Statistical analysis plan

Title	Optimizing a self-directed mobile coping skills training intervention to improve cardiorespiratory failure survivors' psychological distress
Short title	Blueprint
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Activity Log

10/22/21: SAP creation

1 Study Overview

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. To fill this gap, we have developed an innovative, native mobile coping skills training (CST) program that promotes automated care delivery and self-management of symptom-related distress. CST, by improving self-efficacy and adaptive coping, reduces psychological distress symptoms, thereby also improving quality of life.

Previous trials, in which this pilot randomized clinical trial (RCT) is based, have demonstrated that adaptive coping skills training (CST), is an active response for managing stressful events such as the experience of a critical illness. ICU survivors have emphasized in their own words the importance of coping to their perceived quality of life. While the use of adaptive coping skills (e.g., relaxation, positive reframing, problem solving) is associated with decreased psychological distress, ICU survivors infrequently apply such strategies.

This study is a 2 year pilot study that employs CST methods via a mobile app 'Blueprint'. There are 3 arms that participants can be randomized to: Intervention group 1 will receive access to the Blueprint app with a CST therapist introduction call (Arm 1), Intervention group 2 will receive access to the Blueprint app with no introduction call (Arm 2), or a control group of usual care with no access to the Blueprint app or introduction call (Arm 3). All participants will complete surveys at 4 timepoints: baseline (T0), discharge (T1), 1 month post discharge (T2), and 3 months post discharge (T3). The intervention groups will receive access to the Blueprint app which provides a 4 week course of various topics of CST skills. Participants in the intervention group are asked to utilize the app during their first month post-discharge.

1.1 Study Aims

1.1.1 Primary Aim 1

Determine the feasibility and acceptability of the Blueprint app.

1.1.2 Primary Aim 2

Determine the clinical impact on ICU survivors' 1 and 3 month psychological distress symptoms of intervention groups compared to usual care control.

1.2 Study Hypotheses

1.2.1 Primary Hypothesis 1

The primary hypothesis is that the mobile CST app 'Blueprint' will be feasible and acceptable based on comparison of observed to a priori benchmarks.

1.2.2 Primary Hypothesis 2

The secondary hypothesis is, compared to usual care, the intervention participants will have improvement in symptoms of psychological distress (HADS and PTSS scores) at the 1 and 3 month timepoints (T2 and T3).

2 Study Design and Study Population

Participants are patients who were admitted to the ICU and were critically ill with either respiratory failure/insufficiency or cardiac failure/insufficiency. Additionally, participants experienced a high level of distress (HADS ≥8) at baseline.

This is a randomized clinical trial, where participants are consented and randomized to 1 of 3 arms (2 intervention arms, 1 control arm) in a 1:1:1 ratio. A total randomized sample size of 45 participants (15 per arm) was targeted. A method of minimization was used for randomization, with the aim to balance 3 stratification characteristics: ICU service (medical, surgical), baseline HADS score (<14, ≥14), and age (<50, ≥50).

2.1 Inclusion Criteria

Patients included in Blueprint satisfied the following inclusion criteria:

At time of hospital admission:

- Age ≥ 18 years
- Managed in an adult ICU, step-down unit, or specialized care unit for ≥ 24 hours during the time in which inclusion criterion #3 is met.
- Presence of acute cardiac or respiratory failure, defined as having ≥ 1 of the following:
    - Acute respiratory failure / insufficiency, defined as ≥1 of the following:
        - Mechanical ventilation via endotracheal tube for ≥4 hours
        - Non-invasive ventilation (CPAP, BiPAP) for ≥4 hours in a 24-hour period provided for acute respiratory failure in an ICU (not for obstructive sleep apnea or other stable use)
        - High flow / opti-flow nasal cannula or face mask oxygen use
        - ≥25% increase in baseline nasal cannula rate
    - Acute cardiac failure / insufficiency, defined as ≥1 of the following:
        - use of vasopressors for shock of any etiology
        - use of inotropes for shock of any etiology
        - use of pulmonary vasodilators
        - use of aortic balloon pump or cardiac assist device for cardiogenic shock
        - use of diuretic intravenous drip
- Cognitive status intact, defined as:
    - No history of significant cognitive impairment (e.g., dementia)
    - Absence of current, significant cognitive impairment (≥ 3 errors on the Callahan cognitive status screen)
    - Decisional capacity present
- 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:

    - Treatment for severe or unstable mental illness (e.g., psychosis, schizophrenia) within the last 6 months preceding the current hospital admission
    - Active substance abuse that impairs ability to participate
    - Endorsing suicidality at time of admission or informed consent discussion
- English fluency.

At time of discharge:

- Elevated baseline psychological distress symptoms, defined as HADS total score of $\geq$ 8 at the completion of survey 1, T1.

2.2 Exclusion Criteria

Patients were excluded from Blueprint if they satisfied the following exclusion criteria:

At time of hospital admission:

- Complex medical care expected soon after discharge (e.g., planned surgeries, transplantation evaluation, extensive travel needs for follow up care, disruptive chemotherapy/radiation regimen)
- Unable to complete study procedures as determined by staff.
- Lack of access to either reliable smartphone with cellular data plan or wifi

At time of hospital discharge:

- Failure to randomize within 1 month after discharge from the hospital to home.
- Failure to access app within 1 month after randomization.

The following additional exclusion criteria were applied after data collection:

- Any data recorded after a participant has withdrawn

2.3 Data Acquisition

File path for raw data: ..\CRU\Pulmonary\Christopher Cox\Pro00101848 mCST Blueprint\Main Analysis\DATA\RAW

File Name	Description
Blueprint Data Export XXXX.xlsx	Blueprint App data pulled by Jennifer This file has multiple sheets.
BlueprintScreeningAn_SAS_xxxx	Blueprint REDCap data pulled by Alice

Note: Data will be analyzed in SAS 9.4.

3 Outcomes, Exposures, and Variables of Interest

3.1 Primary Outcome(s)

Variable	**Dataset**	**Description**	**Specifications**

hads	Blueprint/Baseline	HADS total score at T0	Continuous
Hads	Blueprint/T1	HADS total score at T1	Continuous (may need to be derived from item scores HADS01—HADS14)
Score_hads	Blueprint/T2	HADS total score at T2	Continuous (may need to be derived from item scores HADS01—HADS14)
Score_hads	Blueprint/T3	HADS total score at T3	Continuous (may need to be derived from item scores HADS01—HADS14)
ptss	Blueprint/T1	PTSS total score at T1	Continuous (may need to be derived from item scores ptss_1—ptss_10)
Score_ptss	Blueprint/T2	PTSS total score at T2	Continuous (may need to be derived from item scores ptss_1—ptss_10)
Score_ptss	Blueprint/T3	PTSS total score at T3	Continuous (may need to be derived from item scores ptss_1—ptss_10)
D3mo_HADS	Blueprint/T3 Blueprint/T1	Change in HADS at 3 months	Derived as Score_hads(T3) - ???
D1mo_HADS	Blueprint/T2 Blueprint/T1	Change in HADS at 1 months	Derived as Score_hads(T2) - ???
D3mo_PTSS	Blueprint/T3 Blueprint/T1	Change in PTSS at 3 months	Derived as Score_ptss(T3) - ???
D1mo_PTSS	Blueprint/T2 Blueprint/T1	Change in PTSS at 1 months	Derived as Score_ptss(T2) - ???
ADLs/IADLs	T1, t2, t3		Not really an outcome but…
Systems Usability Scale	T1		
PHQ-10 physical symptom scale	T1, t2, t3		
Quality of life 100-point VAS	T1, t2, t3		
List		Feasibility	Eligibility: 70% of positive screens Consent: 80% of eligible Randomized: 80% of consented Retention: 80% Adherence: 75% of tasks ***note that these need to be defined a bit more specifically
CSQ-8	`	Acceptability	

3.2 Primary Exposure(s)

Variable	Dataset	Description	Specifications
Plan_name	Blueprint/Participants	Trial Arm	A multi-level categorical variable - Blueprint Screening & Baseline: Exclude - Blueprint (Group 1): Arm 1 - Blueprint (Group 2): Arm 2 - Blueprint (Control): Arm 3

3.3 Other Variables of interest

Variable	**Dataset**	**Description**	**Specifications**

4 Statistical Analysis Plan

All analyses will be done using SAS 9.4. Continuous variables will be summarized with mean/standard deviation/median/Q1-Q3/range and categorical variables with frequency counts and percentages. Number of missing data for each variable will be reported.

4.1 Analysis Plan for Primary Aim 1

1. First, we will describe our cohort. In Table 1 we will summarize participant characteristics overall and by arm. No statistical tests will be provided as this was a randomized trial, and ideally groups should be balanced.
2. To assess Aim 1 for feasibility and acceptability we will evaluate CSQ-8 and SUS scores. Results will be reported in Table 2.

4.2 Analysis Plan for Primary Aim 2

1. To address Aim 2, we will describe the secondary outcomes at each time point by arm, as well as the change in scores at T2 and T3 from T1 in Table 3. Any additional secondary outcomes will be described in this table.
2. To assess if there was change at each timepoint of interest between the arms we estimate mean changes (and 95% CI) from baseline to each timepoint for each distress outcome (HADS, PTSS) using a general linear model (PROC MIXED). Model parameters will include treatment arm (1, 2, 3), time indicator (T1, T2, T3), and an arm by time interaction term. Change estimates and CI's will be reported in Table 4. To quantify clinically important differences, rather than report p-values which is not recommended for pilot studies with

small sample sizes, we will compare the estimated group mean differences and 95% CI's to half (0.5) of the baseline standard deviation (SD) of each outcome score.

5 Appendix I: Planned figures and tables

Figure 1: CONSORT Diagram

Table 1: Demographic characteristics of participants at baseline

Characteristic	**Arm 1: Intervention Group 1 (Blueprint + Therapist) N=**	**Arm 2: Intervention Group 2 (Blueprint only) N=**	**Arm 3: Control (Usual Care) N=**	**Total N=**
Stratification Variables				
Age				
<50				
≥50				
ICU Service				
Medical				
Surgical				
Baseline HADS				
<14				
≥14				
Other Baseline Characteristics				
Age				
Mean (sd)				
Median				
Q1, Q3				
Range				
Gender				
Male				
Female				

Table 2: Feasibility and Acceptability

Characteristic	**Arm 1: Intervention Group 1**	**Arm 2: Intervention Group 2**	**Arm 3: Control (Usual Care)**	**Total N=**

	(Blueprint + Therapist) N=	(Blueprint only) N=	N=		
Feasibility					
% Consented	--	--	--		
% Randomized	--	--	--		
% Retained					
% Completed Surveys					
T1					
T2					
T3					
All timepoints					
% Completed all intervention components			--	--	
Acceptability					
CSQ Score					

Table 3: Participant Outcomes

Characteristic	**Arm 1: Intervention Group 1 (Blueprint + Therapist) N=**	**Arm 2: Intervention Group 2 (Blueprint only) N=**	**Arm 3: Control (Usual Care) N=**	**Total N=**
Hospital LOS (Discharge – admission)				
Hospital discharge disposition				
3 month disposition				

Table 4: Observed and Estimated mean score and differences by Arm and Time for HADS and PTSS outcomes

	Baseline (T1?)	**1 Month (T2)**	**3 Months (T3)**	**Δ 1 month - Baseline**	**Δ 3 months- Baseline**
HADS					
Observed Score					
Arm 1 (BP + Therapist)					
Arm 2 (BP only)					
Arm 3 (Control)					
Estimated Mean Score (95% CI)					
Arm 1 (BP + Therapist)					
Arm 2 (BP only)					

Arm 3 (Control)					
Diff (Arm 1 – Arm 3)					
Diff (Arm 2 – Arm 3)					
PTSS					
Observed Score					
Arm 1 (BP + Therapist)					
Arm 2 (BP only)					
Arm 3 (Control)					
Estimated Mean Score (95% CI)					
Arm 1 (BP + Therapist)					
Arm 2 (BP only)					
Arm 3 (Control)					
Diff (Arm 1 – Arm 3)					
Diff (Arm 2 – Arm 3)					