Behavioral Activation-Rehabilitation to Improve Depressive Symptoms & Physical Function After Acute Respiratory Failure

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JHM IRB - eForm A – Protocol

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1. Abstract

a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

A growing number of Acute Respiratory Failure (ARF) survivors are burdened by depressive symptoms and physical impairments that last for years after intensive care unit discharge. Notably, depressive symptoms are independently associated with subsequent development of new impairments in physical functioning. There are no randomized controlled trials (RCT), in ARF survivors, evaluating any intervention for depression. To improve mental and physical health outcomes in ARF survivors, the following gaps within existing patient-oriented research must be addressed: 1) interventions to improve depressive symptoms and associated physical functioning impairments, 2) evaluation of modifiable psychosocial risk factors for depressive symptoms, and 3) validation of screening instruments to assess depressive symptoms. This K23 application, by Ann Parker, MD, aims to address these gaps by designing and conducting a pilot RCT (Aim 1) of an intervention combining Behavioral Activation and physical rehabilitation (delivered via telephone and 2 home visits over 12-weeks) versus a "usual care" control group, and evaluating its feasibility (primary outcome) and efficacy to reduce depressive symptoms and improve physical functioning (secondary outcomes). Behavioral Activation, as proposed for this pilot RCT, is an evidence-based psychological treatment for depression, which increases adaptive behaviors to achieve patient-valued goals. This project will evaluate the feasibility and efficacy of the BA-R intervention both quantitatively and qualitatively, through semi-structured interviews. Using the combined patient cohort from the intervention and control groups of the RCT, Dr. Parker also will evaluate modifiable psychosocial risk factors for depressive symptoms in ARF survivors and the association between the intervention and these modifiable factors (Aim 2), and the measurement properties of two commonly used depression screening instruments in ARF survivors versus a "gold standard" clinician diagnostic interview that she will be trained to perform (Aim 3).

2. Objectives *(include all primary and secondary objectives)*

Aim 1: To conduct a single-site, pilot RCT (N=54) evaluating the feasibility (primary objective) and efficacy (secondary objective) of a 12-week behavioral activation-rehabilitation (BA-R) intervention versus "usual care", in acute respiratory failure (ARF) survivors.
Hypothesis 1a: A 12-week BA-R intervention in ARF survivors will be feasible, as demonstrated by an average accrual rate of 1.5 patients per month, completion of ≥80% of the 12-week phone calls, and ≤15% of enrolled patients lost to follow-up at the end of the 12-week intervention.
Hypothesis 1b: At the end of the 12-week BA-R intervention, ARF survivors in the BA-R versus "usual care" group will demonstrate decreased depressive symptoms, less impairments in physical function and quality of life, and reduced healthcare utilization
Hypothesis 1c: We will conduct qualitative research, using thematic analysis, to identify key barriers and facilitators to engaging with the BA-R intervention, as well as perceived satisfaction, acceptability and feasibility of BA-R.

Aim 2: To evaluate the association between resilience, coping and social engagement with depressive symptoms and the association between these factors and the BA-R intervention among at-risk ARF survivors from Aim 1.
Hypothesis 2a: Increased resilience, adaptive coping, and social engagement are associated with fewer depressive symptoms using the combined patient cohort from the BA-R and control groups in Aim 1
Hypothesis 2b: At the end of the 12-week intervention, ARF survivors in the BA-R versus "usual care" control group will demonstrate improvements in coping, resilience and social engagement.
Hypothesis 2c: We will conduct qualitative research, using thematic analysis, to identify the role of resilience, coping, and social engagement in recovery from ARF.

Aim 3: To evaluate measurement properties (e.g., sensitivity, specificity, positive/negative predictive values) of two commonly-used depression screening instruments (i.e., Hospital Anxiety and Depression Scale (HADS) and Personal Health Questionnaire Depression Scale-8 (PHQ-8)) for detecting depressive symptom severity using a "gold standard" depression measure (i.e., Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (SCID-5)), in at-risk ARF survivors from Aim 1.
Hypothesis 3: The HADS and PHQ-8 will adequately discriminate depressive symptom severity compared to the SCID-5 "gold standard" using the combined patient cohort from the BA-R and control groups in Aim 1.

3. Background *(briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)*

BACKGROUND AND SIGNIFICANCE: Annually, >750,000 Americans have acute respiratory failure (ARF) requiring mechanical ventilation.[1-3] As the population ages, the incidence of ARF is increasing, with a projected 80% rise by 2026.[4,5] At the same time, due to medical advances, ARF survival is improving,[6] leading to a growing number of survivors who frequently experience significant psychological sequelae (e.g., depression)[7] and physical morbidities (e.g., impairments in physical functioning).[8-12] After ARF, the cumulative incidences, over 2 years, of new depressive symptoms and impairment physical functioning are 40% and 66%, respectively.[10] Psychological and physical impairments may synergistically yield worse outcomes,[13] with ARF research, conducted by my mentors, showing depressive symptoms are an independent risk factor for new onset of impaired physical functioning.[10]

As part of the scientific premise for this proposal, prior work, conducted by co-mentor, Mark Hegel, PhD, showed that only treating depression in other medically ill populations with functional impairments is NOT sufficient to achieve optimal improvement in patient outcomes. With depressed, medically ill older

adult outpatients, there were improvements in emotional outcomes, without improvements in physical functioning.[14] In a depression prevention study in older adults with low vision, depression incidence was halved at 2-month follow up, but the benefit was not maintained at 6 months.[15] However, a depression prevention study that included BOTH a depression treatment (Behavioral Activation (BA)) and an occupational therapist (OT) rehabilitation intervention again halved the incidence of depression that was then sustained for 4 months AND improved physical function.[16] These findings support including physical rehabilitation with psychological interventions for at-risk chronically ill populations.

In ARF survivors, in addition to a paucity of efficacious interventions to address impairments in physical function and depressive symptoms, gaps remain in the existing literature regarding understanding and measuring depressive symptoms. First, while prior studies have identified risk factors for depressive symptoms in ARF survivors,[7] few have evaluated important psychosocial factors, such as social engagament,[17-20] resilience[21-24] and coping,[18,25-29] that may be important in designing interventions. Moreover, a "gold standard" depression diagnostic outcome measure is not feasible for large studies,[7,30] and no existing depression screening instruments have been evaluated against a "gold standard" clinician diagnostic interview in ARF survivors.[31]

The urgent need to identify modifiable risk factors for depressive symptoms and develop new strategies that address the multi-faceted nature of impairments after ARF has been recognized by the American Thoracic Society and Society of Critical Care Medicine.[13,32] Further, as per the NHLBI's new Strategic Vision, there is a need to develop interventions, within a multidisciplinary framework, to facilitate behavioral modification for disease treatment and incorporate such interventions into community-level patient care.[33]

SCIENTIFIC PREMISE: Gaps in Existing Literature on Risk Factors for Depressive Symptoms in ARF Survivors: Resilience,[34,35] coping style[36] and social support and engagement[37,38] are inter-related psychosocial factors associated with depressive symptoms in other populations, but have been evaluated in only 2 studies in ARF survivors.[7,39,40] Moreover, resilience and coping are important in mediating the positive effects of depression interventions in other populations,[41-43] but have had little study in ARF survivors. Moreover, engaging social support networks may enhance interventions to address depressive symptoms.[44] Hence, there are major gaps in existing literature for these factors.

No Validation of Depression Screening Instruments against a "Gold Standard" in ARF Survivors: A recent Scoping Review of outcome measures in ARF research reported the Hospital Anxiety and Depression Scale (HADS)[45] was the most common depression instrument (60% of ARF studies).[30] The Personal Health Questionnaire-9 (PHQ-9), likewise, is widely used both clinically and in research studies.[46] The PHQ-8 and PHQ-9 are highly correlated,[47] differing only in omission of 1 question regarding self-harm, and for medicolegal reasons, the PHQ-8 is often preferred for research.[48,49] While both the HADS and PHQ-8 are valid and reliable in other populations, their measurement properties have never been evaluated against a "gold standard" clinician diagnostic interview in ARF survivors. Importantly, ARF patients may differ from other populations in etiology and manifestations of depressive symptoms given the potential contribution of co-morbidities[50] and the physiologic stress of critical illness (e.g., prolonged inflammatory state).[7] Indeed, our systematic review demonstrated that traditional risk factors for depressive symptoms in the general population (e.g. sex) did not apply to ARF survivors, suggesting that other factors, such as neuro-inflammation, might play a larger role in these patients.[7] These issues make validation[51] of depressive screening instruments in this unique ARF survivor population essential to the validity of future research in the field.

Strengths and weaknesses of Existing Research in ARF Survivors: Compared to the large number of studies describing impairments in ARF survivors, a systematic review reported that the number of interventional studies is modest, and interventions with proven effects are "rare."[52,53] Recent systematic reviews demonstrate there are no existing trials specifically evaluating evidence-based depression interventions and only one[54] evaluating a combined psychological/physical intervention in ARF.[7,52,53,55,56]

Three randomized trials in ARF survivors offer insights. First, an 8-week, home-based exercise intervention with home visits and phone calls from a physical therapist (PT) versus usual care in 195 ARF survivors discharged to home found no significant effect on physical function, measured via 6-minute walk test (mean outcome: ~400 meters) and SF-36 survey (mean outcome: ~1.5 SD below norm) at the end of treatment (8 weeks), with little change at 26 weeks.[57] The investigators hypothesized poor adherence to the exercise intervention influenced this null finding. Second, an exercise intervention in 150 ARF patients randomized to rehabilitation in-ICU and continued for 8 weeks as outpatient versus usual care showed no significant effects on 6-minute walk test (primary outcome) or quality of life at discharge, 3, 6, or 12 month follow-up.[58] Adherence with the outpatient rehabilitation intervention was poor (41%) and investigators hypothesized that (1) a home-based (vs. clinic-based) intervention may be superior to improve adherence and (2) failure to address psychological problems contributed to null results. Finally, the authors suggested that future studies use outcome measures focused on participation restrictions in the home (e.g. patient-reported physical function), which may demonstrate treatment effects beyond standardized performance-based physical measures (e.g., 6-minute walk test). Third, a United Kingdom (UK) trial,[54] which randomized patients to a rehabilitation manual vs usual care, demonstrated better quality of life scores (via SF-36 survey) at the end of the 6-week intervention. However, there was no difference in depressive symptoms between the two groups. Given vastly lower access to outpatient physical rehabilitation, as part of "usual care" in the UK vs. USA, these results are not generalizable to the USA setting.

Lack of Clinical Trials Demonstrating Effective Interventions to Improve Depressive Symptoms in ARF: In a systematic review by our group, there was a paucity of clinical trials evaluating an intervention specifically to reduce depressive symptoms in ARF survivors,[7] and there was preliminary evidence supporting post-ICU outpatient physical rehabilitation interventions to improve depressive symptoms in ARF survivors.

Behavioral Activation is Effective & Accessible Treatment for Depression: For depression, behavioral activation (BA) is the primary behavioral treatment within the class of evidence-based psychotherapies known as Cognitive Behavioral Therapy.[59,60] BA theory holds that inadequate environmental reinforcement (i.e., behaviors leading to positive or desired outcomes) and/or too much environmental punishment (i.e., behaviors leading to aversive or undesired outcomes), can contribute to depression via extinction of adaptive behaviors and avoidance of taking action.[60,61] BA addresses these issues by "activating" depressed persons to re-engage with their environments. BA interventions for depression have shown large effect sizes (e.g., 0.87).[62] BA is superior to cognitive therapy (the most widely studied psychotherapy for depression) with comparable effect to antidepressant medication, even for severely depressed patients.[63] Moreover, these positive effects of BA were retained 2 years later and comparable to continued medication treatment.[64] Finally, BA is time-efficient, not requiring advanced skills or complex training, making BA suitable for wide-scale dissemination.[62] For additional SCIENTIFIC PREMISE, see Section 3.1

Summary of Significance: Given the increasing number of ARF survivors, and associated public health burden due to long-lasting mental and physical impairments, research evaluating modifiable psychosocial risk factors and establishing validated screening instruments for future research is a priority as per the American Thoracic Society, Society of Critical Care Medicine and NHLBI's strategic vision. Moreover, designing effective interventions to address co-existing, long-lasting psychological and physical impairments is essential to enhancing recovery in ARF survivors as per existing literature. Existing studies are limited, focused primarily on physical interventions, and not demonstrating efficacy. Improving existing interventions by addressing depressive symptoms, physical functioning AND adaptation to ARF survivorship is a key component missing in prior studies; the proposed BA-R intervention addresses this gap.

PRELIMINARY DATA: Depressive Symptoms and Physical Impairments are Very Common in ARF: Our research team has conducted seminal studies on the psychological and physical impairments of ARF

survivors. These papers, several of which were authored by Dr. Parker, include systematic and narrative reviews regarding post-ARF depression,[7,56,65] PTSD,[65-67] anxiety,[65,68] neuromuscular abnormalities,[69-71] and physical impairments.[72-75] Importantly, our recent systematic and scoping reviews found limited prior research in ARF survivors regarding: 1) modifiable risk factors (e.g. resilience, coping) for depressive symptoms,[7] 2) consensus regarding depression screening instruments,[30] and 3) comparison of any depression screening instrument against a "gold standard" diagnostic interview.[31] Our research demonstrated high prevalences of depressive symptoms and physical impairments after ARF (40% and 66%, respectively), and depressive symptoms are independently associated with new impairments in physical functioning (OR=2.7, P=0.02).[10]

Behavioral Intervention Research in Medical Populations: Mark Hegel, PhD (co-mentor) previously designed a psychological intervention similar to the proposed BA intervention, called Problem Solving Therapy (PST), administered by nurses in primary care,[76] for the largest geriatric depression treatment trial (N=1801): Project IMPACT.[77] Participants receiving PST (vs. a community-based therapy control) showed significantly improved depressive symptoms at 12 months post-intervention.[78] Thereafter, his group conducted RCTs to evaluate PST to prevent depression in older adults after stroke[79] and with macular degeneration.[15,16] PST was superior to usual care controls, and equivalent to antidepressant medication. More recently, Dr. Hegel evaluated delivery of PST via Skype (Tele-PST) to homebound elders with depression, showing that Tele-PST was highly acceptable.[80-82] This evidence shows that this intervention, that is closely related to BA, is effective in adults with medical co-morbidities and functional impairment, when administered in-person, by phone or by Skype. These studies demonstrate our group's proficiency with conducting RCTs of psychosocial, phone-assisted interventions. Drs. Hegel and Lyons (co-mentors) also conducted research integrating Behavioral Activation with PST and occupational therapy (OT) interventions (BA-Rehabilitation or BA-R) for cancer survivors[83-86] and for older adults with macular degeneration.[16] The following theories provide the foundation for the prior research: (1) OT, which emphasizes participation in daily activities, is synergistic with BA and PST, (2) having BA provided by OT and other non-mental health providers expands its accessibility (BA requires less psychotherapeutic expertise than PST), and (3) the unique treatment focus of OT may extend the effectiveness of BA for improving both psychological and physical functioning.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

<u>Overview of Research Methods for Aims 1, 2, & 3</u>

A single cohort of patients will be used for all 3 Aims (i.e. both intervention and control groups recruited into the randomized controlled trial (RCT) will form a single cohort for analyses in Aims 2 and 3). We will enroll 54 patients from all Johns Hopkins Hospital adult ICUs. If patients are lost to follow-up, we will enroll up to 10 additional patients to obtain 12-week outcomes assessments on a total of 54 patients (27 in each group). Oral informed consent will be obtained from all participants.

Aim 1 Methods: We will conduct a single-site, pilot RCT (N=54) evaluating the feasibility (primary objective) and efficacy (secondary objective) of a 12-week behavioral activation-rehabilitation (BA-R) intervention versus "usual care", in acute respiratory failure (ARF) survivors. We will evaluate the BA-R intervention via an RCT study design, with blinded outcome assessments. We will test the feasibility of this intervention (primary outcome) and its efficacy (secondary outcome) at the end of intervention. Figure 2 shows study timeline.

After return home, consented patients will be randomized to: (1) behavioral activation and rehabilitation (BA-R) intervention or usual care. Randomization will occur via web-based tool, using variable-sized

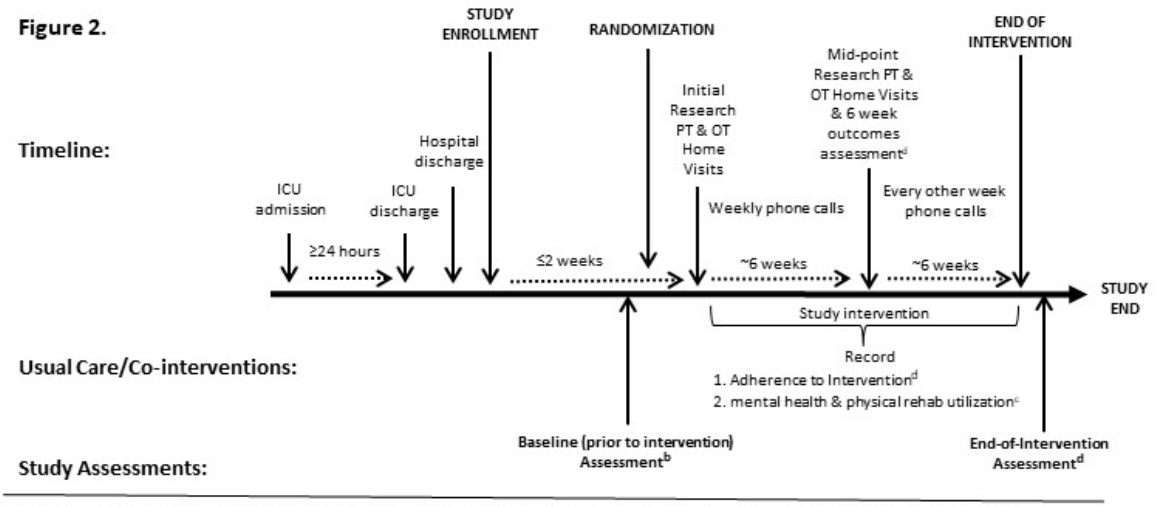
blocks from 2 to 4, and stratified by history of depression prior to ICU admission (based on chart review and patient interview). Baseline variables are detailed in Table 1 below.

Table 1: Baseline Variables

Variable	Collection	Measurement Scale
Patient Variables		
Age/sex/race	***Chart review***	***Continuous/Binary/Categorical***
Education (number of years/highest attainment)	Patient interview	Continuous/Categorical
Employment & Health Insurance status	Patient interview	Categorical
Comorbidity indices: Charlson (CCI)[a] & Functional (FCI)[b]	Chart review	Ordinal
Alcohol intake/misuse / Drug abuse	chart review	Categorical
Physical function at baseline: AMPAC-CAT[87,88] [c]	Patient interview	Continuous
ICU and Hospital Variables		
ICU admission diagnosis (e.g., sepsis, renal failure)	Chart review	Categorical
Severity of illness: APACHE II[d]	Chart review	Continuous
Benzodiazepine use and dosing[56,89,90]	Chart review	Continuous
Daily ICU Sedation Status: RASS[91]	Chart review	Ordinal
Daily ICU Delirium Status: CAM-ICU[92,93]	Chart review	Categorical
Daily Minimum Glucose[90]	Chart review	Continuous
ICU and Hospital Length of Stay	Chart review	Continuous
Before start of intervention, once participant at home[c]		
Depressive Symptoms: HADS[45]	Patient interview	Continuous
Coping Style & Social Engagement: Brief Cope[94] & BADS[95]	Patient interview	Continuous
Resilience: CD RISC[96]	Patient interview	Continuous

Abbreviations: AMPAC-CAT = Activity Measure for Post-Acute Care- Computer Adaptive Test, RASS = Richmond Agitation Sedation Scale, CAM-ICU = Confusion Assessment Method for the ICU, HADS= Hospital Anxiety and Depression Scale, PHQ= Personal Health Questionnaire, SCID-5= Structured Clinical Interview for DSM-5 (Mood Disorders Section only), BADS= Behavioral Activation for Depression Scale, CD RISC= Connor Davidson Resilience Scale, SF-36= 36 item Short Form Survey
a:Charlson index: a score derived from 19 comorbidities, with an increased score reflecting increased 1-year mortality[97]
b:Functional Index: derived from 18 comorbidities using physical function as outcome; increased score predicts decreased function[98]
c: See Section 3.3.8 for description of instruments
d: APACHE II: severity score that accounts for age, medical conditions, and 12 acute physiologic variables in ICU[99]

Figure 2.



Footnote: Timing of home visits and phone calls are estimates. **(a)** Not drawn to scale; **(b)** See Table 1 for Baseline Assessments **(c)** See Table 2 for Usual Care Descriptions **(d)** See Table 4 for Outcomes Assessments

Physical and Occupational Therapy Initial Home Visits: Within about 2 weeks of arriving home, participants will receive an audiovisualvisit from a physical therapist (PT) and occupational therapist (OT). The PT will (1) assess home safety, (2) recommend environmental modifications (e.g., grab bars) and (3) when indicated, use standardized, validated and feasible tests for ICU survivors to assess strength (via manual muscle testing)[9,73] and mobility (via 4 meter timed walk).[100] Given current restrictions (as of March

13, 2020) due to the coronavirus pandemic, home visits have been converted to audiovisual visits. The PT will provide resources to obtain low cost equipment (e.g., walkers), if required. In both groups, acute need for PT/OT services will be as per standard of care (i.e., physician referral); study participation (in either randomized group) will not impact standard care. The OT will then assist the patient in identifying valued activities (i.e., activities performed for their intrinsic worth) in the participant's life. The OT will guide and facilitate developing goals for completing valued activities, based on ratings of importance and satisfaction with performance on the COPM and performed in the participant's home, by the end of the first week. The OT will then evaluate the participant's ability to perform the prioritized activities. The OT will work with the participant to set BA goals for these selected activities, by embedding physical exercise (as recommended by PT) into valued daily routines. Goals will be divided into step-by-step plans, which incorporate appropriate expectations for participant activity during recovery. If the necessary steps to achieve these goals are not readily apparent to the participant, the OT will implement standard problem-solving strategies.[16,83,85] The visit will end with the OT entering the identified goals for the valued activities into the participant's Progress Worksheet (see below).

BA-R Phone intervention: WEEKS 1-6: Approximately one week after the OT home visit, and weekly thereafter throughout the initial 6-week intervention period, the participant will receive a phone call from the OT. During each call, the OT will query participants' success with BA-R goals and adherence barriers (e.g., need for assistance, lack of motivation). If goals are met, the OT will help the participant establish goals for the next week, and these goals along with an action plan will be delineated in a Progress Worksheet. If the goals are not met, the OT will assist the participant in addressing barriers as detailed above. WEEKS 7-12: At about 6 weeks, the PT will conduct a second audiovisual visit. Given current restrictions (as of March 13, 2020) due to the coronavirus pandemic, home visits have been converted to audiovisual visits. The PT will assess if the exercise level should be changed (e.g., increase or decrease intensity/duration). The OT will review progress on the action plan. Depending on achievement, participant preferences, and recovery trajectory, the OT and participant will develop new goals for participating in valued activities over the next 2 weeks. An action plan to achieve these goals will be entered into the Progress Worksheet. Phone calls will continue every 2 weeks during weeks 8-12. This will allow the OT to determine whether the participant has mastered the concept of goal setting and can stay on track with less contact.

Usual Care Control Group: Participants randomized to this arm will receive usual care only, in order to reflect a real-world comparator. This group is expected to include primary care, possibly outpatient physical therapy, mental health, and home health nurses. As per Table 2, these data will be collected to describe usual care received by the control group. These same data also will be collected for the intervention group to characterize usual care received outside of the BA-R intervention. These data will be recorded from the time of enrollment until end of the intervention.

Table 2: Mental Health & Physical Rehabilitation "Usual Care" Data Collection (<u>both</u> Intervention & Control Group)

<u>Mental Health Care</u>

1. **Psychiatric pharmacotherapy** (e.g., anti-depressant, anti-anxiety meds)
    a. Including drug name, dose, frequency & duration of use
2. **Provider Visits*** (including psychotherapy, counselling and support)
    a. Number, frequency & duration
    b. Type,** frequency & duration of intervention

<u>Physical Rehabilitation Care</u>

1. **Provider Visits:** Physical therapist, Occupational therapist, Physiatry/Rehabilitation Physician
    a. Number, frequency & duration
    b. Location (clinic vs. home-based)

* categories for Psychiatrist, Psychologist, Social Worker, Counselor, Support Group, and Primary Care Physician (if mental health services provided)

** including goal setting, homework, problem solving, family meetings, discussion of personal relationships, group interactions and relaxation techniques

Methods for Aims 1c & 2c: Using thematic analysis, semi-structured telephone interviews will be conducted by Dr. Parker and a trained research assistant using a written interview guide. The guide will be

developed by Dr. Parker with input from Drs. Eakin and Needham (co-mentor & primary mentor, respectively) and the questions will be iteratively refined throughout the study period in order to optimize information gained about themes as they arise. The interviews will begin with open-ended questions about patient experiences in recovery after ARF. Broad questions will then be followed by more specific questions about: 1) resilience, coping and social engagement; 2) key barriers and facilitators to engaging with the BA-R intervention; and 3) perceived satisfaction, acceptability and feasibility of BA-R. The anticipated duration is 25-30 minutes per interview.

Methods for Aim 3: The 3 instruments required for Aim 3 are described in Table 4 and under Secondary Outcomes below – all instruments are measured at the end of the 12-week intervention. The SCID-5 will be administered by Dr. Parker blinded to results of HADS and PHQ-8. The HADS and PHQ-8 will be administered by a research assistant blinded to the SCID-5.

b. Study duration and number of study visits required of research participants.

As described above, the intervention will start within approximately 2 weeks of hospital discharge and last about 12 weeks. After the 12 week intervention period, all participants will be contacted for outcomes assessments via telephone. This will take place as soon as possible after the end of the intervention. They will also be contacted by phone weekly for weeks 2-5 and then every other week for weeks 8-12.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

Participants cannot be blinded to the intervention. Treatment allocation will be concealed, except to staff performing the intervention. Research staff performing all outcome assessments will be blinded (except Dr. Parker who will not be masked to treatment assignment and will administer the SCID). Patients will be instructed (using standard language, as per prior research)[101-103] not to discuss treatment allocation with staff prior to each assessment. Adequacy of blinding will be assessed by asking assessors to indicate if they were un-blinded and for their "best guess" of patients' treatment allocation.[103]

d. Justification of why participants will not receive routine care or will have current therapy stopped.

All study participants in the usual care group will receive routine care. Participants in the intervention group will receive the intervention in addition to routine care.

e. Justification for inclusion of a placebo or non-treatment group.

We chose to compare our intervention against a "usual care", rather than a sham control that would attempt to control for extra attention but does not represent real-world usual care. We will measure usual care for both control and intervention groups (Table 2). Participants in the usual care group will not be deprived of any known potential benefits by not being included in the intervention group (no proven benefit yet in the ARF population).

f. Definition of treatment failure or participant removal criteria.

Participants will only be removed from the study if they withdraw consent.

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

If a participation in the study ends prematurely, the participant will continue to receive usual care. Ending the intervention prematurely does not pose any harm to the participant.

5. Inclusion/Exclusion Criteria

Table 3. Eligibility Criteria

Inclusion Criteria:
≥18 years old
Living at home before the current admission (not in a facility)
Acute respiratory failure managed in the ICU ≥ 24hrs (≥1 of the following):
1) Mechanical ventilation via an endotracheal tube or tracheostomy > 12hrs (and not ventilator-dependent before admission) OR
2) Non-invasive ventilation (CPAP, BiPAP) > 4 hours in a 24 hour period provided for acute respiratory failure (not for OSA or other stable use) OR
3) High flow nasal cannula with FiO2 ≥ 0.5 for ≥4 hours in a 24hr period
At least mild depressive symptoms (score ≥2 on PHQ-2 scale[46])
Exclusion Criteria:
Pre-existing cognitive impairment (based on review of medical records, or proxy-administered IQ-CODE[104] score >3.3)
Declines informed consent or not capable of providing informed consent
Non-English speaking
Homelessness
Bedbound prior to the current admission
Expected survival < 6 months according to ICU attending
ICU LOS > 30 days
Not discharged home from the hospital
Complex medical care expected soon after discharge (e.g. multiple planned surgeries, transplantation evaluation, extensive travel needs for hemodialysis, chemotherapy or radiation therapy, etc)
Active substance abuse or psychosis
Pregnancy
Suicidality
Incarcerated
Lack of access to telephone or inability to use telephone independently
Pregnancy
Suicidality

6. Drugs/ Substances/ Devices

N/A

7. Study Statistics

a. Primary outcome variable.

The primary outcome variable is feasibility. We will assess the total number of intervention phone calls completed per patient as a proportion of the number of intervention phone calls each patient is intended to complete (i.e., 9 intervention calls – weekly during first 6 weeks and bi-weekly for second 6 weeks of the 12-week protocol). We also will assess total number of intervention phone calls completed by all study participants as a proportion of total intervention phone calls expected in the study (i.e., 9 calls/patient x 27 intervention patients = 243 calls). We will calculate the number of patients completing the 12-week follow-up session as a proportion of the number of patients enrolled to measure of loss to follow-up.

b. Secondary outcome variables.

Hospital Anxiety and Depression Scale (HADS)[45]: The HADS (Tables 1 and 4), separately assesses depressive and anxiety symptoms in a wide variety of patients, is valid, reliable[45,56,65,105,106] and highly correlated with psychiatric evaluation in other populations,[107] but never validated in ARF survivors. A HADS score ≥8 indicates clinically important depressive symptoms. Scores of 8-10 indicates "mild" symptoms, 11-14 "moderate", and ≥15 "severe". HADS is the most commonly used measure of depressive symptoms in ARF survivors[10,56,108] and is considered to be particularly appropriate in ARF patients because

HADS does not emphasize the physical symptoms of depression that may be confounded by post-ARF physical morbidity.

Personal Health Questionnaire (PHQ-8)[46]*:* The PHQ-8 uses a 4-point Likert scale to assess depressive symptoms (Scores 5-9 indicate "mild" symptoms, 10-14 "moderate", and ≥20 "severe" depressive symptoms). While PHQ-9 has been validated for diagnostic accuracy in many other populations, it has not been evaluated against a "gold standard" clinician diagnostic interview in ARF survivors. As commonly done for medicolegal reasons in research, the PHQ-8, rather than PHQ-9, is used since it removes a question regarding suicidal ideation.[48]

Structured Clinical Interview for the DSM-5 (SCID-5) – Mood Disorders Section[109]: is a semi-structured, clinician-based psychiatric interview for making diagnoses according to Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5).[110] Prior versions are validated[143;144] and demonstrate high inter-rater reliability for the diagnosis of major depression.[111-114]

Activity Measure for Post-Acute Care Computer Adaptive Test (AMPAC-CAT*):* will be licensed for this study to evaluate the functional status of participants. The AMPAC has 269 items across three domains (basic mobility, daily activity and applied cognitive). The computer adaptive test, validated for use in the currently proposed post-acute care settings, requires a mean of 22 items from the item bank (administration time: 6 min.).[87,88,115,116] The test will be administered, using a computer, by blinded research staff.[117]

Health-Related Quality of Life (HR-QOL): will be measured using the EQ-5D-5L.

Healthcare Utilization: We will collect data on the post-discharge healthcare utilizations, including in-patient admissions to hospitals, and skilled nursing, acute and sub-acute rehabilitation facilities (Table 4). Moreover, we will collect data on utilization of out-patient mental health and physical rehabilitation services (Table 1). We will evaluate these measures using existing methodology from our prior research in ARF survivors.[118-121]

Table 4. Secondary outcomes

Description	Instrument (# items; time to complete (minutes))	Baseline	Week 6	End of Intervention
Depressive Symptoms	HADS (7 items; 2min) PHQ-8 (8 items, 2min) SCID-5[a] (30 min)	x	x	x x x
Functional status	AMPAC-CAT(~22 item; 6 min) Return to baseline work/activity (8 items; 3 min)	x		x x
Health-Related Quality of Life	EQ-5D-5L (2 min)			x
Employment status				x
Health Care Utilization and Estimated Costs	Admission to hospital, nursing & rehabilitation facilities; plus mental health & physical rehab utilization (8 min)			x
Survival status	Patient/Proxy (<1 min)			x
Coping Style	Brief Cope (28 items; 10 min)	x		x
Social Engagement	BADS (25 items; 5 min)	x		x
Resilience	CD RISC (25 items; 10 min)	x		x
Cognitive Function	MoCA-BLIND (8 questions; 5 min)			x
PTSD	IES-R (22 items; 6 min)			x

Abbreviations: HADS= Hospital Anxiety and Depression Scale, SCID-5= Structured Clinical Interview for DSM-5 (Mood Disorders Section only), AMPAC-CAT= Activity Measure for Post-Acute Care--Computer Adaptive Test, BADS= Behavioral Activation for Depression Scale, CD RISC= Connor-Davidson Resilience Scale
a: semi-structured interview

Brief Cope: Coping strategies will be assessed using the self-reported 28-item Brief Cope Scale.[94] The scale is a valid and reliable, used in medical populations, with strong measurement properties.[94,120,122] It will assess active (e.g. problem solving) versus avoidant coping (e.g., behavioral disengagement, self-blame).

Behavioral Activation for Depression (BAD) Scale: This 25-point scale[95] assesses social engagement and other aspects of behavioral activation. We demonstrated BADS's validity in medical populations with depressive symptoms and its sensitivity to change with depression treatment.[16]
Connor-Davidson Resilience Scale (CD RISC): This 25-item scale[96] assesses resilience. It has been validated in a variety of patient populations and specifically used in research involving ARF survivors.[102,105,106]
Adherence to the BA-R Intervention: will be evaluated as done in prior studies[83,85] by: (1) measuring the number of phone attempts needed by the OT to reach the participant for each session, and (2) calculating the proportion of sessions fully completed (with sub-analysis for number partially completed).
Montreal Cognitive Assessment (MoCA) – BLIND: is a validated phone-based version of the original MoCA,[123] a rapid screening instrument for mild cognitive dysfunction. The MoCA - BLIND assesses different cognitive domains including attention and concentration, memory, language, conceptual thinking, calculation and orientation. It will take 5 minutes to administer the MoCA-BLIND.
Impact of Events Scale – Revised (IES-R): This is the most commonly used instrument for assessing PTSD symptoms in ARF survivors.[107] It has 22 items, is reliable and valid.[124]

c. Statistical plan including sample size justification and interim data analysis.

Sample Size: As a pilot RCT, we aim to enroll a convenience sample of ~1.5 patients/month, for a total of 54 patients (based on 36 months of recruitment; see Timeline-Candidate Statement). Extensive experience enrolling ARF patients in prior studies by our group[10,121,125-127] suggests this rate is feasible for a K-23 award at this study site. We expect an overall <15% missing completion rate due to mortality and loss to follow-up (in our prior study of >500 ARF survivors, loss to follow-up was 2% with 7% mortality at 6 months[125]), thus, we expect 54 patients to complete the intervention. With 54 participants (27 in each group), assuming 5% alpha, 80% power and HAD SD of 4.2 points based on our prior research in ARF survivors[89,90], for our secondary aim of efficacy, we can detect a 3.1 point difference in HADS score between the 2 treatment groups, which approximates HAD's 2.9 point minimum important difference (MID) in ARF survivors,[128] This proposed enrollment rate and sample size is consistent with existing pilot/feasibility trials in ARF research.[101,129,130]

Statistical Analysis
Hypothesis 1a: A 12-week BA-R intervention in ARF survivors will be feasible, as demonstrated by an average accrual rate of 1.5 patients per month, completion of ≥80% of the intervention phone calls, and ≤15% of enrolled patients lost to follow-up for outcomes assessments at end of the 12-week intervention.
We will assess the total number of intervention phone calls completed per patient as a proportion of the number of intervention phone calls each patient is intended to complete (i.e., 9 intervention calls – weekly during first 6 weeks and bi-weekly for second 6 weeks of the 12-week protocol). We also will assess total number of intervention phone calls completed by all study participants as a proportion of total intervention phone calls expected in the study. We will calculate the number of patients completing the 12-month follow-up session as a proportion of the number of patients enrolled to measure loss to follow-up.

Hypothesis 1b: At the end of the 12-week BA-R intervention, ARF survivors in the BA-R versus "usual care" group will demonstrate decreased depressive symptoms, less impairments in physical function and quality of life, and reduced healthcare utilization. Analyses will follow a modified intention-to-treat principle and a 2-tailed $p<0.05$ is statistically significant. Patient mortality is expected to occur infrequently (see Sample Size above) and not to differ by treatment vs. control group; therefore, all analyses will be conducted for 12-week survivors only. The analysis will include separate comparisons of the effect of the BA-R intervention vs usual care control on each of the blinded outcomes in Table 4. These analyses will estimate the average treatment effect, i.e. the difference in the mean 12-week outcome comparing the BA-R intervention to the usual care control, using the precise locally efficient augmented simple estimator (PLEASE) described in Colantuoni and Rosenblum[REF: 135]. This method for estimating the average

treatment effect is similar to the analysis of covariance (ANCOVA) approach in that it incorporates the baseline outcome (if measured) which, if correlated with the 12-week outcome, can improve the precision of the estimated average treatment effect [Ref 134]. This method also accounts for more general patient drop-out models than the ANCOVA approach. Specifically, the ANCOVA approach is valid under completely at random drop-out, whereas the PLEASE is valid under missing at random drop-out, i.e. when patient drop-out differs by treatment group or across levels of the baseline outcome or other measured variables at baseline. The PLEASE requires a priori specification of three models: an outcome regression model (fit separately for each treatment group) that will include age, gender and the baseline outcome (if measured), a propensity score model that will include age, gender and the baseline outcome (if measured) and a drop-out model (fit separately for each treatment group) that will include age, gender, and the outcomes measured at baseline (HADS, Brief Cope, CD RISC, BADS). As exploratory analyses, the 12-week outcomes (e.g. HADS scores) will be summarized (summary statistics including counts of missing values and histograms) and the correlation of the baseline (if appropriate) and 12-week outcomes will be computed, separately by treatment arm. Patient mortality, drop-out and missing data will be described for all variables, separately for treatment vs control groups. Patient characteristics will be compared between those with vs. without missing outcomes (due to drop-out and missing values).[136-138]

A series of secondary analyses will be conducted to improve our understanding of the changes in the outcomes over time under the BA-R intervention and usual care control and to improve the design of subsequent larger randomized trials evaluating the effect of the BA-R intervention. Specifically, the outcomes over time within each treatment group will be visualized using spaghetti plots to display each patient's data with the mean outcome over time trajectory over time highlighted. Longitudinal linear regression models for the longitudinal outcomes (i.e. baseline, 6-week and 12-week outcomes) will be constructed that account for time (factor), treatment and the interaction of treatment and time. These longitudinal models will be fit using weighted least squares and will allow for the possibility that the variance in the outcomes can change over time and that outcomes measured on the same patient over time may be correlated. In addition, we will explore the prognostic ability of other baseline variables (e.g. age, sex and history of depression) for the 12-week outcomes using the method described by Colantuoni and Rosenblum.[135] Specifically, we will compute the leave-one-out cross-validated relative R-square which compares the R-square obtained when modeling the 12-week outcomes as a function of selected baseline variables, separately for each treatment arm, to that obtained by predicting the 12-week outcomes with the treatment arm specific mean. The statistic (1 – 1/relative R-square) is roughly the sample size reduction that can be achieved if the selected baseline variables are incorporated into an adjusted treatment effect estimator compared to using an unadjusted estimator. This assessment will provide relevant information to improve the design and analysis of subsequent larger randomized trials evaluating the effect of the BA-R intervention; specifically, by informing which additional prognostic baseline variables to include in the ANCOVA approach described above to further improve the precision of the estimated treatment effects.

Hypothesis 1c: We will conduct qualitative research, using thematic analysis, to identify key barriers and facilitators to engaging with the BA-R intervention, as well as perceived satisfaction, acceptability and feasibility of BA-R. All interviews will be audio recorded using a digital recorder and subsequently transcribed on a rolling basis. Using a data-driven approach, the first five interviews and associated interviewer field notes will be independently read by Dr. Parker and a second coder with expertise in qualitative research methods. The data will be segmented by identifying information pertinent to the research question then categorizing and giving identifying names (codes) to the patterns that emerge. Following the review of the five initial interviews, the two investigators will meet to discuss common findings and key themes. A code book will then be developed to guide the analysis of the transcripts through an iterative process of discussion and review. Transcripts will be reviewed on an ongoing basis to identify when thematic saturation is reached, defined by at least 3 interviews without additional information. Nvivo software will be used to organize the data for analysis. Coding will be compared

between the coders using percentage agreement and Cohen's kappa coefficient. Discrepancies will be reviewed and resolved through discussion between reviewers and a third review, if needed.

Hypothesis 2a: Increased resilience, adaptive coping, and social engagement are associated with fewer depressive symptoms using the combined patient cohort from the BA-R and control groups in Aim 1. Our primary outcome is depressive symptoms from the Hospital Anxiety and Depression Scale (HADS). First, descriptive statistics (i.e. mean, standard deviation, histograms) will be performed for the baseline HADS and the exposure and confounding variables. Next, a bi-variable analysis will be conducted for the HADS vs the baseline exposure variables for Aim 1 (i.e., CD-RISC 10, Brief COPE, BADS) using linear regression. In multivariable analyses, we also will include potential confounding variables (Table 1), including no more than 4 covariates in each model to avoid overfitting with sample size 54 (after accounting for mortality and loss to follow-up). These analyses will be conducted for all patients in the combined cohort in Aim 1.

Hypothesis 2b: At the end of the 12-week intervention, ARF survivors in the BA-R versus "usual care" control group will demonstrate improvements in coping, resilience and social engagement. Analyses for the comparison between the intervention and usual care groups will follow a modified intention-to-treat principle, with a 2-tailed $p<0.05$ is considered significant. Analysis will include separate comparisons of the intervention vs control for each of outcomes (Brief Cope, CD RISC, BADS), in accordance with the description above for Hypothesis 1b.

Hypothesis 2c: We will conduct qualitative research, using thematic analysis, to identify the role of resilience, coping, and social engagement in recovery from ARF. See analysis plan above for Hypothesis 1c. This analysis will include all patients in the combined cohort from Aim 1.

Hypothesis 3: The HADS and PHQ-8 will adequately discriminate depressive symptom severity vs. the SCID-5 "gold standard" using the combined patient cohort from the BA-R and control groups in Aim 1. All analyses will be conducted using only the 12-week outcomes data. The RCT inclusion criteria (in Aim 1), which establish the patient cohort for Aim 3, include only patients with PHQ-2 ≥ 2 (i.e., at least mild depressive symptoms). Therefore, for Aim 3 analyses, we will categorize depressive symptoms based on severity category for the SCID-5 (mild vs moderate to severe). We will then examine the screening characteristics of HADS and PHQ8 total scores vs the SCID-5 using a receiver operating characteristics (ROC) curve, including the area under the ROC curve (AUC), and sensitivities, specificities, and positive and negative predictive values at each HADS and PHQ8 total-score cut point. Our sample size (N=54 patients) is adequate to permit an assessment of criterion validity that is rated, at least, as "good" quality according to the COSMIN standard for psychometric analyses.[131] In addition to assessment of criterion validity, we will assess internal consistency of the PHQ-8 using Chronbach's alpha, with a result of ≥ 0.7 and <0.95 indicating "good" quality as per COSMIN[132] (HADS has an existing publication demonstrating good internal consistency in ARF survivors so no such analysis will be repeated for HADS)[133].

d. Early stopping rules.

There will be no interim analyses to determine early stopping for efficacy or futility with respect to the main efficacy hypothesis. The primary outcome for this study is feasibility.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

1) Depression: Participants will be asked questions about depression using the PHQ-8, HADS and the SCID. While asking questions, we may detect that the patient has worsening depressive symptoms.

2) Breach of confidentiality: We will be collecting data about the participant, and hence, there is a risk of breach of confidentiality.

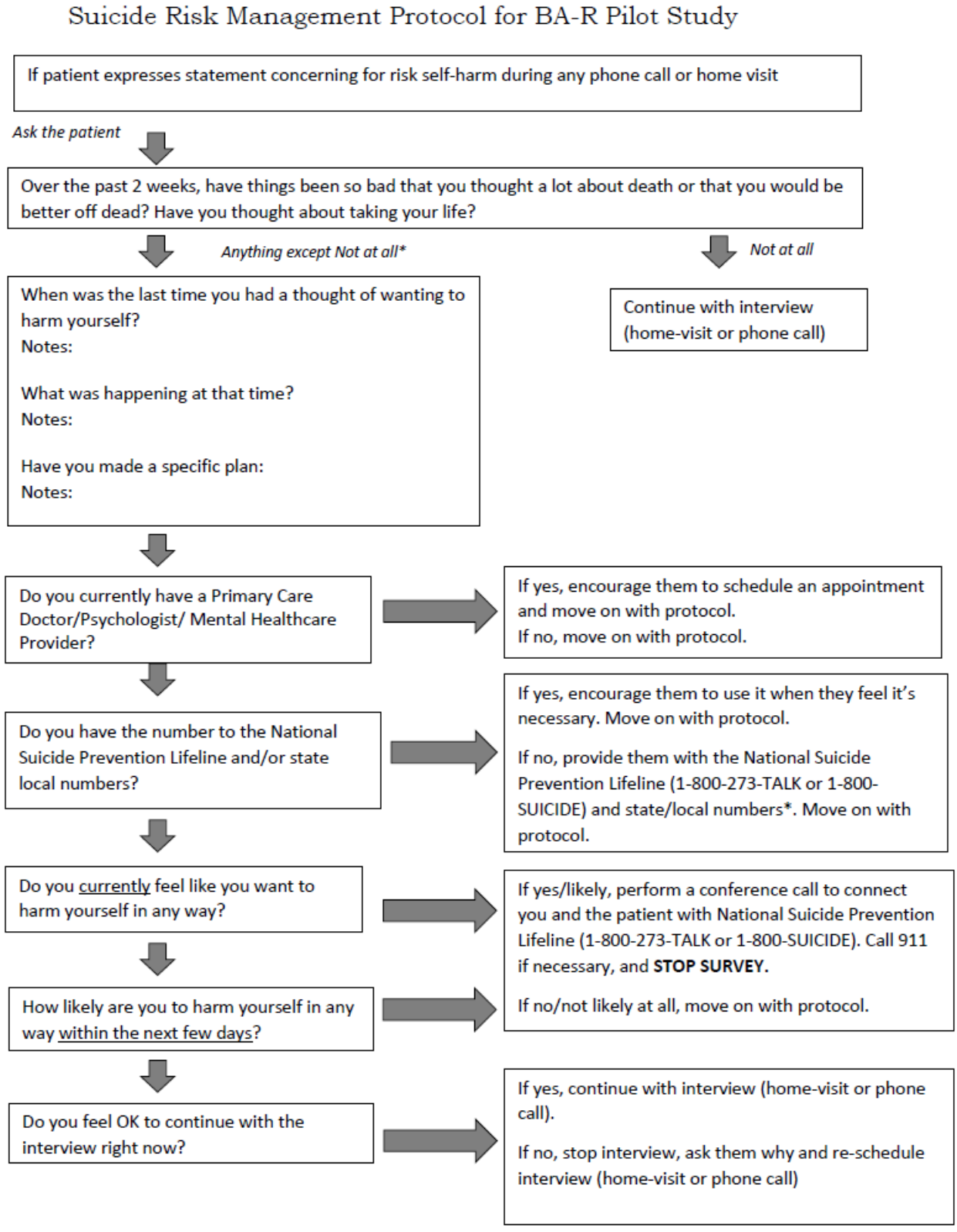
b. Steps taken to minimize the risks.

Depression (PHQ-8, HADS and SCID): All potential participants who have worsening depression symptoms will be informed that they may be depressed and advised to consult with their health care provider.

If there is any potential concern regarding safety of a participant, a physician on our study team will become involved. The research assistant will be instructed to take the steps outlined in Figure 2 below.

- Complete a Serious Adverse Event Report (SAE) form documenting the outcome of this questionnaire and subsequent action taken.
- If unsure about the patient's risk, contact a study physician to notify them immediately and discuss action to take.

Figure 2. Suicide Risk Management Protocol



Adapted from Suicide Risk Management Protocol in Post-Cardiac Arrest Survivors: Development, Feasibility, and Outcomes by RA Bucy et al Ann Am Thorac Soc. 2016 Dec 16; Article in Press)

***Suicide prevention helpline by state:**

State Number	Local County/City wise
Maryland 1-800-422-0009 http://www.suicide.org/hotlines/maryland-suicide-hotlines.html	• Baltimore • Baltimore Crisis Response- 410-752-2272 • Suicide Prevention Hotline (410) 521-3800 • Columbia (410) 531-6677 • Frederick (301) 662-2255 • Glen Burnie (Serving Baltimore County) (410) 931-2214 • Hyattsville (Serving Anne Arundel, Calvert, Charles, Montgomery, Prince George's & St. Mary's Counties) (301) 864-7130 • Rockville (240) 777-4000 (240) 777-4815 TTY • Salisbury (410) 749-4357(HELP) (410) 749-4363
Washington D C 703 527 4077 (Arlington)	• Arlington (703) 527-4077
Virginia 703 527 4077 For DC Metropolitan area http://www.suicide.org/hotlines/virginia-suicide-hotlines.html	• Arlington (703) 527-4077 • Dumfries(703) 368-4141 • Richmond (804) 819-4100 • Roanoke(540) 344-1948 (8:15 am to midnight) • Winchester (540) 667-0145
Delaware	• Milford (Kent/Sussex Mobile Crisis Unit) 1-800-345-6785 • Wilmington 1-800-262-9800 302-761-9100 Mobile Crisis Intervention Service 1-800-652-2929 (302)577-2484 • Brandywine Program Tressler Center of Delaware (302)633-5128
Pennsylvania	Adams, Cumberland, Dauphin, Franklin, & Perry Counties • Carlisle(717) 249-6226 • Harrisburg(717) 652-4400 • Adams, Franklin, Perry, Upper-Dauphin 1-800-932-4616
..contd for Pennsylvania	• Allegheny County Allegheny County Department of Human Services 1-888-424-2287 • Altoona (814) 946-9050 • Beaver County (724) 728-3650 • Bucks & Delaware Counties Lower Bucks (215) 355-6000(215) 547-1889 Central Bucks(215) 340-1998 Upper Bucks(215) 536-0911 Mainline & Delaware County (610) 649-5250 Philadelphia Area 1-888-855-5525 • Camp Hill (717) 763-2345, 1-800-722-5385 • Chester County (610) 918-2100 1-877-918-2100 • Dauphin County (717) 232-7511 • Erie (814) 453-5656 • Hanover (717) 637-7633, (717) 334-0468, 1-866-325-0339 • Lancaster County (717) 394-2631 • Lehigh County (610) 782-3127 • Luzerne-Wyoming Counties (570) 455-6385, (570) 735-7590 • York (717) 851-5320 , 1-800-673-2496

Breach of confidentiality: We will keep all participant information confidential in accordance with Public Health Services Act (42 USC 299a-1(c)). There is a low risk of a breach of confidentiality.

We will maintain subject confidentiality by keeping all study files in locked cabinets in locked rooms accessible only to study personnel with permission to examine study files. Electronic data will be password protected with daily back up procedures. Once data is entered into an analytic file, all identifying information will be removed.

c. Plan for reporting unanticipated problems or study deviations.

The primary investigator (Dr. Parker) is a board-certificated Internal Medicine physician practicing in the intensive care unit at Johns Hopkins. She will be involved in the daily conduct of the clinical trial and closely supervise the daily screening for patient eligibility, informed consent, and study procedures such as outcomes assessments and safety monitoring during the trial. Consequently, immediate knowledge of any unanticipated problem or study deviation that may arise will be available to the P.I. (Dr. Parker) on a timely basis for immediate action and reporting to the IRB as necessary. If Dr. Parker is unavailable, the study will maintain a list of clinicians who are co-mentors to Dr. Parker on this study who can provide medical guidance.

If clinically important, unanticipated adverse problems or clinically important study-related, serious adverse events occur, they will be recorded on a designated case report form. All events that are serious and unanticipated, or study-related and adverse will be reported to IRB within the required reporting timeline.

Definitions:

Adverse event: any untoward medical occurrence associated with the use of a drug in humans, whether or not considered intervention related.

Serious Adverse Event (SAE) - an adverse event will be considered "serious" if, in the view of the investigator, it results in any of the following outcomes: death, a life-threatening adverse reaction, re-hospitalization, a persistent or significant incapacity, or substantial disruption of the ability to conduct normal life functions.

Suspected Adverse Event - any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Unexpected Adverse Event - an adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, of an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

All patient data will be confidential and secure due to physical and electronic data security measures, including locked offices and locked filing cabinets for records and computers, and password protection for computers and electronic data storage. All participant-identifying information will be removed from the dataset before analysis. Only study staff who are required to, will know the linkage between the unique identifier and participant-identifying information. We will keep all patient information confidential in

accordance with Public Health Services Act (42 USC 299a-1(c)). There is low risk of a breach of confidentiality.

e. Financial risks to the participants.

There are no expected financial risks to the participants.

9. Benefits

a. Description of the probable benefits for the participant and for society.

Currently, there are few therapeutic options with proven, or potential, efficacy to prevent or minimize depressive symptoms in acute respiratory failure survivors. Hence, this study offers important new knowledge through testing the BA-R intervention in this patient population. The BA-R intervention has been demonstrated to improve depressive symptoms in other chronically ill populations. Given the prevalence of depressive symptoms in acute respiratory failure survivors, gaining information regarding the feasibility and potential benefit of BA-R in this pilot study has great importance. This therapy is especially ideal in acute respiratory failure survivors because it can be delivered via phone with only 2 home visits required by PT and OT. The potential benefits far outweigh the minimal potential risks of this intervention.

If successful, the use of BA-R therapy may improve post-acute respiratory failure depressive symptoms, improve physical function and decrease healthcare utilization while improving quality of life.

10. Payment and Remuneration

a. *Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol*.

For each assessment during the study, <u>both</u> intervention and control group patients will be remunerated as follows: $25 for baseline assessment prior to intervention period, and $50 for assessment at the end of the intervention period.

In addition, the intervention group <u>only</u> will be remunerated $100 for completion of all intervention visits.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

There will not be any additional costs to participants beyond routine financial obligations for their hospitalization.

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