Official Title: ASPIRE: A Study Promoting Critical Illness Recovery in the Elderly

NCT02963558
IRB-Approved: 3/21/2023

ASPIRE: A Study Promoting Critical Illness Recovery in the Elderly

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Sponsor or funding source:
Wake Forest University Translational Science Center
Wake Forest University Pepper Center
Wake Forest University Critical Illness Injury and Recovery Research Center
Wake Forest Center for Diabetes, Obesity, and Metabolism
Departmental Start-Up Funds
Ri, LLC (providing equipment only)
NIA 1R03AG060076 - 01A1

Background, Rationale and Context

Advances in the care of critically ill patients have led to increased survivorship. However, survivors of critical illness are faced with a variety of short- and long-term complications, the most notable of which is intensive care unit acquired neuromuscular weakness (ICUAW).[1] Older patients have a higher incidence of acquiring a critical illness, and muscle wasting in this population appears more severe.[2,3] Though we and others have shown that exercise administered during an intensive care unit (ICU) stay (early rehabilitation) can attenuate the severity of ICUAW,[4,5] not all studies of rehabilitation have yielded positive outcomes.[6,7]

Both pre-clinical animal studies from our lab and clinical studies suggest timing of rehabilitation may be key— EARLY (within 1-2 days) but not LATE (days 5 and beyond) initiation of ICU rehabilitation therapies in critically ill patients have generally led to improved functional outcomes.[4,5,8-11] Unfortunately, significant barriers exist to the early implementation of ICU rehabilitation, most notably delirium and the use of sedating medications in the early phases of critical illness.[12-14]

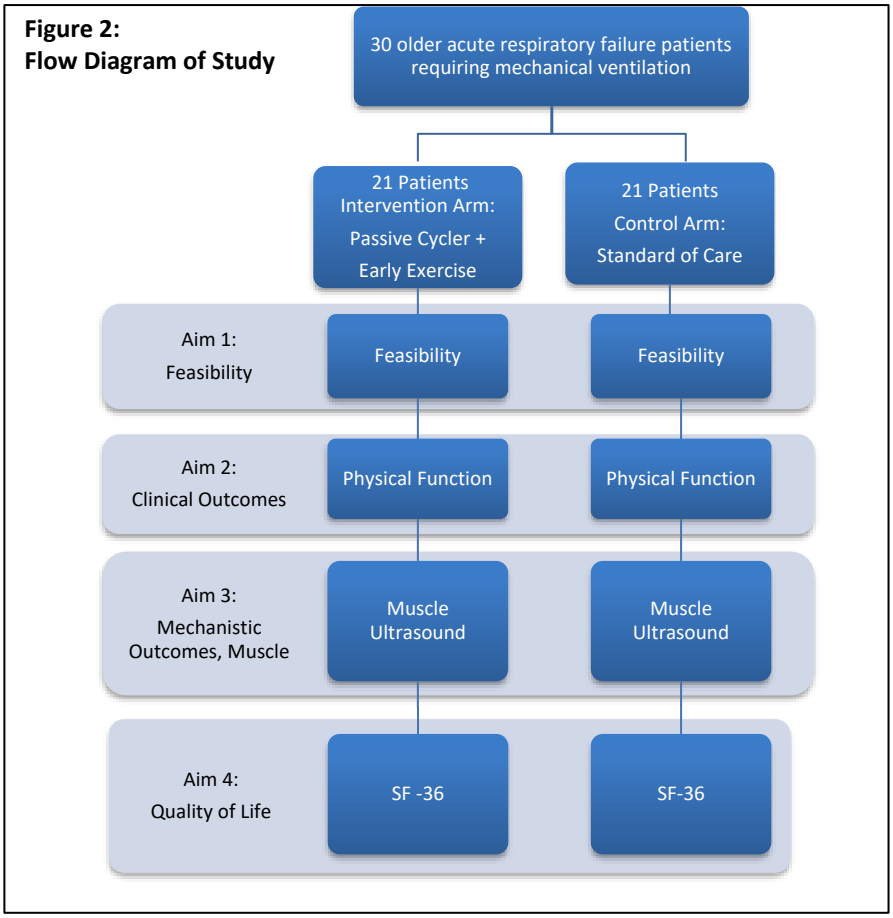
In this proposal, we will test the hypothesis that EARLY application of a novel early rehabilitation therapy in critically ill patients will improve functional outcomes, and change the functional trajectory of this population. We will perform a pilot study of early mobilization with a cycle ergometer (MOTOmed, see Figure 1) and translate into humans the pre-clinical mechanisms that may mediate the effects of early mobility.

Figure 1: Use of a MOTOmed in a mechanically ventilated patient

Objectives

1) To assess the feasibility of the application of a novel ICU early rehabilitation intervention.
2) To obtain preliminary data to estimate the treatment effect size. This will allow power calculations for a larger, NIH-funded clinical trial.
3) To understand if the application of a novel early ICU rehabilitation intervention attenuates the loss of muscle mass over time through inhibition of the E3 ubiquitin ligase muscle ring finger 1 protein.
4) To determine the effects of exercise on energy utilization, mitochondrial function, and CPT-1 activity.
5) To determine the effects of the early ICU rehabilitation intervention on muscle mass.
6) To determine the effect of the early ICU rehabilitation intervention on quality of life in critically ill older adults.

Figure 2:
Flow Diagram of Study



Methods and Measures

Design:

Single-center randomized controlled pilot/phase II trial of a novel ICU early rehabilitation intervention.

Setting:

Wake Forest Baptist Medical Center Intensive Care Unit

Subject selection criteria:

Older adults with age ≥55 years old who are critically ill with acute hypoxic respiratory failure requiring mechanical ventilation with an expected duration of ≥3 days.

- **Inclusion Criteria**

Age ≥55 years old *(Rationale: Older patients have a higher incidence of acquiring a critical illness, and muscle wasting in this population appears more severe. Therefore, this intervention may be most effective in this population.)*

Admission to a Wake Forest Baptist Medical Center Intensive Care Unit

Acute Hypoxic respiratory failure on mechanical ventilation (MV) for <48 hours with a P:F ratio of <300 (or equivalent S:F ratio) with expected MV for at least 24 more hours

Previously Functional (over past 3 months, as reported by proxy): Physical Function: Able to walk 4 m (with or without assistive device)

- **Exclusion Criteria**

  Neuromuscular Disease
  Cardiopulmonary Arrest with return of spontaneous circulation <6 hrs
  Palliative Goals of Care; withholding life-sustaining therapy
  Raised Intracranial Pressure (>20 mm Hg)
  BMI>45; absolute weight >= 150 kg
  Inability to cycle (including absent limbs, body length <1.5m, body habitus not fitting the cycle, inflammatory arthritis, significant joint problems including inability to bend arms/legs; pelvic and/or lower extremity fracture, lower extremity vascular bypass surgery)
  Pregnancy
  Use of continuous neuromuscular blockade
  Temporary Pacemaker or Swan Ganz catheter or femoral ECMO catheter/IABP
  Rhabdomyolysis with most recent CK >5000
  Clinical Diagnosis of Dementia on Medication
  Moribund
  Possible Exclusion: If the patient is on spine precautions, a discussion with the spine team will be necessary to determine eligibility for this study

Sample Size

We will randomize 21 subjects to the intervention group (novel ICU early rehabilitation) and 21 subjects to the control group. This sample size is based on the fact that this is a pilot proposal and that we want to optimize study procedures. We also have preliminary data which shows that this sample size might be large enough to detect a difference between groups based on SPPB at ICU discharge.

The primary analysis of the phase II part of the study is to compare SPPB at ICU discharge between the two groups using analysis of covariance (ANCOVA), adjusted for age, **sex**, and BMI. Under our assumptions of attrition (estimated at 15%) and mortality (SPPB=0 if patient has passed), with the current sample size (n=42), we will be able to detect an effect size of 0.98 or higher in the SPPB at ICU discharge with a power of 81% and a two-sided significance level of 0.05. This effect size is based on our pilot data and corresponds with the known minimal clinically important difference in SPPB of 0.5-1.3.[15,16]

Interventions and Interactions

We will randomize patients to intervention or control groups. Patients will receive therapies according to their group assignment until hospital discharge or day 14, whichever comes first.

The intervention group will receive in-bed cycle ergometry within 48 hours of randomization if safety criteria (below) are met. In-bed cycle ergometry has been shown to be safe and feasible in the critically ill and is FDA-approved for use in this population.[8,17-19] Subjects enrolled in the intervention arm will be screened at least 5 days per week to evaluate if they meet pre-defined safety criteria based on other studies of early mobilization and cycling in the ICU (see Table 1).[4,5,8,17-20] Patients who meet the safety criteria will be positioned in the semi-recumbent position for cycling as per ICU guidelines. The cycler will provide 3 different possible modes of cycling—passive, active-assisted, and active. We will start with passive cycling and the patient may progress to active-assisted and active cycling. The goal duration of cycling will be 30 minutes. Subjects will receive in-bed cycling at least 5 times per week for the duration

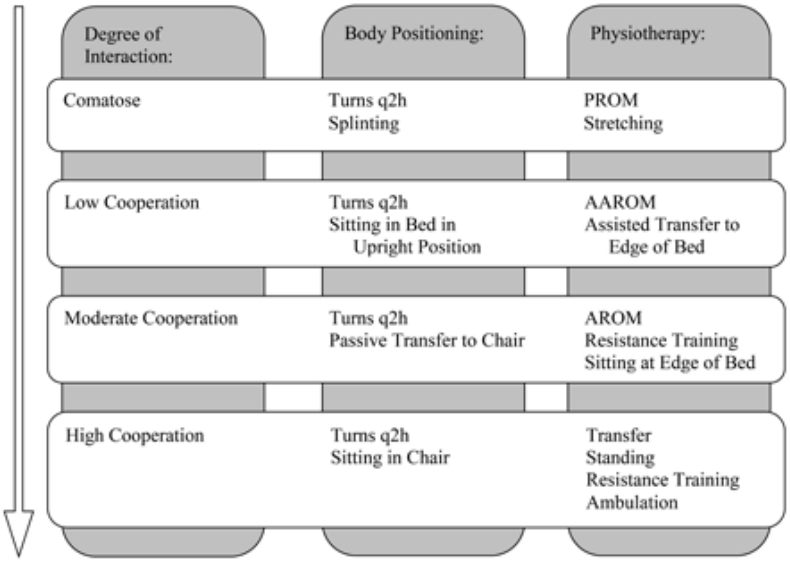
of the ICU stay or until day 14, whichever comes first. During cycling and therapy sessions, study staff will also complete a case report form noting vital signs, level of mobilization, and other safety measures.

We have updated our safety criteria based on other completed and ongoing cycle trials in the critically ill (NCT03021902 and NCT03471247 and NCT02377830.) See table below.

	Daily Exemption Criteria	In-Session Stopping Criteria
Neurologic Criteria	• Uncontrolled Pain • Severe Agitation with a RASS +3 or +4	• Severe Agitation with a RASS +3 or +4
Respiratory Criteria	• PEEP >15 • FIO2 >80%	• Unplanned Extubation • Sustained O2 desaturation <85% • Marked vent asynchrony
Circulatory Criteria	• An increase in vasopressor/inotrope by >5 mcg/min in past 2 hrs • Levophed >50 mcg/min to maintain goal MAP • Active myocardial ischemia • Unstable or uncontrolled arrhythmia	• Sustained symptomatic bradycardia (HR<40), tachycardia (HR>140), hypotension (MAP<60), or hypertension (MAP >130) • Concern for myocardial ischemia • New unstable or uncontrolled arrhythmia
Other Criteria	• Change in goals of care to comfort • Team perceives therapy to be inappropriate (eg new hemorrhage, new wound) • Patient Refusal	• Catheter or tube dislodgement • Team, subject, or surrogate request termination of session

In addition to cycling, the intervention arm will receive early physical therapy. This physical therapy (PT) will be performed according to a protocol of additional ICU and hospital-administered rehabilitation strategies previously developed in the Wake Forest MICU.[4] Patients will receive 30 minutes of PT at least 5 times per week when they are conscious. If unconscious (as in Level 1 below), then they will only receive passive range of motion (PROM) for 10 repetitions per body part daily. Once conscious, subjects will progress through the different levels of PT with an emphasis on ambulation.

Therapy for the intervention arm patients will continue while on the floor. Outpatient therapy will be provided at the discretion of the patient's treating physicians.



The control group will receive usual care physical therapy as ordered by the treating team both in the ICU and on the floor through hospital discharge. These subjects will also receive therapy as outpatients only as ordered by their regular physicians.

Outcome Measure(s)

1) To assess the feasibility of the application of a novel ICU early rehabilitation intervention.
    a. Primary Outcome for the pilot phase: Feasibility will be assessed by quantifying the ability to apply the MOTOmed device for at least a 15-minute session within 48 hours of randomization and meeting safety criteria.
2) To obtain preliminary data to estimate the treatment effect size. This will allow power calculations for a larger, NIH-funded clinical trial.
    a. Short Physical Performance Battery (SPPB). We will measure SPPB at ICU and hospital discharge. Our primary outcome for the phase II study will be SPPB at ICU discharge.
    b. Handgrip strength and dynamometry at ICU discharge and hospital discharge. ICU length of stay, Hospital length of stay will also be measured.
    c. Healthcare utilization (ED visits, re-admissions) at 1, 3, and 6 months
    d. Ventilator free days at 28 days.
    e. Mortality at ICU discharge, hospital discharge, and 3 and 6 months
    f. Short Form-36 (SF-36) at hospital discharge (in-person) and 3 and 6 months (by phone)
3) To understand if the application of a novel early ICU rehabilitation intervention attenuates the loss of muscle mass over time through inhibition of the E3 ubiquitin ligase muscle ring finger 1 protein.
    a. Serial Skeletal Muscle Ultrasounds at days 0, 3, 5, ICU discharge, hospital discharge
        Muscle thickness, size and echogenicity in the vastus and the rectus femoris muscles
    b. Serial Plasma at days 0, 1, 3, and 5 and ICU and hospital discharge
        i. Plasma acylcarnitine profile
        ii. Will be banked for future studies
    c. Blood on 1st day of exercise (for 5 intervention patients only) will be evaluated for leukocyte kinetics in response to exercise (exploratory analysis) based on animal data. This is completed.

4) Pilot study: To determine the effects of exercise on energy utilization, mitochondrial function, and CPT-1 activity. Phase II: To determine the effects of exercise on energy utilization.
    a. Continuous non-invasive CO2 monitoring, day 0 through day 5
    b. Accelerometer activity monitor, day 0 through 2 weeks post-discharge.
    c. Nutritional Assessments, blood sugar levels, day 0 through ICU discharge

Updated Testing Battery:

TABLE 5: TESTING BATTERY	Day 0	Day 1	Day 3	Day 5	ICU D/C	Hosp D/C	Phone: 3 months	Phone: 6 months
Aim 1: Physical Function:								
Feasibility	X	X	X	X	X	X	X	X
MAT-sf	X				X	X		
SPPB					**X***	X		
Handgrip/ quad strength					X	X		
MoCA / MoCA Blind					X	X	X	X
Aim 2 Muscle Mass:								
Ultrasound	X		X	X	X	X		
Aim 3: Quality of Life:								
SF-36						X	X	X
Exploratory Outcomes:								
ICU LOS					X			
Hospital LOS						X		
Vent-Free Days (28)					X	X		
Healthcare Utilization							X	X
Mortality					X	X	X	X
Blood	X	X	X	X	X	X		
Energy	X	X	X	X	X	X		

NB—Inpatient assessments may be completed up to 1 day before or after the specified time point, and may be carried over to another assessment. Outpatient assessments may be completed up to 2 weeks before or after the specified time point. Muscle biopsies may be performed up to 1 day before or 2 days after the specified time point.

Data Collection for demographics and baseline information: Demographic Information will be obtained on all patients. Additionally, the Acute Physiology and Chronic Health Evaluation (APACHE), Charlson index, and the comorbidity indices will be calculated. Other variables which will be collected will include medications and information about ICU and hospital stays.

Muscle ultrasounds will be completed per protocol with standard views required to examine the size and echogenicity of patient muscles. Gel will be applied to the skin, the ultrasound probe will be placed on the gel, and then with minimal pressure, the required images will be obtained. A Sonosite ultrasound machine will be used. Bony landmarks will confirm that the probe is placed perpendicular to the muscle. Images will be saved on a laptop computer and then analyzed with Image J software.

The Short Physical Performance Battery (SPPB) is based on timed measures of standing balance, walking speed, and ability to rise from a chair. Each measure is assigned a score ranging from 0 to 4, with a total possible summary score of 12. The SPPB was developed for functional evaluation of the geriatric population. Given the target population of this study, this is an ideal instrument to measure physical function in this cohort.

Handgrip will be assessed with a Jamar hand-held dynamometer. Three trials with brief pauses will be performed for each hand. A recording of hand dominancy will also be made.

Skeletal muscle strength will be measured in the lower extremities. An electronic strength dynamometer (MicroFET 2MT Dynamometer, Hoggan Health Industries, Salt Lake City, UT) will be used to collect strength measures of the ankle and knee, bilaterally. Three trials with brief pauses will be performed for each muscle group. The best performance of three trials will be selected for each side.

Non-invasive continuous volumetric C02 (vC02) will be performed using either a NM3 device (*Phillips-Respironics)* or ventilator capable of vC02 measurements. Daily energy expenditure (divided into 12 hour segments) will be calculated using the formula validated by Stapel et al. vC02 measurements will not be used for clinical decision making. The use of NM3 device poses minimal harm to enrolled patients.

The activity monitors will be given to the patients when enrolled in the study to wear throughout their hospitalization. Patients will be asked to wear the accelerometer and return it in with a pre-paid envelope.

Health related quality of life will be assessed using the Short Form-36. The SF-36 is a self-reported generic measure of health related quality of life. It consists of 36 items which can be used to provide summary measures of physical and mental health and eight distinct dimensions of health.

The Montreal Cognitive Assessment (MoCA) and the MoCA- BLIND will be used to measure cognitive status. The MoCA and the MoCA-BLIND are validated tools of 22-30 questions which assesses: short-term memory recall, visuospatial abilities, executive function, attention, concentration, and working memory, language, conceptual thinking, calculations, and orientation to time and place. They are highly sensitive and specific to detect mild cognitive impairment.

The Mobility Assessment Tool short form (MAT-sf) is a video animated tool for assessing self-perception of mobility. Items consist of a video and a corresponding measurement item. The video depicts a wooden mannequin performing a wide range of physical activities and the measurement item consists of a question about the participant's ability to perform the task, measured on a discrete scale.

Healthcare utilization and mortality will be determined through a variety of mechanisms including a review of the electronic medical record, phone calls to patients/ families/ contacts provided at the start of the study, and a query of the NC State Death Index.

Analytical Plan

Phase I pilot study:

Given that this is a pilot study, all analyses other than the feasibility assessment and basic descriptive statistics will be performed solely to inform a larger trial. Power calculations will not be utilized for this study given it is a pilot study.

We have a growing ICU population over the past 5 years. In 2013 alone, we had >1300 older adults admitted to just the MICU. Thus, we should have a large population of patients on which to draw from for enrolment in the study.

Patient demographics will be evaluated with descriptive statistics. The objectives will be evaluated as described below.

1) The feasibility of compliance to the application of the novel ICU early rehabilitation intervention will be assessed by the number of patients in the intervention arm out of the total intervention patients (10) who are able to undergo a 15 minute cycling session within the first 48 hours of randomization and meeting safety criteria.
2) SPPB, handgrip strength/dynamometry, calorimetry, ICU and hospital lengths of stay, healthcare utilization (SPPB), ventilator-free days, mortality, and SF-36 and MoCA scores will all be analyzed with descriptive statistics. Tests for trend will be evaluated and adjusted analyses will also be performed. Analysis of co-variance will be used, adjusted for age, gender, and BMI and other adjusted analyses will be performed as necessary. We will also explore the longitudinal effect of the intervention with linear mixed effect models.
3) And 4) Muscle ultrasound measures, skeletal muscle biopsy measures, and plasma analyses will also be analyzed with descriptive statistics, tests for trend including with linear mixed effect models , and adjusted analyses.

In sum, results will be analyzed initially using descriptive statistics. Comparison between groups will be done using chi square tests for proportions, and t-tests or ANOVA procedures for continuous variables. Regression analysis will be performed to identify independent outcome predictors. Other inferential statistical analysis will be conducted as appropriate.

Phase II: The primary analysis is to compare SPPB at ICU discharge between the two groups using analysis of covariance (ANCOVA), adjusted for age, gender, and BMI. Under our assumptions of attrition (estimated at 15%) and mortality (SPPB=0 if patient has passed), with the current sample size (n=42), we will be able to detect an effect size of 0.98 or higher in the SPPB at ICU discharge with a power of 81% and a two-sided significance level of 0.05. This effect size is based on our pilot data and corresponds with the known minimal clinically important difference in SPPB of 0.5-1.3.[15,16] We will perform similar analyses for SPPB at hospital discharge and explore the longitudinal effect of the intervention, using linear mixed effect models to compare the trajectories of SPPB over time. We will analyze secondary outcomes including hand grip, quadriceps dynamometry, RF CSA and echogenicity, quadriceps depth, TA depth and echogenicity, and QOL in a similar fashion. For this study, the services of the Pepper Center Biostatistics and Research Information Systems Core will be used.

Human Subjects Protection

Please see attached document.

Subject Recruitment Methods

Our ICU research team will screen patients admitted to the ICU for inclusion/ exclusion criteria for entry into the study. We will only access necessary information (using a minimal amount of PHI) for screening through the electronic medical record. PHI necessary will include name, geographic information, dates, telephone number, medical record, and access to this information will be sought under a limited HIPAA waiver. All information will remain confidential in a password protected file on a password protected

computer. If deemed eligible, subjects (or their surrogates if unable to consent for themselves) will be approached for consent. If the patient/ surrogate does not consent for the study, the study team will maintain a record of those not enrolled which will be kept in a password protected file on a password protected computer. This record will be destroyed 3 years after study completion and publication.

We will not differentially approach women or minorities for inclusion in this study. However, please note that given the small sample size of this project, we will likely have imbalances.

Informed Consent

Signed informed consent will be obtained from each subject or from a surrogate decision-maker. If a surrogate decision-maker is used for initial consent, then when the patient is mentally able to consent for him/herself, he/she will be re-approached by the study coordinator or investigators for consent. All consents will take place in the ICU.

Confidentiality and Privacy

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a linkage file, stored separately from the data. The linkage file will be kept secure, with access limited to designated study personnel. We will input data into the RedCAP web based data entry system as it is highly secure and is regularly backed up. Following data collection subject identifying information will be destroyed three years after publication of the study, consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data and Safety Monitoring

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff.

Additionally, a Data and Safety Monitoring Board will be convened by the PI. This DSMB will monitor all serious/unexpected adverse events as well.

Reporting of Unanticipated Problems, Adverse Events or Deviations

Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB and sponsor or appropriate government agency if appropriate.

Appendix

Copies of each questionnaire or surveys that will be used
Consent form

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