Background and Significance:

Acute respiratory failure (ARF) is an extremely variable and heterogeneous syndrome that can be defined as an acute cardiopulmonary dysfunction requiring emergent artificial ventilation support. ARF is a common reason for admission to Intensive Care Units (ICU) in the United States (US). In the US, ARF results in 1.1 million of the 4.4 million ICU admissions each year \(^1\). For patients with ARF, the mortality rate is higher than the general ICU mortality, with estimates ranging from 15-40% depending on the subgroups evaluated \(^2, 3, 4\). In a recent report on ARF, the in-ICU mortality was 31% and the overall in-hospital mortality rate was 37% \(^2\). Annually, 500,000 patients die in US ICUs \(^1\), 400,000 with ARF \(^2\). Despite the high mortality, average hospital length of stay (LOS) for patients is high. In a 2004 cohort of 5000 patients with ARF, the mean ICU LOS was 8 days and hospital LOS was 17 days \(^2\). ICU patients requiring longer than 5 days of ICU care make up only 20% of the overall number of ICU admissions, although they account for 61% of ICU days \(^5\), with median hospital costs greater than $30,000 \(^6\). These data suggest that an intervention, such as Standardized Rehabilitation Therapy, that may shorten ICU or hospital stay for patients with ARF, may result in significant cost reductions for US healthcare.

Acute Respiratory Failure survivors experience difficulties in function and quality of life for Months following hospital discharge

Most outcomes research regarding acute respiratory failure has examined short-term endpoints such as in-hospital mortality and morbidities, yet the human cost of these illnesses extends well beyond the period of hospitalization. In a large prospective cohort study of 1,075 survivors of acute respiratory failure, at five months post-discharge 48 percent needed help with at least one activity of daily living, and 27 percent reported their quality of life as fair or poor \(^7\). Twenty-four percent of patients reported needing assistance with more activities
of daily living five months post-discharge as compared to pre-hospitalization\textsuperscript{7}. Several investigators have reported on the decrease in health-related quality of life in survivors of the acute respiratory distress syndrome (a subset of ARF)\textsuperscript{8,9}, but the reasons for this impairment seemed disproportionate to the improvements in respiratory distress syndrome to date (86 percent with follow-up data at one year), there was a high prevalence of persistent muscle weakness and fatigue. These data illustrate the deleterious effects that acute respiratory failure has on post-hospital patient function and quality of life. They also signal the importance of including measurements of function and quality of life in the study design of an intervention study such as Standardized Rehabilitation Therapy, in order to capture not only the immediate hospital endpoints of LOS, but to more importantly to capture the intervention’s effect on post-hospital patient status.

**ICU Care imposes immobility which contributes to weakness**

Deconditioning may be described as the multiple changes in organ system physiology that are induced by inactivity and reversed by activity\textsuperscript{11}. In the clinical setting, acute deconditioning refers to changes that occur within days to a few weeks of a sudden decrease in activity\textsuperscript{12,13}. Concern regarding bed rest in hospitalized patients is not new\textsuperscript{14}. In current practice, admission to an ICU implies almost certain imposed immobility, particularly with mechanical ventilation. In numerous reports from zero gravity (NASA) research, the immobilization of healthy subjects, i.e. without an acute illness, induces muscle atrophy mechanisms with resultant weakness in otherwise normal muscles. However, in addition to immobility, in a new ICU weakness paradigm, the weakness seen in patients with ARF results from multiple potential injuries\textsuperscript{15,16}. Another potential injury is the exposure to systemic inflammation. Injury caused by immobility and acute inflammation may be accentuated by ICU medications such as corticosteroids and neuromuscular blockers\textsuperscript{17}, as well as hyperglycemia\textsuperscript{18}. For those patients with ARF who survive mechanical ventilation, there are reports of substantial difficulties with deconditioning, muscle weakness, joint contractures and dyspnea\textsuperscript{19}, and the most severe forms have become known as critical illness polymyoneuropathies (CIP)\textsuperscript{20}. 
For patients with ARF there is variability of administration of in-hospital rehabilitation strategies and a lack of guidelines for an organized ICU rehabilitative approach

Despite a general notion by many groups that mobility and exercise may play a strong role in facilitating a return to pre-hospital functional status for patients with ARF, the exact manner in which to administer mobility and the appreciation of the safety of mobility maneuvers administered to critically ill patients are not clear. Overall, rehabilitation research for ICU patients has not received much attention. The proposed work has the potential to serve as the standard for practice, to prioritize the in-hospital rehabilitation of patients with ARF and produce improvements in these patients’ functional status and quality of life.

Significance

There is a high prevalence of ARF in critically ill patients and their prognosis for improved physical functioning and health related quality of life, if they survive, is poor. Rehabilitation has great potential to restore lost function in critically ill patients, but traditionally has not been started until after ICU hospital discharge\textsuperscript{21}. Such patients are often viewed as ‘too sick’ to tolerate physical activity early in their illness and their immobilization is frequently ‘inevitably’ prolonged. This delayed intervention may only enhance deconditioning and might further complicate the clinical course of patients with ARF.

Skeletal muscle dysfunction similarities between older adults and ICU patients with ARF suggest that survivors of ARF could benefit, both with respect to physical function and health related quality of life, from participating in a standardized rehabilitation therapy program. Our preliminary data suggest that rehabilitation for critically ill patients with ARF was associated with a shortened hospital length of stay. However, conclusive evidence to support this notion is lacking. To date, there are no studies showing that standardized rehabilitation therapy has a beneficial effect on physical function and health related quality of life in patients with ARF, despite numerous calls for such work \textsuperscript{21}. This is further illustrated by the fact that a recent consensus statement encouraged interdisciplinary research in the science of critical care \textsuperscript{21}.
Immobility per se produces acute muscle atrophy. Therefore, a standardized rehabilitation therapy that commences very early within the ICU stay could provide the optimal preventative, as well as therapeutic effect, to counter the deleterious effects of immobility, neuromyopathic drugs, and systemic inflammation.

Since there are no approved standards to the delivery of rehabilitation therapy in the ICU, our approach is novel. We designed a safe mechanism to realize the potential of rehabilitation therapy by daily delivery of safe amounts of rehabilitation therapy, easily applied tools to assess readiness, and with the structure being inclusive of both physical therapy and exercise training principles. This study examines a particularly important aspect of hospital care that has practice implications for a significant proportion of US hospitalized patients. If this study’s aims are met and rehabilitation therapy with an ICU initiation is successful in reducing hospital length of stay, this new knowledge will significantly impact how ICU and hospital services will be delivered to future patients with ARF.

Objectives/Specific Aims:

While our research and that of others has shown that rehabilitation therapy can increase functional outcomes while lowering biomarkers of inflammation in the frail aged and other clinical populations 22, it is not known whether such rehabilitation therapy can result in improved functional capacity and functional performance and reduce inflammation in ARF patients. We do, however, have data showing convincing evidence for the feasibility and safety of rehabilitation therapy in ARF patients, with important trends toward reduced hospital length of stay (LOS) 23. Therefore, we propose a two-arm, randomized trial in 326 patients with ARF to compare Standardized Rehabilitation Therapy initiated in the ICU and administered throughout the hospitalization vs. usual care (control). Standardized Rehabilitation Therapy will consist of: passive range of motion, physical therapy and progressive resistance exercise (strength training). The regimen will be administered 7 days/week by a Mobility Team consisting of a critical care nurse, physical therapist and nursing assistant.
We will determine whether standardized rehabilitation therapy will reduce hospital LOS, improve functional
capacity and performance, improve quality of life, reduce inflammation and reduce hospital costs as compared
to usual care. To answer this question, we will propose the following aims:
Primary Aim:

Aim 1: To determine whether standardized rehabilitation therapy will decrease hospital length of stay.

Hypothesis: Compared to usual care, standardized rehabilitation therapy will reduce hospital length of stay for patients with Acute Respiratory Failure.

Secondary Aim:

Aim 2: To determine whether standardized rehabilitation therapy will improve functional capacity and performance, and quality of life.

Hypothesis: Standardized rehabilitation therapy will improve functional status measures and health related quality of life at 6 months post-enrollment.

The proposed study is a natural extension of our prior work, is supported by extensive preliminary studies, is highly innovative, and is strongly responsive to recent society consensus statements\textsuperscript{9}. Our unique environment allows us to be particularly well suited to perform this study. We have a hospital-funded, experienced Mobility Team (7 days/week) consisting of a Critical Care Nurse, Physical Therapist and Nursing Assistant to administer this protocol that has the support of our hospital administration to continue through the duration of this grant. For this project, we have assembled a multidisciplinary team of co-investigators and consultants with complementary strengths and common interests (Exercise Physiology & Training, Physical Therapy, Nursing, Medicine, Basic Science, Health Economics).
Setting:

Study participants will consist of 326 patients with ARF admitted to the Intensive Care Units of Wake Forest University Baptist Medical Center.

Methods/Measures:

Design: The proposed study will be a patient-randomized, single center, with blinded assessment analysts, Phase III investigation with two arms: 1. Intervention (Standardized Rehabilitative Therapy initiated in the ICU, administered throughout hospitalization) and 2. Control (Usual Care). Patients will remain in the study from enrollment, through their hospital discharge and through a 6-month follow-up period. Study subjects randomized to the standardized rehabilitative therapy arm will receive Standardized Rehabilitation Therapy within the hospital only, from the time of enrollment through hospital discharge, including days spent in a regular floor bed. There will be no delivery of Standardized Rehabilitation Therapy from hospital discharge through the 6-month follow-up period, although both arms will undergo functional testing, HRQoL assessments and muscle ultrasounds at hospital discharge, 2, 4 and 6-months post-enrollment, performed by research analysts blinded to the arm of the study.

Subjects: Study participants will consist of 326 patients with ARF admitted to the Intensive Care Units of Wake Forest University Baptist Medical Center. A study nurse will screen newly admitted ICU patients for acceptability into the study. Patients who meet the entry criteria will be invited to participate. Inclusion and exclusion criteria are listed in Table 1. These criteria were designed to target a population in which a rehabilitation program would have reasonable chances of success of achieving the patient’s pre-acute illness ambulatory status.

Table 1

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
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</thead>
<tbody>
<tr>
<td>Age ≥ 18 years</td>
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<tr>
<td>Mechanically ventilated via an endotracheal tube or mask</td>
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<tr>
<td>Lung Injury</td>
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<table>
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<tr>
<th>Exclusion Criteria</th>
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<tbody>
<tr>
<td>Previously enrolled in this study</td>
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<tr>
<td>Inability to walk without assistance prior to acute ICU illness (use of a cane or walkers not exclusions)</td>
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<tr>
<td>Cognitive impairment prior to acute ICU illness (non-verbal)</td>
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<tr>
<td>Acute stroke</td>
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<tr>
<td>Body mass index (BMI) &gt;50</td>
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<tr>
<td>Neuromuscular disease that could impair weaning (myasthenia gravis, ALS, Guillain-Barre)</td>
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<tr>
<td>Hip fracture, unstable cervical spine or pathological fracture</td>
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<tr>
<td>Mechanically Ventilated &gt; 80 hours</td>
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<tr>
<td>Current hospitalization or transferring hospital stay &gt; 7 days</td>
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<tr>
<td>DNR/DNI on admission</td>
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<tr>
<td>Ineligible cancer treatment within the last 6 months</td>
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<tr>
<td>Upon Principle Investigator discretion, patient not suitable for study</td>
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<tr>
<td>Moribund</td>
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<tr>
<td>Other Research Study</td>
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</tbody>
</table>
Randomization: Patients will be randomized to receive Standardized Rehabilitation Therapy or Usual Care with equal probability, using blocked randomization to ensure approximately equal accrual to each treatment throughout the study. Block sizes of varying length will be determined randomly to ensure that future assignments cannot be inferred from past assignments. Treatment assignments will be generated using nQuery Advisor 6.0, and the generated file will be stored in an area of the study’s server that is only accessible by the study programmer.

Study Arms:

Standardized Rehabilitation Therapy Arm:
Participants randomized to the Standardized Rehabilitation Therapy arm will receive three types of interventions throughout a day: Passive Range of Motion (PROM), Physical Therapy (PT) and Progressive Resistance Exercise (PRE). The standardized rehabilitation therapy protocol will be administered by the ICU Mobility Team. The Protocol will be delivered 7 days a week. Study subjects will be assessed daily and if appropriate will receive 3 separate sessions of activity each day. When patients are unconscious, they will receive three sessions of only PROM. When the patient regains consciousness, the three sessions per day will consist of one PROM, one physical therapy session and one PRE strength training session depending on the subject's level of consciousness. Consciousness will be determined by the responses to the following commands: “Open (close) your eyes”, “Look at me”, “Open your mouth and put out your tongue”, “Nod your head”, and “Raise your eyebrows when I have counted up to 5”\(^{17}\).

The patient will have to respond correctly to three of the five commands to be considered sufficiently alert to participate in Physical Therapy and PRE training. Patients will be advanced as they become more alert and able.
<table>
<thead>
<tr>
<th>Event</th>
<th>ICU Admit</th>
<th>ICU D/C</th>
<th>Hosp D/C</th>
<th>2-mo</th>
<th>4-mo</th>
<th>6-mo</th>
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<td>Consent</td>
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<td></td>
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<tr>
<td>Randomization</td>
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<td>Baseline Acuity</td>
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<td>X</td>
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<tr>
<td>Readmission</td>
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</table>
Passive Range of Motion (PROM)-PROM therapy will be administered to all upper and lower extremity joints by one of the Mobility Team nursing assistants. Five repetitions of PROM will be provided for each joint. For the upper extremities PROM includes finger flexion and extension; wrist flexion, extension and ulnar and radial deviation; elbow flexion, extension, supination, and pronation; shoulder flexion, abduction, and internal and external rotation. Shoulder extension will be deferred due to positioning in bed. Lower extremity PROM includes toe flexion and extension; ankle dorsi flexion, plantar flexion, inversion, and eversion; knee flexion and extension; and hip flexion, abduction, adduction, internal and external rotation. Hip extension will be deferred due to positioning in bed.

Physical Therapy-Patients randomized to the rehabilitation therapy arm will receive a function-based physical therapy intervention targeted toward identified functional deficits. This intervention is based on the protocol described in section 4 and includes bed mobility, transfer training and balance training. As patients progress, the Physical Therapy will increasingly focus on the functional activities such as transfer to edge of bed; safe transfers to and from bed, chair, or commode; seated balance activities; pre-gait standing activities (forward and lateral weight shifting, marching in place), and ambulation. Bridging will also be started to improve functional strength for bed mobility. The bridging maneuver asks the patients to plant both feet firmly on the surface of the bed and raise their pelvis vertically with the goal to have the pelvis completely off the surface of the bed. If the subject can do double leg bridges, single leg bridges with opposite leg held in hip flexion with slight elevation off bed will be started. Being free from mechanical ventilation is not a pre-requisite for any these activities.

Progressive Resistance Exercise (PRE) Training- Once the patient is alert and can complete Physical Therapy active range of motion exercises unassisted, PRE training will be added to the mobility training. The PRE for each subject will consist of a separate Physical Therapist-directed second daily session with a focus only on PRE. The subjects will be progressed from bed level exercise, to exercises done while sitting on the edge of the bed (EOB) as detailed below. Patients will participate in PRE every day while in the ICU and hospital. The goal is for patients to complete 3 sets of 8 repetitions for each exercise. Resistance will be applied using Thera-Band elastic resistance bands. Patients will begin using the tan colored Thera-Bands which exert 1.1
pounds of force at 100% elongation. Once the patient can complete 3 sets of 8 repetitions, the resistance will be increased using the next-highest resistance band. Exercise intensity will be monitored by recording the color of the band used, and the number of repetitions and sets completed.

**Bed-Level Supine PRE:** If a participant cannot move from supine to sitting positions with at least moderate assistance and can hold their sitting balance for >5 minutes with only standby assistance from the Physical Therapist, they will be deemed suitable for bed-level supine exercise. If the subject is on a bed that converts to a chair position, the PRE session will be held with the bed in the chair position. If there is a vascular access device in place (e.g. femoral vascular catheter or femoral arterial line) compromised by the sitting position, the subject will be seen with the head of the bed no greater than a 60 degree angle.

The subject will first engage in PRE maneuvers that are actively-assisted exercises (performing the maneuver without a TheraBand) and then progress to active maneuvers using good form with a goal of 8 repetitions per exercise. PRE will include dorsiflexion, knee flexion, knee extension, and hip flexion (straight leg raise). Exercises for the upper extremities will include elbow flexion and extension, shoulder flexion. When subjects can achieve 8 repetitions of each exercise independently without loss of form, Thera-Bands® will be introduced using progressively more resistance: yellow (light), red (medium), green (heavy), and if applicable, blue for extra heavy and black for special heavy.

**Sitting Position PRE:** Subjects will be progressed to this level when they can transfer to a sitting position at the edge of the bed with only moderate assistance and can sit > 5 minutes without loss of balance (standby assistance level only). Patients will participate in similar lower and upper extremity exercises as above.
Control Arm:
Patients randomized to the control arm will receive the standard of care for patients requiring mechanical ventilation in the ICU. These patients will not receive the standardized rehabilitative therapy per protocol. Participants in the control group will receive Physical Therapy evaluations as dictated by the patient's attending physician. Follow-up physical therapy sessions for the control group participants will occur as per initial physical therapy consultation recommends.

Data Collection - In this section, we describe the instruments and measures that will be used as dependent variables, covariates, demographic and screening variables, and timetable for collection Table 2.

Data Collection for Demographic, Baseline and On-Study Variables- Demographic information will be obtained on all patients. Additionally, Acute Physiology and Chronic Health Evaluation (APACHE) III scores will be calculated based on values from the initiation of ICU admission. Other variables will be collected, such as medications, fluid administration, and dialysis.

Description of Primary Outcome - The primary endpoint for this study will be Hospital length of stay and is defined as the hospital calendar days (or any portion of a calendar day) at the enrolling hospital and at any long term acute care facility to which the subject is directly transferred. If a subject is subsequently transferred from enrolling hospital to a rehab hospital or skilled nursing facility, the discharge calendar date from the enrolling hospital will end the in-patient hospitalization for the purposes of this study. Discharge is defined as the point at which a patient is considered as having completed medical care as determined by the subject's primary physician team, as in the case of subjects who are homeless, and not the point at which the patient physically leaves the hospital. Of note, none of the research team members will be involved in the decision for hospital discharge, the primary endpoint.
**Description of Secondary Outcomes** - Studies reporting follow-up for patients after ARF suggest that functional status improves markedly between 3 and 6 months post-hospital discharge. Our approach will be to optimize evaluation of the pattern and timing of recovery with post-hospital in-person evaluations scheduled at 2, 4 and 6 months *post-enrollment*, as opposed to post-discharge. The first functional status testing and health related quality of life testing will occur at hospital discharge (unless hospital discharge is within one week of the 2 month follow-up visit). If a patient's hospital discharge is within one week of the 2, 4, or 6 month follow-up evaluation, the results will be used for both the discharge and follow-up analyses.

We chose to use the enrollment date for the timing of the outpatient follow-up visits rather than hospital discharge date to demonstrate functional outcomes at set points with relation to having received rehabilitation therapy.

**Blinding of Functional Status and Health Related Quality of Life Measurements**

There is great difficulty in the design of blinding for non-pharmacologic Critical Care studies. Interventions such as ventilator or fluid administration and in the case of this study, standardized rehabilitation therapy, are difficult to blind to the patient, the bedside practitioners and the research team. However, in the design of this study two separate design aspects address this concern. First, as was the case for the 1st and 2nd pilot studies, the subject’s hospital discharge is not the responsibility of the research team, but is the responsibility of the general medical floor team. Secondly, the research analyst will be blinded to the patient’s randomization so that the outcome measurements of strength testing, functional testing and health related quality of life testing will be obtained in a blinded fashion. Prior to any testing, the patients and family members will be cautioned by the research nurses to refrain from comments concerning in-patient rehabilitation therapy.

**Selection of assessment tools**

The selection of the electronic dynamometer, the short physical performance battery (SPPB), the Medical Outcomes Study 36 Item Short Form (SF-36), and the Functional Performance Inventory Short Form (FPI-SF) were selected to address the issue of preventing missing data during a longitudinal follow-up design. These tools will allow research team members not only to conduct the assessments in clinic, but also perform these
tests in a patient's home and at last resort, some of the tools (SF-36, FPI-SF) perform well in phone administrations. For these reasons, we believe the study's tools allow for a minimum of missing data points in the follow-up portion of the study.

**Schedule of Follow-up visits**

Prior to discharge, subjects will be approached for re-consent if initial consent was by proxy. They will be invited to continue with this study as outpatients at 2, 4, and 6-months post-enrollment (scheduled for +/- 2 weeks of the 2, 4, and 6-month dates). If the subject does not wish to or cannot physically make the outpatient visit, we will ask if our study team personnel to visit the subject at home to conduct the assessments. If neither option is acceptable to the subject, we will request that the HRQoL assessments be performed by phone call. Contact information will be obtained for the subject, his/her legal representative, and (if possible) at least 1 other contact person during hospitalization. All phone calls will be administered by a member of the research team. All data collected will be stored in a secure password-protected database, with limited access. These data will be stored utilizing a subject-specific identifier to protect confidentiality.

Follow-up assessments will start with assessing the subject as alive, at home, and recording any hospitalizations since last contact.

**Functional Status Assessments**: Patients from both arms of the study will undergo functional status assessments at ICU discharge and then at hospital discharge and during in-person follow-up visits scheduled at 2, 4 and 6 months from the date of enrollment. A few patients will still be in the hospital or a medical facility at these time points. The in-person evaluations are structured so that they may be accomplished not only at the medical center clinic but also in the home or other medical facility if the enrolled subject cannot return to WFUBMC for their in-person follow-up visit. Functional status will be evaluated using measures of skeletal muscle strength and the SPPB as surrogates for functional capacity and the FPI-SF as a surrogate of functional performance.

Muscle strength was also assessed using an electronic hand-held strength dynamometer (MicroFET 2MT Dynamometer, Hoggan Health Industries, Salt Lake City, UT). Three trials with brief pauses will be performed for each muscle group. The best performance of three trials will be selected for each side, although all attempts will be collected as part of the database for future analyses, particularly to address factors of endurance. Examiners will be trained with a standardized method and sequence of data collection. Additionally, this specific dynamometer will be used to collect strength measures of the elbow flexion and extension, ankle dorsiflexion, knee extension and hip extension, bilaterally.

Short Physical Performance Battery (SPPB): Physical functioning will be assessed using the SPPB. Briefly, the SPPB score is based on timed measures of standing balance, walking speed, and ability to rise from a chair. Each performance measure is assigned a score ranging from 0 to 4, with 4 indicating the highest level of performance and 0 inability to complete the test. A summary score (range 0-12) will be calculated by adding the three scores. Few studies have looked at functional outcomes post-hospital discharge for patients with ARF. Although the “best” instrument to employ to measure functional outcome after ARF, or any critical illness, is not known, we have explored the SPPB standardized functional assessment tool that was developed for evaluations in the geriatric population. The target population in this study, initially, will be comprised of very low-functioning individuals. Although the SPPB has been validated in the geriatric population, not the post-ICU population, we specifically chose the SPPB tool for its low function discriminatory capabilities. There is no tool validated in the post-ICU population in regards to function assessment. The SPPB is easily conducted, may be conducted in a patient’s home or hospital room, and has been shown to be sufficiently discriminatory to be used in several geriatric intervention studies.
Functional Performance Inventory Short Form (FPI-SF): The FPI-SF provides an overall score of patient self-reported functional performance in the areas of household maintenance, movement, family and social activities, work, avocation and recreation. The instrument has undergone extensive psychometric testing and has been shown to have internal reliability and reproducibility 26.

Health Related Quality of Life Assessments- It has been noted previously that patients with ARF may suffer with significant impairment in their health related quality of life for months following hospital discharge. The long term outcome measurements for this project will be conducted at hospital discharge and at 2, 4 and 6 months post-enrollment. The two tools selected to assess health related quality of life are the SF-36 27,28. The SF-36 is a generic measure of health related quality of life that examines the domains of physical and mental functioning. Given ARF is an extremely variable and heterogeneous syndrome that does not encompass a single disease, we will not be using a disease specific measure of health related quality of life. These tools were selected both for their specific scope and to assess the survivor population as uniformly as possible, given that some follow-up time points may be conducted by phone and others in person.

Exercise Adherence – Adherence to and progress through the PROM, Physical Therapy, and PRE interventions will be monitored daily. The PROM intervention will be recorded as the number of repetitions of PROM exercises, the number of times performed per day and the number of days performed. Similar data will be collected for Physical Therapy sessions. If the patient cannot complete the task, the reason why will also be recorded. The strength training program will be monitored by recording the color of the Thera-Band® used by the patient for a given exercise, number of repetitions and number of sets completed for each exercise performed. Inability to complete the exercise or the required number of sets, and why, will also be recorded. The reasons why a patient would be discontinued appear in the Case Report Form as standardized answers; the research nurse will pick the most appropriate corresponding reason to keep free-text answers to an absolute minimum. We will calculate the number of sessions each participant exercised at the prescribed resistance.
Assessment of Delirium during Physical Therapy and PRE sessions using the CAM-ICU

Standardized physical exam can detect focal weakness in a conscious, cooperative patient. For ICU care, unconsciousness and delirium certainly hamper efforts to evaluate onset and severity of weakness in ICU patients. As well compliance to an exercise regimen may be less complete for those individuals demonstrating signs of delirium (e.g., decreased ability to concentrate on repetitions). Assessment for the presence of delirium will be conducted each day, by applying the Confusion Assessment Method for the ICU (CAM-ICU) 29.

Statistical Considerations

The primary objective of this study is to assess the effect of the overall rehabilitation therapy intervention on the length of hospital stay in patients with ARF. Secondary objectives are to assess the effect of Mobility Training on 1) length of time in the ICU, 2) functional status, 2) quality of life, and 3) adverse events. ICU and hospital LOS will be calculated as the number of days from admission until ICU or hospital discharge, respectively. Patients who die before discharge will be censored in the analyses. Functional status will be evaluated using measures of skeletal muscle strength and the SPPB as surrogates for functional capacity and the FPI-SF as a surrogate of functional performance. Quality of life will be quantified using the SF-36 questionnaire, the TMMSE, and the Caregiver Activity Tool.

Patients will be randomized to receive rehabilitative therapy or usual care with equal probability. Analysis of primary and secondary outcome measures will be carried out based on an 'intent to treat' approach. That is, all randomized patients will be used in all analyses, whether or not they were actually treated or whether or not they were treated according to protocol.

Study Design / Power Calculations: A prospective, randomized phase III design will be used to assess the effect of Standardized Rehabilitative Therapy on the hospital LOS in patients with ARF. As discussed below, the primary analysis used to assess the effect of rehabilitative therapy will be a Cox proportional hazards regression model where hospital discharge will be the ‘event’ of interest. Thus, a greater hazard represents a
greater likelihood of discharge. Assuming an exponential time to discharge distribution (which provided an adequate fit for our pilot data), the hazard ratio (HR) can be interpreted as a percent change in the LOS. Table 3 shows the total number of patients necessary to detect decreases in hospital LOS ranging from 25% to 40% with 80% and 90% power at the 5% two-sided level of significance. These calculations assume that 20% of the patients will die and 5% of the remaining patients will drop out of the study prior to discharge. Note that we only observed 15% in-hospital mortality during the 1st Pilot Study, but, to be conservative, we used the larger percentage in these calculations.

We want to have adequate power to detect a 30% decrease in the median length of hospital stay (a HR of approximately 1.43). This decrease is slightly larger than the decrease we observed in the 1st Pilot Study, but, as described below, we expect a greater effect with the current intervention (see Preliminary Studies Section and discussion below regarding design differences between this and the 1st Pilot Study). A very important feature of the 1st Pilot Study’s design was that the intervention was only delivered in the ICU. In the 1st Pilot Study, Usual Care resumed in the Intervention arm once the patient reached a floor bed. Despite the intervention being limited to the ICU, there was a 24% adjusted reduction in hospital LOS (HR = 1.31). Therefore, in view of the current study proposal’s design to deliver the Standardized Rehabilitation Therapy from ICU admission to hospital discharge and due to the addition of Progressive Resistance Exercise, we expect a much greater clinical effect. As seen in Table 3, 326 patients are needed to detect a 30% reduction in hospital LOS with 80% power at the 5% two-sided level of significance (HR = 1.43). While we believe that rehabilitative therapy will decrease hospital stay, we are using a two-sided level of significance since we would want to report that the Standardized Rehabilitation Therapy increased hospital stay if that happened (as opposed to reporting that it simply failed to decrease hospital stay). Note that the study is powered to detect the HR of 1.43 regardless of the shape of the time to discharge distribution.

<table>
<thead>
<tr>
<th>Decrease in Hospital LOS</th>
<th>HR</th>
<th>80% Power</th>
<th>90% Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>25%</td>
<td>1.32</td>
<td>499</td>
<td>668</td>
</tr>
<tr>
<td>30%</td>
<td>1.43</td>
<td>326</td>
<td>436</td>
</tr>
<tr>
<td>33.3%</td>
<td>1.50</td>
<td>252</td>
<td>337</td>
</tr>
<tr>
<td>35%</td>
<td>1.54</td>
<td>223</td>
<td>297</td>
</tr>
<tr>
<td>40%</td>
<td>1.67</td>
<td>158</td>
<td>212</td>
</tr>
</tbody>
</table>
Secondary Outcomes:

For secondary outcomes, estimates of survivors are based on the literature and our hospital’s data extraction concerning subsequent admissions. Specifically, estimates of the number of survivors for this proposal are based on an approximation of subject drop out other than for death as reported in other critical care literature.

Predictions for patients available at the end of the 6 month out-patient period were performed to insure that the functional tool and HRQoL tools can detect the minimum clinically important difference (MCID) between groups. The 1st Pilot Study’s in-hospital mortality was 15%, but to be conservative, we are assuming 20% in our estimates. This estimate, with a 5% drop out rate in hospital, reduces the 326 enrolled subjects to 248 subjects eligible for the out-patient evaluations. Based on the literature, we have conservatively estimated an additional overall mortality for patients with ARF during their first 6 months post hospital discharge of 15%. Lastly, we expect an approximate out-patient 10% loss to follow-up rate. Therefore, we predict that at the end of 6 months we will have complete data collection on 190 subjects, approximately 77% of discharged survivors.

Retention of Survivors for 6 Month Follow Up: Researchers continue to debate the minimum participant retention rate acceptable to ensure study validity. The social science literature suggests a minimum rate of 70–80% . Despite these guidelines, studies with high attrition rates continue to be published and further underscore the difficulty of retaining study subjects. It is vital to incorporate retention strategies into follow-up protocols. Significant time is required for planning, tracking and retention strategies. Furthermore, adequate budget staff and resources are needed to provide staff time for these endeavors and to appropriately train interviewers to successfully complete longitudinal studies with minimal subject attrition. Use of e-mail and the internet may facilitate retention.

Recently, specific post-ICU long term patient follow-up was reported . Follow-up retention rates of 85-91% have been attained through three key areas for retention of subjects for post-ICU, post-hospital follow-up. We will employ the following concepts to retain subjects: respect for patients, respect for their ideas and their time commitment to the research project; specific tracking strategies, collect information on many patient contacts at
the initiation of the study and outline tracking procedures for subjects lost to follow-up; and study personnel, interpersonal skills must be reinforced, flexible working hours mandated, and support offered.

The strength measures, SPPB, SF-36, and FPI, will be conducted on the anticipated initial 248 ARF survivors at discharge, and at 2, 4, and 6 months post-randomization. As described below, the longitudinal models will use data collected at all of these times to assess contrasts at the individual times. However, we calculated power for the secondary measures using the final 6 month estimates of sample size. Of the 8 domains within the SF-36, the Physical Component Score (PCS) and the Mental Component Score (MCS) represent the two primary outcomes to separately assess physical and mental health. We obtained estimates of the standard deviations for each of these measures from relevant populations reported in the literature. For the MCS and PCS, we obtained estimates from Heyland et al (2005); for the FPI, Larson et al (1998); and for the SPPB, Ostir et al (2007) 35-37. Intervention differences at the six-month follow-up in these secondary outcomes detectable with 80% and 90% power are shown in Table 4. We see that we have at least 90% power for detecting 20% or smaller relative differences between groups at the 5% two-sided level of significance.

**Data Analysis:** Descriptive statistics (means, standard deviations, frequencies, percentages) for patient characteristics (age, sex, race, BMI, APACHE III score) and the outcome measures described above will be presented for each treatment group. Tables, graphs, and plots will be used to illustrate the data when appropriate.

**Primary Outcome:** Kaplan-Meier methods will be used to estimate the time to hospital discharge. A logrank test will be used to assess the unadjusted difference in time to discharge between treatment groups, and Cox’s proportional hazards regression model will be used to assess the effect of rehabilitative therapy after adjusting

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Estimated Mean (SD)</th>
<th>80% Power</th>
<th>90% Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCS</td>
<td>36.4 (12.2)</td>
<td>13.7</td>
<td>15.9</td>
</tr>
<tr>
<td>MCS</td>
<td>45.2 (13.6)</td>
<td>12.3</td>
<td>14.2</td>
</tr>
<tr>
<td>FPI</td>
<td>2.0 (0.4)</td>
<td>8.2</td>
<td>9.5</td>
</tr>
<tr>
<td>MMSE</td>
<td>27.0 (2.9)</td>
<td>4.4</td>
<td>5.1</td>
</tr>
<tr>
<td>SPPB</td>
<td>5.5 (3.3)</td>
<td>17.1</td>
<td>19.8</td>
</tr>
</tbody>
</table>
for stratification factors and other baseline covariates. Predicted survival curves will be generated for various
covariate patterns defined by significant predictors. In addition, parametric survival models (e.g., assuming an
exponential or Weibull time to discharge distribution) and a tree structured survival analysis will be done using
methods described by Segal and compared to the results of the proportional hazards analyses. Separate
models will be fit to allow for time varying covariates such as delirium score and biomarkers. These can be fit
in SAS (for Cox’s model) using the PHREG procedure or by fitting generalized linear models to event history
data as described in Lindsey. Ad hoc methods as described in Allison will be used to examine time dependent
covariates whose values are not known at all event times. From our experience with our 1st Pilot Study, we
will construct detailed analyses regarding exposures to specific ICU parameters and outcomes that may be
associated with hospital LOS.

Secondary Outcomes: Strength measures, SPPB, FPI-SF, SF-36 and TMMSE will be measured at hospital
discharge and at 2, 4, and 6 months post-randomization (also Strength measures only at ICU discharge).
Analysis of covariance will be used to assess differences in these measures between intervention groups at
discharge after adjustment for stratification factors and other patient covariates. These adjustments will be
made to ensure the analyses match the design, to correct for chance imbalances in important prognostic
factors and to improve the precision of the group comparisons by accounting for that part of the variance due
to the variability in the patient characteristics. Regression diagnostics, residual plots, and exploratory
analyses will be done to find appropriate transformations for the variables in these analyses. Order of priority
in choosing a transformation will be to satisfy the 1) linearity assumption, 2) homogeneity of variances
assumption, and 3) normality assumption. Additionally, all repeated measures will be used in a longitudinal
repeated measures model to assess the effect of the intervention on the response profiles of each secondary
outcome. The major hypothesis will be assessed by testing the group by time interaction and the mean
treatment difference. Various covariance patterns will be assessed to account for the within patient correlation,
and choices will be made based on likelihood ratio tests and the AIC criterion. Additionally, random effects
models treating time since randomization as a continuous variable will be considered to reduce the
dimensionality somewhat. There are likely to be missing end point measurements due to missed visits or
patients dropping out of the study. The longitudinal mixed models are appropriate if the data are missing at
random. This assumption can only be assessed indirectly by comparing characteristics of subjects with and without complete data and by assessing if missingness is related to adverse events. If it appears that the missingness is nonrandom, data analysis is more difficult and inferences more conservative. Sensitivity analyses will be used to assess the effect of assumptions made about the missing data. If the results of these analyses differ substantially depending on the assumptions regarding the missingness, further model-based and post-hoc stratification methods will be used.
Data and Safety Monitoring Plan:

A. Data Safety Plan Monitor and Committee

1) Safety Monitoring Committee includes three independent physicians and a senior faculty statistician.

2) Dr. Morris will serve as the Study’s Data Safety Monitor. Responsibilities of the DSM with regards to this study will include:

a) Review of serious, unexpected adverse events, whether or not thought to be related to the protocol's intervention or study procedures.

b) Review of clinical data and other related data at unplanned intervals when appropriate or when safety issues occur.

c) Ensure that analyses performed by or provided to the Safety Monitoring Committee (SMC) are recorded, handled and stored in a way that allows accurate interpretation, verification and reporting of the data.

d) Maintain minutes of all SMC meetings whether in person or via teleconference, including the names of attendees, a summary of the discussion, recommendations and the rationale for recommendations.

e) Make recommendations to the Study’s Co-PI’s, IRB and NINR representatives including the following: suspend study enrollment due to safety concerns, recommend changes to the protocol, procedures and/or informed consent document or continue the current study.
3) In this study, individual reports of adverse events will be reviewed in a blinded fashion unless a need arises to unblind the SMC to the assigned arm of a particular patient. Aggregate reports are not planned for review until the end of the study unless they are requested on an ad hoc basis by the SMC.

B. Data Safety Plan Procedures

1) Study safety monitoring schedule:

   a) The Safety Monitoring Committee will meet after the first 12 calendar months of enrollment as well as a second meeting after 50% of the enrollment is achieved.

   b) The Study’s Project Manager will initiate review of 2 study subjects per quarter, randomly chosen who have completed hospitalization. The case report forms and subject file will be reviewed for:

      o Compliance with IRB requirements

      o Conformance with informed consent requirements

      o Verification of source documents

      o Investigator compliance

      o Missed adverse events
c) Institutional IRB will provide additional oversight if needed. The results of the Project Manager’s review will be presented at the next monthly staff meeting. At our monthly staff meeting, we provide opportunity to discuss new human safety concerns by any of our team. Additionally, we review each of the new subjects enrolled since the last staff meeting in regards to consent form signature and other compliance concerns (such as when the subject was approached to discuss re-consent).

d) We have ongoing weekly review from Public Health Sciences with queries regarding any incomplete data within the case report form.

2) Minimizing research-associated risk

The protocol gives specific information about patient safety during research study participation. All study patients are monitored electronically during the ICU stay and by a critical care nurse presence as well as the continuation of the critical care nurse’s presence during the stay in the hospital during exercise sessions. If patient’s status decreases during session, the session is ended and the critical care nurse communicates verbally with the patient’s assigned bedside nurse, as well as written documentation within the patient’s electronic medical record.

3) Protecting the confidentiality of participant data

The protocol gives guidelines which we follow to protect the confidentiality of patient data. Confidentiality is maintained by limiting access to study related records and maintaining password protection on the database. Also, all records are kept secure in locked offices and are identified by subject study ID.
C. Procedures for identifying, reviewing, and reporting adverse events and unanticipated problems to the IRB, NINR.

The intervention is considered a low risk intervention. The identification, review and reporting process would begin with the Study’s Critical Care Nurse notifying one of the two study physicians, Dr. Morris or Dr. Files of a potential safety event. The physician and nurse will review the potential safety event together. Patient records will be reviewed for evidence of risk to the patient. The Physician and Nurse will follow the NIH guidelines in adverse event reporting and if the potential event is deemed to have met the criteria, the event will be reported. The reporting of adverse events will be the primary responsibility of the Study physicians in conjunction with the Study’s project manager who will notify the IRB and representatives of the NINR.

If applicable, the type and number of events that would halt accrual and it would then generate a review of eligibility, monitoring, assessments, intervention, and how the resumption of accrual would occur.

Severity of Adverse Events, Definitions

https://www.nia.nih.gov/sites/default/files/niaaeandaeguidelinesfinal011012_0.doc.

Classifications include the following:

- **Mild**: Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.
- **Moderate**: Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning.
- **Severe**: Events interrupt the participant’s normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.
D. The advanced plans for interim and/or futility analysis.

The Safety Monitoring Committee recommends a single interim analysis to assess intervention effect on length of hospital stay using O'Brien-Fleming boundaries at the half-way point in subject accrual. The study will be suspended if the two-sided p-value, based on the log-rank test, is less than .0052.
REFERENCES


8. Curtis JR. The long-term outcomes of mechanical ventilation: what are they and how should they be used? RespirCare 2002;47:496-505.


