Clinical Protocol Synopsis

1. Title

A self-directed mobile mindfulness intervention to address distress and burnout in frontline healthcare workers.

2. Background

Emotional distress and burnout are common amongst U.S. health care workers[1,2]. In nurses specifically, observational studies have estimated the rate of burnout to be as high as 50% [(3)]. Nurses are also more likely than the general population to report insomnia, depressive symptoms, and anxiety [4-8]. The onset of the COVID-19 pandemic has led to increased physical and psychological demands on frontline healthcare workers, as they have been asked to work more hours with an increased risk to their own personal health and safety [9,10].

Mindfulness is a type of mind-body therapy that promotes a practice of non-judgmental awareness that can alleviate distress by uncoupling emotional reactions and habitual behavior from unpleasant symptoms, thoughts, and emotions. LIFT is a mobile app which can assess levels of emotional distress via survey, and subsequently offer mindfulness content that has previously been used in ICU patients, where it was shown to reduce symptoms of depression, anxiety, and PTSD[11].

3. Focus of the Study and Specific Aims.

LIFT-HC is a pilot randomized waitlist control trial (RCT) that tests the efficacy of the LIFT mobile app in relieving symptoms of emotional distress amongst nurses directly caring for COVID-19 patients in the Duke University Health System.

AIM 1: To determine the feasibility of using the LIFT app among nurses directly caring for COVID-19 patients. *Hypothesis: Nurses taking care of COVID-19 patients will have high levels of Lift app use and low levels of dropout over the course of 1 month follow up.* Data collected by the app will inform the study team as to the frequency of use and compliance among participants randomized to receive mobile mindfulness content. Participants will be allowed to comment on usability of app and features that they thought worked well and did not work well. A subset of participants randomized to intervention with high app usage and a subset with low app usage will be approached to complete a telephone interview to comment on usability and areas for improvement in the app.

AIM 2: To assess the clinical impact of LIFT compared to control among nurses directly caring for COVID-19 patients at 1 month. *Hypothesis: Nurses using the LIFT app's mindfulness content will have reduced levels of emotional distress compared to usual care.* After completion of baseline studies, 100 nurses will be randomized in a 2:1 fashion to LIFT (intervention) or waitlist (control). Levels of emotional distress for all participants in both arms will be reassessed after 30 days via questionnaire completion. Surveys will assess anxiety (GAD-7), depression (PHQ-9), burnout (MBI), stress (PSS-4) as well as self-reported job performance quality and medical errors.

4. Study Population

This study will enroll nurses working primarily in units where they take direct care of patients with COVID-19.

Inclusion Criteria:

1. Adult ≥ 18 years of age
2. Currently working as a nurse primarily in an adult COVID unit at Duke University Hospital
3. English Fluency

Exclusion Criteria

1. Lack of access to either reliable smartphone with cellular data plan or home internet access.
2. Anticipation of leaving current position in ≤30 days.

5. Screening and Recruitment

No active screening to identify potential participants will take place. The study team will use e-mail and flyers as the main way to recruit participants. There will also be an in-person introduction to the study at nursing huddles, but this will direct potential participants to e-mail or flyers to enroll in the study if they wish to proceed. The IRB approved e-mail will contain a hyperlink to a website (https://lift.duke.edu/nurse/) that describes the study's purpose, duration, and risks and benefits. The e-mail/flyer will also contain a link to a video explaining the LIFT app and mindfulness therapy.

If a participant wishes to enroll, then they will be directed via hyperlinks in the e-mail or QR code in the flyer to download the generic Pattern Health mobile app platform from either the Google App store (for Android phones) or the Apple App store (for Apple phones). Both the e-mail and the flyer will contain contact information for the study PI, Dr. Pratt, so that all questions can be answered prior to consent.

6. Process of obtaining informed consent

Prior to conduct of study procedures, informed consent will be obtained from all participants. Consent will be obtained through Pattern Health app. After downloading the generic Pattern Health app as outlined in section 5., participants will enter the registration code "NURSE" contained in e-mail/flyer. This will then initiate the in-app self-guided consent process where participants sign an IRB-approved informed consent document electronically. A copy of the consent for each participant

will be saved within the Pattern Health server, and will be available for each participant via the app. On a monthly basis, a copy of the consents will be exported into secure, Duke University-approved, password protected, cloud systems (i.e., Box) for long term storage.

7. Data collection

All data will be collected via the LIFT app. Each participant, regardless of randomization arm, will be asked to complete the following surveys at the listed time points below:

- Baseline (upon app registration and randomization); T1
  - Baseline sociodemographic data
  - GAD-7, PHQ-9, MBI, and PSS-4
  - Single item questions regarding impact of COVID-19 on mental health
  - Single item questions regarding perceived job performance and medical errors
- T2 (30 days post-enrollment)
  - GAD-7, PHQ-9, MBI and PSS4
  - Single item questions regarding perceived job performance and medical errors

Participants randomized to the intervention arm will also be asked to complete the following:

- T2 (30 days post-enrollment)
  - An open-ended narrative question commenting on usability of the app

8. Randomization

Randomization will happen via the LIFT app. After completion of the in-app consent process, as well as a baseline demographic survey, participants will be randomized in a 2:1 fashion to intervention vs. waitlist (control). Randomization will be stratified based on baseline PHQ-9 scores and years of experience as a nurse.

9. LIFT-Healthcare Worker procedures.

This is a single site, pilot randomized waitlist control trial exploring feasibility of use and clinical impact of the LIFT app amongst nurses directly caring for COVID-19 patients. We aim to enroll 100 participants. Nurses agreeing to participate will be asked to download and register the LIFT app on their mobile device. Consent will be provided electronically through the LIFT app. After signing consent, participants will be randomized via the LIFT app in a 2:1 fashion into two arms:

- Arm 1: Intervention group (access to LIFT mindfulness content)
- Arm 2: Waitlist (delayed access to LIFT content)

LIFT is a self-directed mobile app platform based on a solid conceptual model that guides participants through a 1-month program. LIFT content includes 4 weekly app-based sessions as previously tested in a pilot RCT (NCT02701361). 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). The app-based approach to non-responders, defined as those whose PHQ-9 score has increased in comparison to the previous week or whose PHQ-9 score is ≥20, uses the app's logic to display hovering messages and notifications within the app that may be applicable to the user. Depending on whether emotional or somatic depression symptoms are dominating the PHQ-9 score for the individual, a unique video is shown within the app that features the study interventionists leading a brief exercise in which the participant is coached by the interventionist in the application of mindfulness for the symptoms the participant has endorsed. The app-based approach to non-responders has 8 unique videos, 2 for each week (i.e., one tailored to emotional symptoms, one tailored to somatic symptoms).

AIM 1, which is to determine the feasibility of using the LIFT app among nurses directly caring for COVID-19 patients, will be assessed via the app which tracks user fidelity and adherence, and the use of an interactive dashboard for administrative users (i.e., study team) to track individual participant use. The open-ended narrative question at T2 will also help provide guidance for improving usability in future studies, as will directed telephone interviews with participants with high and low app usage as outlined above.

AIM 2, which is to assess the clinical impact of LIFT compared to control among nurses directly caring for COVID-19 patients at 1 month, will be assessed by comparing changes from in the GAD-7, PHQ-9, MBI-7, and PSS-4 over the study duration between intervention and waitlist groups.

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

Statistical Design and Analyses Plan

The primary goal of this pilot RCT is to explore the feasibility and impact of the LIFT app in healthcare workers to inform a definitive future clinical trial. To do so, we will test differences between observed and a priori defined benchmarks among LIFT recipients using t-tests for continuous variables and chi-square tests for categorical variables.

The secondary goal is to estimate a reasonable range of clinical effect of LIFT in comparison to a usual care control condition. General linear models will be used to estimate mean changes and corresponding 95% confidence intervals (CIs) in psychological distress (i.e., GAD-7, PHQ-9) for each treatment group over the 1-month study period using SAS PROC MIXED (SAS Institute, Cary NC). We will fit the models with an unstructured covariance matrix to better understand and represent the correlation between repeated measures.

Participants with low baseline levels of emotional distress, as indicated by a PHQ-9<5, will not be excluded from participating in the study, but we do not plan to use them in the primary analysis.

Sample Size and Power

This exploratory trial is not intended to test LIFT efficacy. While the 100-person sample size reflects the pragmatics of recruitment during a short enrollment period, it is large enough both to inform us about feasibility of use as well as to provide meaningful confidence intervals for our estimates as was true for the similarly sized LIFT pilot RCT.

11. Subject Participation and Duration

It will require 1 month (30 days) for participants to complete the entire study, from the time of randomization to completion of T2 surveys.

12. Study Duration

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

13. Costs to the Subject

There are no costs to participants.

14. Compensation

Participants will receive a $10 gift-card for completion of the study.

15. IRB

Duke University Health System (DUHS) IRB will be utilized as the IRB of record for this project pilot randomized, RCT and the future RCT.

16. Risk-benefit assessment

The overall study is believed to be a minimal risk trial. However, there is a potential risk for mild anxiety when answering survey questions although this has not been observed in previous similar studies to date. Participants will be informed that should they need to pause survey completion at any time, they can do so and return at a later time to complete the survey. They may also choose to not answer any questions that make them uncomfortable. The LIFT app also provides numbers for distress resources nationally and at Duke.

Additionally, as with any research, but especially one that involves technology (i.e., mobile app), there is always a potential loss of confidentiality. Appropriate safeguards are in place to ensure confidentiality, as described in the RDSP. Participants can choose not to participate and continue receiving normal standard of care.

Adequacy of protection against risks

Recruitment and informed consent procedures

First, the Duke Institutional Review Board (IRB) will review and approve the safety and ethics of the study protocol before study initiation. Informed consent will be required from all participants. Participant enrollment is completely voluntary, as the potential participants will not be individually approached by study personnel for enrollment.

Protections against risk

General oversight

There are several ongoing mechanisms for monitoring the occurrence of adverse events. The investigators will perform day-to-day monitoring of the study. This research team has demonstrated in research involving nearly 1,500 participants to date that they can keep careful records of participants study engagement and wellbeing. Careful monitoring of all persons entering the study will minimize attrition and will ensure the clinical safety. This monitoring is facilitated by a telephone number (PI's cell phone) and email address (PI's e-mail address) provided to participants upon entry into the study to report concerns related to study participation, weekly meetings between the clinical research coordinators and co-investigators to discuss study progress and any adverse events, and direct supervision of the study by the PIs.

Plans to prevent coercion and to ensure voluntary participation

We will strive to create an environment free of any coercive practices for participants. We will stress that study involvement is absolutely voluntary and that choosing to participate or not participate will not their employment in any way. Dr. Cox will not be involved in any recruitment activities in the medical ICU, as he holds a clinical leadership position in that unit, so as to avoid the appearance of coercion. No nursing managers will be involved in recruitment either, also to avoid the appearance of coercion.

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

17. Data & safety monitoring

Data Accuracy and Protocol Compliance.

The PI will supervise the study, including data management, data accuracy, and protocol compliance. The PI will be the chief data manager and will adhere to established federal and institutional safety and protection guidelines. To assure data accuracy, the PI 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.

Quality Assurance

First, the electronic data entry system "forces" responses to key questionnaire items (e.g., baseline demographics and surveys) before allowing progression to treatment arm randomization and access to app content, thereby minimizing missing data at timepoint 1. Similarly forced responses are required at timepoint 2 before a participant can be noted to have completed the study. 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.

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

It is recognized that there is a slight risk that some participants may experience mild anxiety when answering survey questions. This has not been experienced to date from similar studies previously performed. However, should a participant report symptoms related to increased anxiety/emotional distress, an alert will automatically be triggered via the mobile app and sent to the study team (i.e. the study manager, PI, and co-PI). When necessary, participants who experience psychological distress related to completing questionnaires will be referred for appropriate psychiatric or psychological care. In addition, phone numbers for institutional, local, and national resources for acute distress will be available in the app.

Certain questions in baseline and completion questionnaires will trigger “alert” values (e.g. suicidal ideation). For specific symptoms (such as the suicidal ideation), a delegated study team member (Dr. Cox or Dr. Pratt) will 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 participants and can refer those with concerning symptoms as appropriate.

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

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 due to the ongoing stress of work and the COVID-19 pandemic. Therefore, for this study, only increased levels of distress related to completing the questionnaires or completing the mobile mindfulness therapy 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, or death. All serious adverse events will be reported within the standard timelines required to the IRB as appropriate and when applicable.

It is expected that some LIFT practices will be missed by most participants. 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 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 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.

Characteristics of an Adverse or Serious Adverse Event

To assess relationship of an event to study intervention, the following guidelines are used:

1. Related (Possible, Probable, Definite)
    1. The event is known to occur with the study intervention.
    2. There is a temporal relationship between the intervention and event onset.
    3. The event abates when the intervention is discontinued.
    4. The event reappears upon a re-challenge with the intervention.
2. Not Related (Unlikely, Not Related)
    1. There is no temporal relationship between the intervention and event onset.
    2. 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

Serious (fatal or life-threatening) SAEs that are unanticipated and that are related to the intervention will be reported to the IRB in the following manner:

(a) Immediately (within 24 hours) upon learning of an unanticipated study-related death, study personnel will notify the IRB via e-mail or fax by providing a brief summary of the event. Then, within 1 week (five business days), study personnel will send to the IRB a Safety Event submission in the eIRB.

(b) For a reportable serious adverse event, study personnel will notify the IRB within five business days of the investigator becoming aware of the event. Study personnel will send a Safety Event

submission in the eIRB.

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.

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.

17. Data management.

All data is captured via the electronic data capture system (EDC) has been developed and is supported by programming service providers, Pattern Health. This data will be exported data will be exported from Pattern Health Servers in .CSV format, and stored in secure, Duke University-approved, password protected, cloud systems (i.e., Box). Study staff will complete electronic case report forms (eCRFs) securely integrated within the LIFT platform that includes an electronic database. Study personnel will utilize these data systems to create scheduled reports on the trials' conduct (e.g., study milestones) to enhance the study's quality. We will monitor the quality and consistency of data in a number of ways. Monthly data cleaning will be done by the study team using customized group-blinded reports that will identify missing, outlier, or nonsensical data at time points when remedying them is feasible.

18. Privacy, Data Storage & Confidentiality

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 participant. Further, names, birth dates, telephone numbers, and addresses will be stored securely as described in the RDSP and only accessible by delegated study team members. Study participants cannot view data via the ePRO system or the electronic data capture (EDC) system, supported by Pattern Health. Participants 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 participant reported outcomes (ePRO) function, an electronic data capture (EDC) system, and a separate Duke University-approved, password protected, cloud systems (i.e., Box).

- **LIFT app**: LIFT is 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.
- **EDC:** The electronic data capture system (EDC) has been developed and is supported by programming service providers, Pattern Health. As noted above, Pattern Health maintains all appropriate PHI and HIPAA regulations related to human subject research and data privacy and integrity pertaining to data management and IT security. The EDC will be a central location in which all study related data will be stored. Data will be exported and analyzed for research purposes as described elsewhere.

All data entry will be self-completed by participants using the validated ePRO system accessed via the LIFT app. The LIFT 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 principal investigator will do routine data cleaning.

Confidentiality

Subjects will not be identified on any study reports. University firewalls, multiple passwords, and encryption programs protect the security of the electronic data system, which will be housed on a highly secure Duke University server. All personal computers are located in lockable offices

and are accessible only by frequently changed passwords. The server room is accessible only to designated University Systems Administrators.

References:

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