical trial, Am. J. Respir. Crit. Care Med. 197 (2018) 66–78.
[25] O.J. Bienvenu, E. Colantuoni, P.A. Mendez-Tellez, V.D. Dinglas, C. Shanholz, N. Hussein, C.R. Dennison, M.S. Herridge, P.J. Pronovost, D.M. Needham, Depressive symptoms and impaired physiologic function after acute injury: a 2-year longitudinal study, Am. J. Respir. Crit. Care Med. 185 (2012) 517–524.
[26] C.E. Cox, L.S. Porter, Effects of a telephone- and web-based coping skills training program compared with an education program for survivors of critical illness and their family members. A randomized clinical trial, Am. J. Respir. Crit. Care Med. 197 (2018) 66–78.
controlled trials: a new approach to evaluating complex public health interventions, Soc. Sci. Med. 75 (2012) 2299–2306.

[40] J.E. Davidson, R.A. Ashlakon, A.C. Long, K.A. Puntillo, E.K. Kross, J. Hart, C.E. Cox, H. Wunsch, M.A. Wickline, M.E. Nunnally, G. Netzer, N. Kentish-Barnes, C.L. Sprung, C.S. Hartog, M. Coombs, R.T. Gerritson, R.O. Hopkins, L.S. Franck, Y. Skrobik, A.A. Kon, E.A. Scruth, M.A. Harvey, M. Lewis-Newby, D.B. White, S.M. Swoboda, C.R. Cooke, M.M. Levy, E. Azoulay, J.R. Curtis, Guidelines for family-centered care in the neonatal, pediatric, and adult ICU, Crit. Care Med. 45 (2017) 103–128.

[41] S. Govindan, T.J. Iwashyna, S.R. Watson, R.C. Hyzy, M.A. Miller, Issues of survivorship are rarely addressed during intensive care unit stays. Baseline results from a statewide quality improvement collaborative, Ann. Am. Thor. Soc. 11 (2014) 587–591.

[42] D.M. Needham, J. Davidson, H. Cohen, R.O. Hopkins, C. Weinert, H. Wunsch, C. Zawistowski, A. Bemis-Dougherty, S.C. Berney, D.J. Bienvenu, S.L. Brady, M.B. Brodsky, L. Denzey, D. Elliott, C. Flately, A.L. Harabin, C. Jones, D. Louis, W. Meltzer, S.R. Muldoon, J.B. Palmer, C. Perme, M. Robinson, D.M. Schmidt, E. Scruth, G.R. Spill, C.P. Storey, M. Render, J. Votto, M.A. Harvey, Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders’ conference, Crit. Care Med. 40 (2012) 502–509.

[43] T.R. Insel, Digital phenotyping: technology for a new science of behavior, JAMA 318 (2017) 1215–1216.

[44] E.J. Topol, The future of medicine is in your smartphone: new tools are tilting health-care control from doctors to patients, Available at: https://www.wsj.com/articles/the-future-of-medicine-is-in-your-smartphone-1420828632.

[45] H.M. Krumholz, S.F. Terry, J. Waldstreicher, Data acquisition, curation, and use for a continuously learning health system, JAMA 316 (2016) 1669–1670.

[46] J. Carmody, R.A. Baer, How long does a mindfulness-based stress reduction program need to be? A review of class contact hours and effect sizes for psychological distress, J. Clin. Psychol. 65 (2009) 627–638.

[47] L.M. Collins, J.J. Dziak, R. Li, Design of experiments with multiple independent variables: a resource management perspective on complete and reduced factorial designs, Psychol. Methods 14 (2009) 202–224.

[48] A.E. Turnbull, K.A. Sepulveda, V.D. Dinglas, C.M. Chessare, C.O. Bingham 3rd, D.M. Needham, Core domains for clinical research in acute respiratory failure survivors: an international modified Delphi Consensus Study, Crit. Care Med. 45 (2017) 1001–1010.

[49] A.C. Long, E.K. Kross, D.S. Davydow, J.R. Curtis, Posttraumatic stress disorder among survivors of critical illness: creation of a conceptual model addressing identification, prevention, and management, Intensive Care Med. 40 (2014) 820–829.

[50] D. Wu, T. Wu, Q. Liu, Z. Yang, The SARS-CoV-2 outbreak: what we know, Int. J. Infect. Dis. 94 (2020 May) 44-48, https://doi.org/10.1016/j.ijid.2020.03.004.

[51] C.C. Lai, T.P. Shih, W.C. Ko, H.J. Tang, P.R. Hsu, Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges, Int. J. Antimicrob. Agents 55 (2020) 105924.

[52] J. Qiu, B. Shen, M. Zhao, Z. Wang, B. Xie, Y. Xu, A nationwide survey of psychological distress among Chinese people in the COVID-19 epidemic: implications and policy recommendations, Gen. Psychiatr. 33 (2020) e100213.

[53] J. Lai, S. Ma, Y. Wang, Z. Cai, J. Hu, N. Wei, J. Wu, H. Du, T. Chen, R. Li, H. Tan, L. Kang, L. Yao, M. Huang, H. Wang, G. Wang, Z. Liu, H. Factors associated with mental health outcomes among health care workers exposed to coronavirus disease 2019, JAMA Netw. Open 3 (2020) e203976.

[54] M.S. Herridge, L.M. Chu, A. Matte, G. Tomlinson, L. Chan, C. Thomas, J.O. Friedrich, S. Mehta, F. Lamontagne, M. Levassuer, N.D. Ferguson, N.K. Adhikari, J.C. Rudkowski, H. Meggison, Y. Skrobik, J. Flannery, C.M. Lee, M. Levasseur, N.D. Ferguson, N.K. Adhikari, J.C. Rudkowski, H. Meggison, Y. Skrobik, J. Flannery, C. Thomas, J.O. Friedrich, S. Mehta, F. Lamontagne, M. Levassuer, N.D. Ferguson, N.K. Adhikari, J.C. Rudkowski, H. Meggison, Y. Skrobik, J. Flannery, C. Thomas, J.O. Friedrich, S. Mehta, F. Lamontagne, M. Levassuer, N.D. Ferguson, N.K. Adhikari, J.C. Rudkowski, H. Meggison, Y. Skrobik, J. Flannery, C.