Human Subjects Research Protocol

The Common Human Subjects Protocol Cover Form **must** be completed and accompany this form. This Protocol form should be completed for any human subjects research proposal that does not have a specific "protocol," such as a grant application. This form must be submitted along with a copy of the complete grant proposal and all the information in this form **must** be consistent with that proposal. This protocol form, once IRB approved, will be the working protocol for that research. **When completing this document, do not refer to page numbers within your grant**. If revisions are necessary during the course of the research, amendments should refer to this protocol form, not the grant proposal. Enter responses for all sections. Check N/A if the section does not apply. All materials must be submitted electronically to the IRB via InfoEd. Proper security access is needed to make electronic submissions. Visit the InfoEd Resource Materials page for more information.

PROTOCOL SUMMARY

Project Title:	Protocol Version Date:
Phase I Pilot Safety and Feasibility of a Novel Restraint Device for Critically Ill Patients with Acute Respiratory Failure	10-31-18

Principal Investigator: Renee Stapleton, MD PhD; Dale Needham, FCPA MD PhD

NCT Number: NCT03621475

Lay Language Summary: *(Please use non-technical language that would be understood by nonscientific IRB members to summarize the proposed research project. The information must include: (1) a brief statement of the problem and related theory supporting the intent of the study, and (2) a brief but specific description of the procedure(s) involving the human subjects. Please do not exceed one single-spaced 8 ½ X 11" page.)*

The goal of this Fast-Track STTR project is to optimize and test a novel arm restraint in older critically ill mechanically ventilated patients that increases mobility; reduces agitation, use of sedative medications, and delirium; and exhibits high satisfaction and acceptability among hospital staff, family members, and patients. Older mechanically ventilated patients are often immobilized with wrist restraints to prevent self-extubation and are sedated to reduce agitation caused by their restraints and endotracheal (breathing) tube. This sedation and immobility lead to complications, including delirium and muscle weakness, that are independently associated with long term cognitive impairment, reduced physical functioning, and mortality. Specifically, the incidence and duration of delirium in the ICU are strongly and independently associated with long-term cognitive impairment that is similar to Alzheimer's Disease and Related Dementias.

Healthy Design is developing the novel *Exersides*^{TM} restraint that allows arm mobility but prohibits hands from reaching oral/nasal endotracheal and feeding tubes or intravenous lines. Because it permits mobility, *Exersides*^{TM} may reduce agitation and the need for sedatives. In preliminary pilot testing, *Exersides*^{TM} has demonstrated very encouraging results. The objectives of this STTR Fast-Track project are to optimize *Exersides*^{TM} and evaluate it in a randomized controlled trial (RCT) in older critically ill patients at high risk for delirium and associated long-term cognitive impairment. The multidisciplinary investigator team has expertise in critical care, extensive experience in conducting ICU RCTs, and a history of successful collaboration.

During Phase I, a prospective study will be performed in 8 older mechanically ventilated patients to demonstrate that 1) the revised *Exersides*^{TM} prototype is safe and 2) the RCT proposed in Phase II is feasible. The milestones to proceed to Phase II are to demonstrate that: 1) the revised *Exersides*^{TM} restraint has mean incidence rate <5% across 7 pre-specified safety criteria in mechanically ventilated

older patients who require restraint; and 2) the RCT in phase II is feasible by successfully enrolling 8 ICU patients into the phase I study and completing at least 90% of all proposed outcome measures.

In Phase II, a multi-site within-patient crossover RCT in older mechanically ventilated patients requiring restraint will be conducted to test the following outcomes in *Exersides™* versus traditional wrist restraint: 1) Mobility assessed by actigraphy (primary outcome); 2) Agitation, delirium, and medication use (secondary outcomes); and 3) Satisfaction with and acceptability/perceptions of the device (secondary outcomes). Successful completion of this project will result in an *Exersides™* restraint that is ready for final optimization in preparation for commercialization, and is suitable for larger clinical studies to demonstrate effectiveness reducing long-term cognitive impairment in older ICU patients.

PURPOSE AND OBJECTIVES

Purpose: The importance of the research and the potential knowledge to be gained should be explained in detail. Give background information.

Background and Significance

Every day, >27,000 patients are restrained in US hospitals with physical restraints in intensive care units (ICUs) accounting for 56% of all restraint days, and older patients being 8 times more likely to be restrained than younger patients.[1] Hence, physical restraint is a major issue in ICUs, especially for older adults. Restraints are used in an attempt to reduce dangerous self-removal of endotracheal tubes, feeding tubes, and intravenous (IV) catheters.[2] However, existing restraint devices have major limitations. Especially in older patients, restraints are associated with increased agitation and delirium, often leading to increased use of sedative medications, with associated complications including: immobility, muscle weakness, pressure ulcers, falls, prolonged mechanical ventilation duration, nosocomial infections, increased healthcare costs, and increased mortality.[1] Of particular note, older patients and those with Alzheimer's Disease and Related Dementias are at particular risk of delirium in the ICU.[1] In both younger and older patients, the duration of delirium in the ICU is strongly associated with post-ICU long-term cognitive impairment, with cognitive test scores similar to patients with Alzheimer's Disease and Related Dementias.[1] Moreover, in older adults, delirium is significantly associated with incident dementia (odds ratio (OR) = 8.7) in those without pre-existing cognitive impairment[3] and with accelerated cognitive decline[1] in those with pre-existing dementia, with worsening dementia severity (OR = 3.1) and global function (OR = 2.8).[3] Hence, this Fast Track project is responsive to PAS-17-065 given that the *Exersides™* restraint is designed to increase mobility/activity and reduce sedation, delirium, and sedative medication use, thereby reducing the risk of long-term cognitive impairment in older critically ill patients.

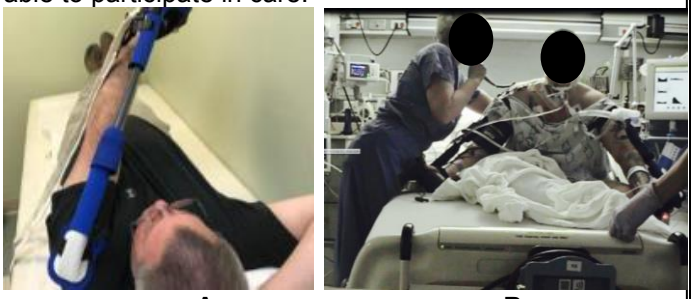
By 2030, more than 74 million Americans will be ≥60 years old.[4] With the aging population, there is an urgent unmet public health need to develop new strategies to protect mechanically ventilated patients from the removal of medical devices AND from the immobility, agitation, sedating medications, and delirium associated with traditional wrist restraints. There is a paucity of randomized controlled trials (RCTs) evaluating physical restraint devices, and a consequential international call for such research, as per the recent *Intensive Care Delirium Research Agenda*, co-authored by Dr. Needham (multiple PI) and leading international delirium researchers.[1] Moreover, the Association of Critical Care Nurses, American Thoracic Society, Society of Critical Care Medicine, and American College of Critical Care Medicine, as well as the Joint Commission and Centers for Medicare and Medicaid (CMS), have strongly voiced this public health need by recommending and mandating the use of 'least restraint necessary' in clinical practice.[1] However, none of the currently available traditional restraint devices optimally meet these complex needs.

The most common restraints used in ICUs are soft wrist restraints that tie to the bedside and substantially restrict movement at the shoulder and elbow.[5] Wrist restraints can be tied more loosely, but this increases the risk of self-extubation and self-removal of the restraints themselves, especially when

patients are unsupervised.[1] Mitt restraints also may be used, but when used without wrist restraints patients may press their hands (in the mitts) together around a tube or line for self-removal. Arm boards and elbow immobilizers are limited by often requiring continuous supervision as patients are able to self-remove the restraint on the opposing arm.

Healthy Design Ltd. Co. is developing the "*Exersides*^{TM}" restraint, a novel, adjustable arm restraint for invasive or non-invasive mechanically ventilated patients.[6-8] *Exersides*^{TM} is designed to prevent self-extubation while improving upper arm mobility, and reducing agitation, delirium, and the need for sedating medications. Unlike traditional wrist and mitt restraints, *Exersides*^{TM} permits arm movement but does not allow the hands to reach endotracheal and feeding tubes (Figure 1). This novel restraint provides the least restrictive restraint possible at any time in a patient's varying ICU course and permits maximum mobility levels commensurate with patient physical and cognitive condition. It is adjustable for patient size and to readily allow varying levels of restraint by bedside nurses. This multi-level restraint will empower nurses to minimize restraint AND sedation simultaneously, rather than relying on sedation to help patients tolerate the restraint. Thus, *Exersides*^{TM} will meet current 'least restraint necessary' regulations and 'best practice' recommendations.

Figure 1. *Exersides*^{TM} restraint prototypes in use. **A**: Healthy volunteer able to move arm from the shoulder but the restrained hand is unable to self-extubate or remove the device. Adjustable levels of restraint possible using resistance or rigid (white) straps. **B**: The *Exersides*^{TM} restraint (both arms) in use by an awake patient mechanically ventilated for acute lung injury and able to participate in care.

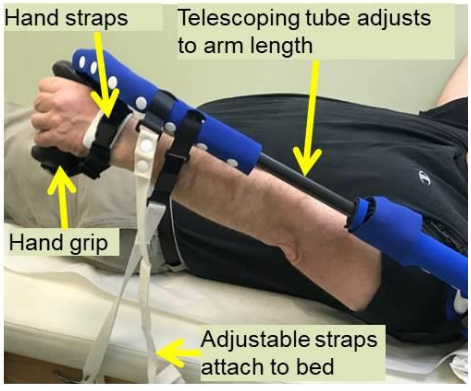


A **B**

Preliminary Studies and Data

1. A prototype of the novel *Exersides*^{TM} restraint was designed to prevent self-extubation while minimizing immobility, agitation, and sedation. Supported, in part, by a sub-award from R24HD065703, the prototype (shown in Figure 2) was designed to allow complete rotational capacity of the shoulder joint, with comfort flexion at the elbow, while providing a squeezable ergonomic hand grip. The straps that secure the hand at the grip are designed to avoid the anterior wrist to permit use of a radial arterial catheter, when clinically indicated, and render the posterior aspect of the hand accessible for peripheral IVs, if clinically indicated. The device also allows easy access to the arm for blood pressure cuffs and IVs. *Exersides*^{TM} telescopes to adjust to the variable arm length of each patient and has a soft outer shell for cushioning. The wrist straps do not bind circumferentially, as with traditional wrist restraints, to help prevent possible compromise in vascular circulation. Two attachments at the distal arm offer a resistance band tie and a non-flexible tie that can be affixed to a hospital bed, if desired. Configurations for adjustable levels of restraint are: 1) no tie for a calm patient, 2) resistance tie (intermediate level of restraint) for a patient with flailing arms OR for resistance exercise as might be supervised by a physical therapist or nurse, and 3) rigid tie for temporary tighter restraint for an agitated or aggressive patient or as a temporary restraint during a procedure when the arm must be immobilized.

Figure 2. Healthy volunteer wearing the *Exersides*^{TM} restraint. Adjustable white straps (lower left) attach to bed and can be titrated to patient needs.



2. An evaluation in healthy subjects demonstrated that the first *Exersides*^{TM} prototype was feasible to use and comfortable for subjects. The prototype was tested in 6 registered nurse (RN)

volunteers who, following consent, were videotaped and acted in both their staff role (bedside RN) and simulated patient role (performed in a hospital bed). In the patient role, volunteers were instructed to act as: 1) a calm and cooperative patient, 2) a confused patient with moving arms, and 3) an agitated patient. Results, summarized in Table 1, demonstrate high satisfaction.

Table 1. Healthy volunteer survey (N=6) demonstrating high satisfaction with the *Exersides™* restraint

	Strongly Agree or Agree	Neutral/Disagree/ Strongly disagree
From perspective of simulated PATIENT		
Comfortable	5	1
Safe	6	0
Effective	6	0
Preferable	6	0
More humane	6	0
From perspective of simulated STAFF		
Easy to don/doff	3	3
Easy to change level	5	1
Safe for staff	5	1
Effective	6	0
Preferable	5	1
More humane	6	0

3. A pilot study of first prototype *Exersides™* restraint in ICU patients demonstrated feasibility and potential benefit. An IRB-approved pilot study was conducted in one Vermont hospital ICU, where 10 mechanically ventilated patients were alternatingly assigned to wear *Exersides™* or traditional wrist restraints (n=5 in each group, 64±7 years old, 30% women). On day #3 of intubation, all patients were continuously videotaped for 4 consecutive hours while wearing their assigned device. All 5 patients in the *Exersides™* group tolerated the device with no adverse events (defined as no self-extubation, feeding tube or IV dislodgement, self-removal of restraint, skin breakdown or bodily trauma to patient or nurse). Activity and agitation were qualitatively assessed by analyzing the video recording, demonstrating that patients were active and awake while using *Exersides™*, with rare agitation observed in the *Exersides™* group. Sedation medication dosing (propofol in all patients) was measured immediately before and then during the 4-hour period (Table 2). Propofol use, sedation score, time spent moving, and time spent interacting were all generally improved with *Exersides™*.

Table 2. Patients using *Exersides™* restraint vs. traditional wrist restraints required less sedation and spent more time moving, and interacting during 4-hour study period

	Pre-study: Propofol dose (mcg/kg/hour)	During study: Propofol dose (mcg/kg/hour)	During study: SAS*	Time spent moving (hours) during 4-hour period	Time spent interacting (minutes) during 4-hour period
Traditional wrist restraints (n=5)	26±18	20±12	3.2±0.4	0±0	2.2±4.4
Exersides™ restraint (n=5)	28±8	11±10	4±0.7	2.6±1.6	66±74

*Sedation-Agitation Scale; 1=comatose, 4=calm and cooperative, 7=dangerously agitated

Themes derived from qualitative feedback from patients, nurses, and occupational therapists are in Table 3. In the Phase I portion of this STTR, we will revise the device based on existing feedback (Tables 1 and 3) and provide expanded data on safety and feasibility in an independent academic medical center (UVM site).

Table 3: Feedback on prototype from patients, nurses, and occupational therapists

Patients	Nurses	Occupational therapists
Straps pushing upward on hands Happy to be able to move Can scratch nose with arm rod	Better to see patient awake Difficult to adjust hand straps Better for IV placement	Grip too large Shoulder piece effective Easier to hold arm rod than arm More rehab done with awake patient

4. Continuous actigraphy is feasible to provide an objective, quantitative measure of mobility/activity in critically ill patients. We published data on feasibility of 48-hour wrist actigraphy monitoring, using the same sensor device proposed herein, in ICU patients. Overall, 35 of 48 (73%) eligible subjects/proxies provided consent. Thirty four of 35 (97%) completed 48-hour actigraphy assessment,[1] and 10 of these 34 (29%) received mechanical ventilation. In the RCT in STTR Phase II, we will assess the effect of *Exersides™* on activity, quantified using wrist actigraphs over 4-hour periods: 9am to 1pm, and 1pm to 5pm. The actigraphs report an activity count per 30 second epoch and the RCT's primary endpoint is the <u>total</u> activity count (from 30 second epochs) within a 4-hour period. Among the mechanically ventilated patients in our published study, median (25^{th}, 75^{th} percentile) 4-hour total activity counts for all observed 4-hour periods were 2654 (1158, 7495), with 1pm to 5pm

having lower median activity counts: 2404 (1253, 13084) vs. 9am-1pm: 2771 (849, 6830). These activity counts in ICU patients are very low compared with reference values of 4-hour daytime activity counts of ~9,600 to ~48,900 in elderly nursing home patients,[1] demonstrating the need for greater activity/mobility in this patient population, as per the objective of this proposal.
In our pilot study (see #3 above), 3 patients wore actigraphs (2 in traditional wrist restraint group and 1 in *Exersides™* group); thus, demonstrating that wearing actigraphs with *Exersides™* is feasible, as expected based on our existing expertise with actigraphy.

6. Usual care restraint and sedation practices at study sites: All 3 study sites for the RCT (Aim 3) use only traditional soft wrist restraints. As per Joint Commission guidelines, a physician order is required for use of restraints, with renewal of order at least once every 24 hours. Additionally, all 3 sites use guideline recommended practices[1] for management of sedation/agitation and delirium/cognitive impairment in their ICUs, that include aiming for patients' wakefulness via use of short-acting analgesics (e.g. fentanyl), short-acting continuous sedation (e.g. propofol) when needed, and minimized use of benzodiazepines.

***References**. Include references to prior human or animal research and references that are relevant to the design and conduct of the study.*

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Objectives: *Clearly state the primary and secondary objective(s) of the study.*

Phase I Specific Aims:

1. To revise the *ExersidesTM* prototype based on feedback obtained from standardized patients in the UVM simulation center.
2. To demonstrate that the revised *ExersidesTM* restraint is safe, and that conducting the proposed RCT (for STTR Phase II) is feasible, by performing a prospective evaluation in 8 mechanically ventilated older patients who require wrist restraint, including pilot testing all proposed measurements and outcomes planned for STTR Phase II

Milestones to progress to Phase II: (A) Demonstrate that the revised *ExersidesTM* prototype is safe in older mechanically ventilated patients who require restraint (i.e., has mean incidence <20% across pre-defined safety criteria, including: skin breakdown and laceration, reportable injuries to patients and clinicians, self-removal of the restraint, and damage to ICU bed or equipment), and (B) Demonstrate feasibility of the RCT planned for STTR Phase II, including enrollment of 8 ICU patients and completion of >90% of all outcomes/measures.

Phase II Specific Aims:

3. To conduct a multi-site, within-patient crossover RCT in older mechanically ventilated patients requiring restraint to test the following **hypotheses** regarding *Exersides*^{TM} vs. traditional wrist restraints:
   a. *Exersides*^{TM} allows greater upper extremity **activity**, as measured by actigraphy (primary outcome)
   b. *Exersides*^{TM} reduces **delirium, agitation, and use of sedatives**, analgesics and antipsychotics
   c. *Exersides*^{TM} has high satisfaction, assessed via both **quantitative and qualitative evaluations,** among ICU clinicians, families and patients.

Study Design, Procedures, and Statistical Analysis Plan (all included here for Phase I and then Phase II):

PHASE I (small cohort study to assess feasibility and safety)

Aim 1: To revise the *ExersidesTM* prototype based on pre-existing user feedback

- For this Aim, we and the company (Healthy Design, Ltd) will utilize the UVM Simulation Center to test the current device in 3 standardized patients. During this session, comfort, safety, and satisfaction will be evaluated in a simulated hospital setting. Following this session, any revision of the novel device needing to occur based on feedback obtained will be performed by the manufacturer before proceeding to Aim 2. Prevention of safety issues listed below in Aim 2 will be addressed during device refinements by surveying for sharp edges or hard protrusions and adding padding, as well as ensuring that securing straps are appropriately positioned, wide and padded.

Aim 2: To demonstrate safety of the *Exersides*^{TM} restraint and the feasibility of conducting an RCT (Aim 3, STTR Phase II) by performing a pilot cohort study to assess the restraint in 8 older ICU patients.

- **Study Site:** UVM, a large regional hospital with extensive ICU RCT experience, is located close to Healthy Design, with Drs. Pavini and Stapleton having a pre-existing collaborative working relationship.
- **Patients (n=8):** We will conduct a study of 8 elderly ventilated ICU patients requiring restraint per an active physician order. See inclusion and exclusion criteria below in Table 4.

Table 4: Inclusion and Exclusion Criteria for Study Entry into STTR Phase I and Phase II Studies

Inclusion Criteria	Exclusion Criteria	Rationale for Exclusion
1. ≥60 years old 2. Physician order for use of bilateral wrist restraints 3. Requiring invasive or non-invasive mechanical ventilation with actual or expected total duration of ≥48 hours 4. Expected ICU stay ≥3 days after enrollment (to permit adequate exposure to proposed intervention) 5. Not deeply sedated (Richmond Agitation Sedation Scale [RASS] score ≥ -2)[1]	1. Upper extremity impairments that prevent use of novel restraint device (e.g. amputation, arm injury)	Unable to receive proposed intervention
	2. Limited mobility of either upper extremity prior to admission (e.g. frozen shoulder, severe arthritis)	Inaccurate data for primary outcome assessment during RCT (i.e. actigraphy)
	3. Pre-existing primary systemic neuromuscular disease (e.g. Guillain-Barre)	
	4. Neuromuscular blocker infusion (eligible once infusion discontinued if other inclusion criteria met)	
	5. Pre-existing severe cognitive impairment or language barrier prohibiting outcome assessment	Unable to perform outcome assessments
	6. Expected death or withdrawal of life-sustaining treatments within 6 days from enrollment	Patients unlikely to complete proposed outcome assessment protocol
	7. Incarcerated	Vulnerable population; ethical issues
	8. Severe skin breakdown on either upper extremity	Unable to receive proposed intervention

- **Consent:** As most eligible patients will be unable to make decisions, written informed consent will most often occur via legally authorized representatives (LARs) with participant re-consent upon regaining capacity. See below under section on Consent.

- **Description of restraint intervention:** All 8 patients will wear both the *Exersides*^{TM} and traditional wrist restraint devices on both arms, sequentially, over 2 study days. On Day 1, they will wear the *Exersides*^{TM} restraint on both arms from 9am-1pm and wrist restraints on both arms from 1pm-5pm. On Day 2, they will wear the restraints on both arms in the opposite order. During each 4-hour period, subjects will be observed by research and nursing staff, with validated and reliable hourly assessments of sedation/agitation (RASS) status,[1] and validated and reliable delirium assessment (CAM-ICU) at the start and stop of each period (see Aim 3, Outcome 2 for description of RASS and CAM).[1] Subjects will wear actigraphs on both wrists to measure mobility/activity continuously. A digital video camera will be set up at the foot of the patient's bed to continuously record his/her movements during the study sessions. Overnight between Days 1 and 2, subjects will resume traditional restraints, per MD order. Intervention ends on Day 2. Satisfaction/acceptability/perceptions of device will be assessed in nurses, family members, physicians, and patients as per RCT protocol (see Aim 3, Outcome 3).

- **Phase I Outcomes:**

1. Demonstrate that revised prototype is safe, with <20% mean incidence across 7 safety criteria in the 8 subjects enrolled. Safety criteria in STTR Phase I will include: 1) clinician or patient laceration (Grade 2b or higher, per STAR laceration grading criteria[9]) from any sharp edges of device, 2) development of pressure ulcer from device of Stage 3 or greater per 2016 National Pressure Ulcer Advisory Panel Pressure Injury Stages,[10] 3) reportable injury (per local institutional standards) of patient by device, 4) reportable injury (per local institutional standards) to clinician by device, 5) self-removal of device, 6) damage to hospital bed rendering it non-functional, and 7) damage to ICU equipment (e.g. ventilator) rendering it non-functional..
2. Demonstrate that conducting the proposed RCT in Aim 3 is feasible, by consent/recruitment rate and pilot testing measures/outcomes for the RCT, via the following tasks:
    - Consent/Recruitment: 8 patients consented and enrolled within ≤7 months
    - Outcomes/measures: At least 90% of all outcomes planned for the RCT in Aim 3 (STTR Phase II) will be measured in the 8 patients: 1) actigraphy counts, 2) RASS sedation/agitation score,[1] 3) CAM-ICU delirium score,[1] 4) medication use, 5) satisfaction/ acceptability/perceptions of novel restraint. Incidence of self-extubation will also be reported in addition to the following measures of efficacy: 1) patient-reported satisfaction measures including comfortable, safe, effective, preferable and more humane; and 2) staff-reported satisfaction measures including easy to don/doff, easy to change level, safe for staff, effective, preferable and more humane. See Aim 3 for these RCT measures.

- **Data collection/management, quality assurance & analysis:** See Aim 3.
- **Sample size:** N=8 was based on feasible enrollment from the single study site during the 9-month Phase I period (i.e., ~1 patient/month). Literature suggests that there is no advantage to including more than 6-10 subjects per group in a Phase I study, and most chemotherapeutic phase I studies have N=3 per cohort.[1] Thus, N=8 is adequate for the proposed Aims to prepare for the RCT in Aim 3.
- **Phase I Study follow-up.** The engineer will prepare a report on the outcomes of all assessments based upon STTR Phase I, and will decide (in consultation with the project leadership team) which device improvements/modifications will be required before use of device in Aim 3 (STTR Phase II).

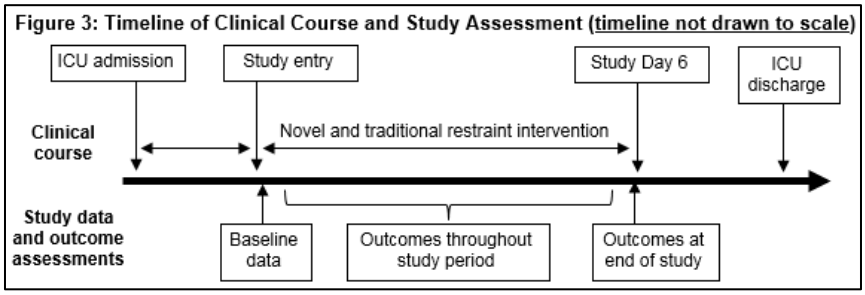
PHASE II (3-site RCT to compare the novel restraint to traditional wrist restraints)

Aim 3: To conduct a multi-site, within-patient randomized crossover trial in older critically ill mechanically ventilated patients who require restraint, to compare the *Exersides™* restraint *vs.* traditional wrist restraints.

Overview and Study Design Phase II. The objective of the Phase II project is to conduct an RCT to measure 3 outcomes:

1. Mobility/activity evaluated by actigraphy (primary outcome)
2. Agitation, delirium, medication use (sedative, analgesic, and antipsychotic), and incidence of self-extubation (secondary outcomes)
3. Satisfaction with, and acceptability/perceptions of, the device by patient, family, and clinicians (secondary outcomes)

- **Study Sites:** We will recruit patients from 3 hospitals: UVM, JHU and UCLA**.**
  These sites were selected due to successful prior collaborations, experience in ICU RCT recruitment, similar sedation practice (Prelim Data 6), experience in ICU mobility/actigraphy, and similar "usual care" (Prelim Data 6). A study overview is in Figure 3.



- **Data Coordinating:** Data coordination will occur through integrated efforts between Healthy Design and all 3 study sites, with full support for design, conduct, monitoring, and analysis. An employed data coordinator will create a study database in RedCAP and will manage data from all 3 enrolling sites. Data coordination, cleaning, and subsequent analyses will be overseen by Drs. Colantuoni (PhD biostatistics faculty/ co-I) with Drs. Stapleton, Needham, and Pavini. Dr. Stapleton will oversee RCT conduct, including regulatory/ NIH reports. And employed study monitor will conduct site monitoring visits during the RCT.

- **Study Leadership of RCT:** To address leadership and communication issues, an Executive Committee ("EC": Drs. Stapleton, Needham, and Pavini, along with Ms. Ardren [Project Manager, UVM]) will meet twice monthly by phone to discuss RCT conduct. For issues that require broader input, the RCT also will have a Steering Committee that includes the EC plus Drs. Kamdar (UCLA site PI), Colantuoni (Biostatistician), Pandian (Nurse co-investigator), Neufeld (aging/delirium co-investigator) that will meet monthly or as needed. Each site-PI will supervise daily operations, along with site research staff supported by per-patient capitation payments. All investigators will co-author publications, with author order mutually agreed upon in advance.

- **Patients (n=54):** Eligibility criteria are identical to the cohort study in Aim 2 (Table 5).
- **Consent:** As in the study in Aim 2 (STTR Phase I), consent will most often occur via LARs with participant re-consent upon regaining capacity. See below under section on Consent.
- **Randomization:** After consent, patients will be randomized (1:1) to Group A vs B (Fig. 4) via UVM's web-based system (24 hrs/day), with variable-sized blocks of 2 or 4, stratified by site.
- **Blinding:** Due to the nature of restraint devices, we cannot blind patients, families, or ICU clinicians. To minimize bias, the primary outcome (actigraphy) will be analyzed by an outcome assessor blinded to patient identity or study group (Dr. McGinness) and key co-interventions will be standardized with planned analyses to evaluate balance between groups (see Statistical Analysis Plan).
- **Standard ICU co-interventions for all patients:** Important aspects of routine care will be standardized for BOTH study groups based on existing protocols at all sites, including: 1) turning by RN every 2 hr while in bed; 2) sedation/delirium management as per published practice guidelines (see Preliminary Data #6); 3) daily spontaneous breathing trials and ventilator weaning protocols, and 4) nutrition as per registered dietician consultation. These co-interventions are recorded electronically to easily facilitate the study monitoring plan.
- **On-study data collection:** Demographic, laboratory, physiological, and rehabilitation data will be collected (see Tables 5 and 6).

Table 5: Patient Variables -- Collected at Enrollment

Patient Variables – collected at enrollment/baseline	Collection Method	Measurement Scale
Demographic data (e.g. age, sex, race, marital status)	Chart review	Continuous/Binary/Categorical
Height & weight; body mass index	Chart review	Continuous
Comorbidities: Charlson[a] & Functional Indices[b]	Chart review	Ordinal
Baseline function: Katz Activities of Daily Living,[11] and Clinical Frailty Scale[12]	Proxy interview (see Outcomes below)	Continuous/Ordinal
ICU admission diagnosis (e.g. sepsis, renal failure)	Chart review	Categorical
Severity of illness: APACHE II[d]	Chart review	Continuous
Alzheimer's disease and related dementia: IQCODE-SF survey[e] ; Delirium Risk Score	Chart review;	Categorical

[a]Charlson Index: a score for in-patients derived from 19 comorbidities; an increased score reflecting increased 1-year mortality.[13]
[b]Functional Comorbidity Index: an 18-diagnosis scale for ICU patients predicting 1-year SF-36 physical function;.[1]

[d]APACHE II: Severity index using age, medical conditions, & acute physiology. Scores reflect increased short-term mortality.[14]
[e]IQCODE-SF (Short Form of Informant Questionnaire of Cognitive Decline in the Elderly) is a validated proxy-based measure of baseline cognitive impairment commonly used in studies of hospitalized and critically ill patients[1]

Table 6: ICU-Related Variables – Collected at Enrollment and DAILY During ICU Stay

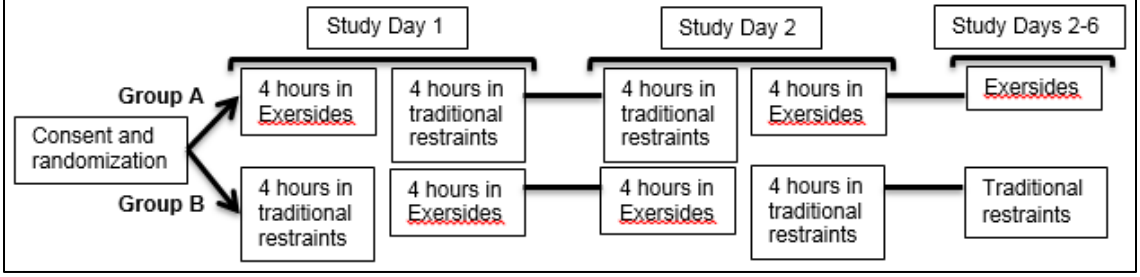
ICU Variables – collected at enrollment and daily during ICU stay	Collection Method	Measurement Scale
SOFA[a] organ failure score (with lab, medication and physiological data)	Chart review	Continuous
Nutrition received (calories/protein)	Chart review	Continuous and categorical
Exercise/rehab received as part of routine clinical care (type, duration)	Chart review	Continuous and categorical
Compliance with proposed intervention regimen	CRF review	Continuous and categorical

[a]*SOFA: A validated composite score of 6 organ systems used to assess the severity of ICU organ dysfunction.* [15]

Implementation of the RCT intervention:

- **Study design**: An innovative crossover design will allow each patient to serve as their own control (Figure 4), enabling us to assess both devices early in the study period while minimizing confounding by dynamic temporal changes in these critically ill patients, followed by a longer 4-day assessment with each patient wearing one device that will allow us to measure outcomes better assessed over days (rather than hours). Subjects will be 1:1 randomized to either Group A or B, with both groups receiving both novel and traditional restraints. On Days 1 and 2, subjects will wear each device for 4 hours (9am-1pm and 1pm-5pm), during which time they will be observed by research and nursing personnel, with validated and reliable hourly assessments of sedation/agitation (RASS score). A digital video camera will be set up at the foot of the patient's bed to continuously record his/her movements during the study sessions. Overnight between study Days 1-2 and 2-3, subjects will resume traditional wrist restraints, as per MD order. No sensor or video data will be recorded during overnight periods when study staff are not available. Starting on Day 3 morning, subjects who continue to require restraints (per MD order) will be placed in either traditional or novel restraints device, as per their original randomization (i.e. the device worn for first 4-hr study period on Day 1) for up to 4 more days (i.e. until earliest of restraints no longer needed, death, or ICU discharge). This novel within-patient crossover design allows for increased precision with fewer subjects (see Sample Size) because it controls for confounding effects of patient-specific characteristics via each patient serving as their own control when comparing outcomes (i.e. arm activity) of the novel vs. traditional restraint during Days 1 and 2, along with reduced bias due to randomized allocation of initial study group (novel vs. traditional). Moreover, this design permits more prolonged comparison of novel vs. traditional device (over Days 3 to 6) to measure secondary outcomes (e.g., agitation, delirium, and medication use) that are more accurately evaluated over longer periods of evaluation. The randomization feature of this study design also controls for potential temporal differences in movement (e.g., patient more awake/mobile from 9am-1pm vs. 1pm-5pm). Patient eligibility criteria also help ensure that the study occurs when patients require restraint and are readily assessed for the primary and secondary outcome measures.

Figure 4: Flow of Crossover RCT in STTR Phase II



- **Recurrence of clinical need for restraint and/or ICU readmit:** If a patient ceases to need restraint during the 6-day study period, but then is deemed to need restraint again, the randomly allocated intervention will resume (up to 6-day maximum), with study ending upon ICU discharge (without re-starting if ICU re-admit).

Table 7: Primary & Secondary Outcomes of Efficacy RCT in Aim 3				
Outcome		**Instrument**	**Scale**	**Assessment Timing**
Primary Outcome				
1	Upper extremity mobility	Actigraphy (total activity counts per 4 hours)	Continuous	Continuously throughout study
Secondary Outcomes				
2	Sedative, analgesic, and antipsychotic medication dose and use	Chart review	Continuous	Baseline and then daily
	Agitation	RASS score[1] Video recording	Ordinal Continuous	Baseline, every 60 min days 1-2, then every 4 hours days 3-6 All study sessions
	Delirium	CAM-ICU score[1]	Binary	Baseline, every 4 hours days 1-2, then every 12 hours days 3-6
3	Satisfaction with novel restraint (nurses, family, physicians, and patients when able)	QUEST 2.0 score[16]	Ordinal	Survey at conclusion of study period
	Perceptions of novel restraint (nurses, family, physicians, and patients when able)	Semi-structured interviews and response to specific satisfaction measures in Table 1.	Qualitative	Daily for bedside nurses and conclusion of study period for others

- **Training and quality assurance:** Training on study procedures (e.g. placement of restraints, data collection) will occur via Healthy Design staff traveling to each site before study start and in Year 2 of the RCT. To ensure fidelity of intervention implementation, research staff will use daily checklists of key tasks and protocol violations will be transmitted real-time to the Clinical Data Manager. At least twice during the study, in-person monitoring visits to each site will occur to assess protocol compliance and conduct source verification. Centrally, we will use standard data quality control procedures, including ongoing review of quality metrics, missing data, and data outliers.

STTR Phase II Outcomes (see Table 7).

Outcome 1: Mobility evaluated by actigraphy.

- **Primary outcome – Mobility assessed by actigraphy** (**Table 7**)**.** Upper extremity mobility will be evaluated by actigraphy. The Philips Respironics Spectrum Plus® actigraph is a commercially-available actigraphy device weighing 16 grams. It contains a battery-powered activity monitor and uses a highly sensitive accelerometer to monitor the occurrence and degree of motion. This device was chosen as it is widely used in research.[1] Moreover, **we have published on feasibility of using this device in ICU patients**.[1] We hypothesize that *Exersides™* will allow greater upper extremity **mobility**, as measured by actigraphy. Movement recorded on the sensors will be compared with the video recordings to determine if the movement was purposeful or caused by agitation.

Outcome 2: Agitation, delirium, and medication use will be assessed as secondary outcomes.

- **Agitation:** Agitation will be measured via RASS (Richmond Agitation Sedation Scale) score[1] assessed by research staff every 60 minutes during the four 4-hour periods (Days 1 and 2) when subjects are using novel and traditional restraints, and then every 4 hours during Days 3-6 when subjects are using their randomly assigned device. RASS is a validated and reliable ordinal measure of sedation/agitation status in the ICU ranging from -5 to +4.[1] All study personnel will be trained in measuring RASS score. We hypothesize that *Exersides™* will reduce **delirium, agitation, and use of sedatives**, analgesics and antipsychotics.
- **Delirium:** Delirium will be measured via CAM-ICU (Confusion Assessment Method for the ICU) at its maximum appropriate frequency of every 4-hours during Days 1-2, and then every 12 hours during Days 3-6. The CAM-ICU score is a validated and reliable binary measure of delirium status in the ICU.[1] All personnel will be trained in measuring CAM-ICU. Our group has extensive experience with CAM-ICU.[1]
- **Sedative, analgesic, and antipsychotic medication use:** Throughout the 6-day study period, use and dose of medications will be assessed by chart review. Medications in these categories include, but are not limited to, opiates, benzodiazepines, typical and atypical antipsychotics, propofol, and dexmedetomidine.

Outcome 3: Satisfaction with and acceptability/perceptions of the device

Satisfaction and acceptability will be assessed by the Quebec User Evaluation of Satisfaction with Assistive Technology (QUEST 2.0) survey and by semi-structured interviews. We hypothesize that *Exersides*^{TM} will demonstrate high satisfaction, assessed both quantitatively and qualitatively, among ICU clinicians, families and patients.

- **Satisfaction**: The QUEST 2.0 is a valid, reliable, and widely used 12-question survey assessing satisfaction with technological devices.[1] It is scored from 1-5, with >3.26 considered high satisfaction. The QUEST 2.0 has 2 subscales (satisfaction with device and with services). Satisfaction with the *Exersides*^{TM} restraint will be assessed using the device subscale, which has good test-retest stability (ICC 0.82).[17]

- **Acceptability/perceptions**: Daily for nurses, and at the conclusion each subject's study period for family members, physicians, and patients, device users will undergo semi-structured interviews (Table 9) to assess perceived barriers and facilitators of using the novel device. Responses will be recorded digitally and will be subject to open coding and analysis with grounded theory.[18] Patients and health care providers will also answer the same satisfaction measures as shown in Table 1.

Table 8: Open-ended questions for semi-structured interviews about novel restraint

1. What did you like about the *Exersides*^{TM} restraint? And what do you NOT like about it?
2. What did you find makes the *Exersides*^{TM} restraint is easy to use? And what makes it difficult to use?
3. If you could change the *Exersides*^{TM} restraint, what would you change?
4. Do you think that some patient movements were related to agitation instead of "normal" mobility? (Y/N) If yes, how can you tell the difference? How were those movements different between devices?
5. Any final thoughts or comments about the *Exersides*^{TM} restraint and usual restraint devices?

Data Collection, Management, and Quality Control for RCT

- A REDCap web-based database will be used for research data using unique identifiers for subjects and staff.[19] Data collection will be protocolized, with staff trained on those protocols, and regularly monitored by our Clinical Data Manager (Ms. Howard) and via site monitoring visits (see Aim 3C). Moreover, missing or inconsistent data will be detected at data entry. Early, random audits will be performed shortly after start of study and every 4 months thereafter, such that a total of ~10% of all records will be audited by the employed data coordinator. Additionally, Steering Committee meetings will each occur twice monthly (Aim 3D).

Statistical Considerations for RCT

- **Sample size:** Sample size was determined for the primary outcome, arm activity, as assessed by actigraphy over Days 1 and 2 (defined as total activity counts per 4-hour period: 9am-1pm and 1pm-5pm). Although Phase II is 24 months long, there are only 18 months for recruitment, as we need 3 months for startup and 3 months for close out (Table 10). Across the 3 study sites, we expect to recruit 1 patient per site per month during the 18-months, yielding a total N=54. Experience enrolling ICU patients in RCTs at each site.[1] suggests that 1 patient/month/site is feasible and mirrors empirical data, with our analysis of 33,106 patients from 23 RCTs, demonstrating median (IQR) enrollment of 0.90 (0.50–1.79) patients/month per site.[20]

  Assuming N=54, we calculated the treatment effect (i.e. the relative change in the median total activity) that can be detected with 80% power and 5% Type I error rate. We used the following assumptions (these data were informed by our preliminary data with modest adjustments for expected differences for the proposed 3-center study): (1) 9am-1pm median total activity = 3000, (2) 1pm-5pm median total activity = 2700, (3) variance of Log(total activity) set conservatively to 2.5 and 6.0 for 9am-1pm and 1pm-5pm periods, respectively, (4) Log(total activity) has 0.85 correlation within a patient over time, and (5) no cross-over effect of the restraints. Using N=10,000 simulation, the 54-patient sample size can

detect a 56% relative increase in median total activity comparing the novel vs. traditional restraint (median of 3000 vs. 4674).

- **Statistical Analysis Plan**

  a) Summary for all Aims: All analyses **will follow the intention-to-treat (ITT) principle.** A 2-tailed p-value <0.05 will be statistically significant. As described in the Study Design (Section 3K), the within-patient crossover design removes patient-specific effects from evaluation of the treatment effect. Potential pitfalls of this design include order effects, carryover effects, and patient dropout. To avoid order effects, we randomize whether patients start the trial with the novel vs. traditional restraint (Figure 4). Carryover effects (i.e. one part of the study affecting subsequent parts) and drop out considerations are discussed further below.

  During the first 2 Days, the primary endpoint (activity) is measured for each period on each day, such that each patient will contribute 4 longitudinal measurements. This primary endpoint is measured as total activity, the sum of the recorded activity counts for the corresponding period/day. Secondary endpoints include agitation (normal vs. sedated/agitated as defined by RASS), delirium (positive vs. negative for delirium based on CAM-ICU, among patients who are not comatose [RASS -4, -5]) and medication use (quantified by computing the total dose of medications received within each class (Outcome 2) using standard equivalency conversions for drugs within each class, as done in our prior research.[1] Analysis will include summary statistics (mean, median, standard deviation and quantiles) of the key co-interventions (see Aim 3I above) and the RCT endpoints (Table 8), separately for each period over the 2 days, stratified by treatment group.

  To estimate the effect of the novel restraint, a linear model will be fit for the Log(total activity) as a function of main terms for treatment (Group A vs. B), time period (1pm-5pm vs. 9am-1pm), and treatment order (BA/AB vs. AB/BA). The natural logarithm is applied to the primary endpoint to reduce right skew in the distribution of total activity, with the exponentiated regression coefficient for the main term for treatment (A vs. B) in the linear regression model representing the relative difference in median total activity comparing the novel vs. traditional restraint, which will quantify the treatment effect. The linear model will be fit using weighted least squares to account for the correlation in the primary endpoint within a patient over time; the correlation structure will be specified as unstructured and allow for the possibility that the variance of the primary endpoint may be different in each period/day. The same linear models will be applied to the continuous secondary endpoints (e.g. medication dose). For the binary secondary endpoints, the effect of the novel vs. traditional restraint will be quantified using a longitudinal logistic regression model as a function of the same covariates (treatment, period, and treatment order). The longitudinal logistic regression model will be fit using generalized estimating equations allowing for an unstructured within-patient correlation structure. Activity, agitation, delirium and medication use will continue to be measured up to ICU discharge, death or Day 6. Starting on Day 3, the endpoints will be expressed as every 4-hour total activity counts, agitation assessment and total medication use, as well as every 12-hour delirium. With the data starting on Day 3, we will explore the long-term effects of the restraints by fitting linear and logistic longitudinal regression models that include main terms for treatment and time and the interaction of treatment and time. Time will be modeled as a restricted cubic spline with degrees of freedom selected by model fit statistics. As secondary outcomes are hypothesis-generating, we will not correct for multiple comparisons, but will consider the number of comparisons when interpreting results.

  Subgroup analysis will be performed in eligible patients with baseline history of Alzheimer's disease and related dementia. To evaluate the potential effect of time-varying patient factors (not strictly controlled via a within-patient crossover design – e.g. organ failure status (Table 7)) on the primary results, sensitivity analysis of the above regression results will be conducted by including such variables into regression models. **To evaluate for any sex-specific effect in this study, sex will be included in the regression model as a co-variate and as a statistical interaction term with the main term for treatment (A vs. B) to fully address NIH requirements.**

b) Minimizing missing data: Our primary outcome is assessed during the first 2 study days when missing data are uncommon in our prior studies.[1] Missing data will be minimized through ongoing contact with participants/families and ICU nurses to increase likelihood of obtaining data. Missing data will be described for all variables, and patient characteristics will be compared between those with vs. without missing outcomes.[1] Based our preliminary data and experience with other studies using similar eligibility criteria, we expect <5-10% missing data due to death or other patient loss, and any missing will not be associated with treatment allocation; thus, no imputation will be performed and we would enroll up to 60 total patients, if needed, to compensate for missing data to obtain the primary outcome on N=54 patients.

c) Data safety monitoring board (DSMB) meetings: The DSMB (see Data Safety document) will meet before the RCT (in STTR Phase II) begins, and after half of the patients have been enrolled into the RCT to review safety and recruitment data only. As this is a small RCT, there will be neither interim analyses to evaluate efficacy nor stopping rules for efficacy or futility.

For research involving survey, questionnaires, etc.: *Describe the setting and the mode of administering the instrument and the provisions for maintaining privacy and confidentiality. Include the duration, intervals of administration, and overall length of participation. (describe and attach all instruments)*

☐ ***Not applicable***

During both the Phase I cohort study and Phase II RCT, we will conduct **qualitative assessment** of the *Exersides™* restraint. Family members and clinicians (e.g., nurses and physicians) caring for patients enrolled into the cohort study (STTR Phase I) or into the RCT (STTR Phase II) will be asked to complete satisfaction questionnaires (QUEST questionnaire attached), provide feedback on satisfaction measures (Table 1), and participate in a brief semi-structured interview (see questions in Table 8) to assess their satisfaction with, and perceptions of, the *Exersides™* restraint. Family members may be the Legally Authorized Representatives (LARs) who provide consent for the patient to participate in the RCT, but additional family members beyond the LARs also may be asked to participate, and they will be identified via observation of them visiting the consented participant while in the ICU. Only family members >18 years of age will be included. Family members will undergo verbal consent, and no identifiable information will be obtained from them. Consent from participating medical personnel (nurses, physicians) will be inferred by their willingness to answer our questions, complete the survey and provide feedback.

Completion of both the QUEST questionnaire, feedback questions, and the semi-structured interview will occur in private space near the medical ICU, and we anticipate this will take approximately 15 minutes. These will only occur once toward the end of the study.

Risks/Benefits: *Describe any potential or known risks. This includes physical, psychological, social, legal or other risks. Estimate the probability that given risk may occur, its severity and potential reversibility. If the study involves a placebo or washout period, the risks related to these must be addressed in both the protocol and consent. Describe the planned procedures for protecting against or minimizing potential risks and assess their likely effectiveness. Where appropriate, discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. Discuss the potential benefits of the research to the subjects and others. Discuss why the risks to the subjects are reasonable in relation to the anticipated benefits to subjects and others. Discuss the importance of the knowledge gained or to be gained as a result of the proposed research and why the risks are reasonable in relation to the knowledge that reasonably may result. If there are no benefits state so.*

RISKS TO HUMAN SUBJECTS

Human Subjects Involvement, Characteristics, and Design

This research includes 4 components where human subjects will be enrolled:
(A) Testing the revised *Exersides™* restraint device on 3 healthy subjects (STTR Phase I);
(B) A prospective cohort study in 8 older critically ill patients (STTR Phase I) where feasibility of doing a larger RCT will be demonstrated;
(C) A multi-site randomized controlled trial (RCT in STTR Phase II) in which 54 patients will be enrolled; and
(D) Feedback from family members and from clinicians (e.g., nurses, and physicians) caring for patients enrolled into either the studies in (B) or (C), from above, about their satisfaction with, and perceptions of, the

Exersides^{TM} restraint.

Potential Risks

There are potential risks for all participants regarding potential breach of confidentiality and invasion of privacy. If a critically ill patient regains decisional capacity and is approached about the study for re-consent (after a legal next of kin has already provided informed consent for the patient), he or she may experience stress and/or discomfort.

Potential risks from the *Exersides*^{TM} restraint device are very low. Our own preliminary data demonstrate safety in that no adverse or severe adverse events (i.e. no self-removal of endotracheal tubes, feeding tubes, intravenous lines, etc.) – these preliminary data are from a pilot study that has already taken place that enrolled critically ill patients in a single intensive care unit. Although self-removal of tubes and lines is a risk, as occurs with any existing currently available restraint device, we anticipate that this risk is very low due to the design of the *Exersides*^{TM} restraint that intentionally was created to further reduce this risk in comparison to traditional restraints. Other potential risks include skin breakdown from the *Exersides*^{TM} restraint device, and a theoretical increased risk of increased removal of upper extremity peripheral IVs, but we did not observe any of these events in our pilot study.

There are few alternative treatments to participating in this RCT. Use of the *Exersides*^{TM} restraint device is not standard of ICU care at any clinical center. However, this study will not alter clinical care that occurs with regard to other aspects of critical illness. Specifically, only patients whose physicians have already written an order requiring physical restraints will be considered for the study. The novel *Exersides*^{TM} restraint device will only be used while such an order is active, as part of routine clinical care (i.e. no patient will receive the *Exersides*^{TM} restraint device without a need for physical restraint as documented/ordered by the ICU clinicians). All study sites currently follow (and will continue to follow throughout the duration of the study) Joint Commission requirements for re-assessment and re-ordering restraints at least once every 24 hours. If a restraint is no longer required/ordered as part of routine clinical care, then use of the *Exersides*^{TM} restraint device will immediately stop and not re-start unless a renewal of a restraint order is done, as required by clinical circumstances. In no way will the study have any influence over the ordering of restraints as part of clinical care in the ICU.

ADEQUACY OF PROTECTION AGAINST RISKS

Recruitment and Informed Consent

a) Critically ill older patients recruited into cohort study (STTR Phase I) and multi-site RCT (STTR Phase II)

All patients who meet inclusion and exclusion criteria will be invited to participate in this study. Using observation/review of the electronic medical record and daily hospital rounds, study staff will identify consecutive patients admitted to the ICU who meet the basic eligibility criteria. After this initial screen for eligibility, study personnel will proceed as per local IRB requirements, including contacting the patient's ICU physicians to confirm appropriateness for the study and obtain permission to approach the patient/legal next of kin for discussion of the study and to undertake the informed consent process. If the physicians agree, study staff will approach the patient in-person or, if the patient doesn't have decisional capacity at the time of enrollment, a legal next of kin in-person (via in-person meeting). Most patients participating in this study will require mechanical ventilation and will therefore be receiving some amount of sedative medications at the time of enrollment. Hence, we anticipate that a large proportion of patients will lack the capacity to provide informed consent at the time of study eligibility and therefore, we expect that study staff will go through the process of informed consent and review the consent materials with the legal next of kin. Consent will be documented, in writing, on an IRB-approved consent form. No minors will be considered in the proposed research; therefore, parental permission and child assent is not applicable to this application. All conversations with the patient/legal next-of-kin regarding the study will be held in a private setting; study staff will allow for patients' desire to have family present and/or to confer with family, and to make participation decisions according to his or her own time. Once patients who did not have decisional capacity at the time of initial consent regain that capacity, they will be re-consented for ongoing participation in the study.

b) Family members, nurses and physicians caring for patients enrolled into the STTR Phase I or Phase II studies. All family members of patients participating in the cohort study (STTR Phase I) or the RCT (STTR Phase II) will be invited to provide information about their satisfaction with, and assessment/perceptions of, the

Exersides^{TM} restraint. Only family members >18 years of age will be included, and they will be identified by visiting their loved one in the ICU. After being approached by research personnel, they will undergo informed consent, but importantly no personal identifiable information will be obtained from them as we will only ask for satisfaction scores and qualitative feedback about the device. Nurses and physicians caring for the patients in the RCT also will be asked to complete the satisfaction questionnaire and semi-structured interview. Their enrollment and consent will be in accordance with institutional IRB policy.

Protections against Risk

All subjects will be informed of the research nature of the activity, including the completion of any measures and questionnaires, the estimated time required to complete the activities, and that participation is voluntary, without any compromise on the current medical care if they decline participation. All study personnel will be trained in the protection of human subjects and HIPAA. To protect against disclosure, all subjects will be assigned a unique study identification number. It is this number that will accompany study materials and data. The information that would allow for a link between this study ID number and the direct identifiers will be kept securely and separately from the datasets. All participant-identifying information will be removed from the dataset before analysis. Identifying information and de-identified paper study records will be kept in locked file cabinets and password protected computers that reside within locked offices with security personnel and other physical safeguards. All study databases will be maintained on password protected computers and routinely backed up to password protected servers. Identifying information will be deleted at the earliest possible date. We will keep all patient information confidential in accordance with Public Health Services Act (42 USC 299a-1(c)). As previously described, fetuses, neonates, minors, and prisoners are not part of this study. Pregnant women will also not be included as only people >60 years old will be eligible Research study staff will take several steps to address the risks listed above. During screening for eligible critically ill patients, attending physicians will have the opportunity to exclude a patient who, in the physician's judgment, would not be an appropriate participant. Reasons for exclusion include (but are not limited to): legal or risk management concerns; psychological illness or morbidity; and cognitive limitations. A patient's decisional capacity will be determined by his or her treating physician using accepted standards for determining decisional capacity and will be confirmed, in a similar manner, by the research staff, as part of the informed consent process. For all participants, it will be emphasized that participation is voluntary, that all steps involved with participation are voluntary, and that they are allowed to decline to complete any activity or to answer any question they are asked. For all participants, it will be emphasized that they may withdraw from the study or any study procedures at any time without any loss of rights or benefits to which they are otherwise entitled and without losing status or standing within the institution. Healthy volunteers will receive $50 plus the cost of parking as compensation for their time (which is estimated as up to 3 hours). Critically ill patients and their family member will not receive compensation or tokens of appreciation provided for participation to minimize potential coercion or the appearance of coercion.

As mentioned above, risks of the *Exersides*^{TM} restraint are very low. Nevertheless, we have taken the following steps and safeguards in the study protocol to minimize such risks and protect against them:

1. Data will be kept secure and confidential
2. Treating physicians will be allowed to exclude patients from the study

Additionally, we will submit a plan for monitoring of adverse events to the study's Data and Safety Monitoring Board (DSMB). Serious adverse events that might bear any relationship to the intervention will be reported to the local IRB as well as the University of Vermont Human Subjects Committee (parent site) and the DSMB, which may elect to restrict or cease enrollment. See Data and Safety Monitoring Plan. Furthermore, a medical/site monitoring plan is in place whereby a Study Monitor will visit each site at least twice during the study to assess protocol compliance and conduct source verification. During the site visit, case report forms will be reviewed for quality control.

Finally, data presentations will include only group data and will be presented in a way that ensures individual participants cannot be identified. If respondents may be identified by a specific subgroup analysis due to the low numbers of these types of respondents (e.g., patients aged >90), these subgroup data will not be presented in isolation in any format. There is a small risk of breach of confidentiality with the addition of video recording of subjects while in the novel and wrist restraints. We will take steps to minimize this risk by angling the camera to reduce capture of medical personnel and family members who are also in the room. A sign will

be posted on the door to alert anyone entering the room that a camera is in use. The recordings will be removed from the video camera / storage card as soon as possible, and downloaded to a secure server. We will encrypt the recordings for storage during the study, and require two-factor authentication for access. The footage will be reviewed by authorized study staff in a timely manner and the extracted data will be identified only by the subject's Study ID. After the data is extracted, the video recordings will be destroyed.

We recognize that in the current crossover design where subjects wear the device bilaterally for a 4-hour period on 2 consecutive days, we may encounter problems with a slow "wash out" period for sedative medications given before the start of a 4-hour period and thus reducing mobility during the observation period. This issue will be minimized because all study sites use short-acting, as-needed, bolus dosing of medications (Preliminary Data 6) and subjects will wear both devices in opposite order on Days 1 and 2.

POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO HUMAN SUBJECTS AND OTHERS

a) Healthy volunteers to test revised *Exersides™* restraint

There will be no benefit to healthy volunteers participating in this research. However, they will contribute to new knowledge from which future ICU patients may benefit if our intervention is found to improve outcomes.

b) Critically ill older patients recruited into cohort study (STTR Phase I) and multi-site RCT (STTR Phase II)

There may be some benefit to the critically ill participants enrolled in this research, as literature suggests that patients who participate in clinical trials overall have improved outcomes compared to patients who do not participate.[2,3] Individual subjects enrolled in this trial may also receive direct benefit if the intervention is found to improve patient outcomes such as mobility, agitation, delirium, and use of sedative medications. Currently there are few therapies known to improve outcomes of ICU patients.

The objective of this proposal is to perform a multi-site RCT of a novel restraint device in older ICU patients. If this intervention is ultimately shown to be beneficial in future trials, it will substantially expand the armamentarium of the critical care clinician. Given the potential benefit that may result from this therapy in treating a population of elderly patients with high mortality and morbidity rate, the limited risks are reasonable.

c) Family members, nurses and physicians caring for patients enrolled into STTR Phase I or STTR Phase II studies

The patient surrogate involved in the consent process may benefit from interaction with the research team who can provide explanations and answer questions regarding the patient's critical illness and issues related to restraint, as well as the patient's functional status during and after hospitalization.

When providing satisfaction and acceptability information, family members, nurses, and physicians will not have any direct benefit from participating in this research. However, future ICU patients may benefit if our intervention is found to improve outcomes.

Contact PD/PI: Stapleton, Renee D

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IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

Because critical illness is common and is a major cause of mortality as well as morbidity among survivors, developing and testing novel therapies is paramount. In this study, we propose to perform a multi-site RCT of a novel restraint device in older ICU patients to improve mobility, agitation, sedation, delirium, and sedative medication use. The information gained from this investigation may represent a major leap forward in therapy for older critically ill patients; thus the minimal risks to subjects are reasonable. Even if the intervention is not beneficial, this study is designed to provide important information that will guide future interventions.

PROTECTION OF HUMAN SUBJECTS REFERENCES

1. Truong AD, Kho ME, Brower RG, Feldman DR, Colantuoni E, Needham DM. Effects of neuromuscular electrical stimulation on cytokines in peripheral blood for healthy participants: a prospective, single-blinded Study. Clin Physiol Funct Imaging 2017;37:255-262.

2. Braunholtz DA, Edwards SJ, Lilford RJ. Are randomized clinical trials good for us (in the short term)? Evidence for a "trial effect." J Clin Epidemiol 2001;54:217-224.

3. Peppercorn JM, Weeks JC, Cook EF, Joffe S. Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review. Lancet 2004;363:263–270.

Therapeutic Alternatives: *List the therapeutic alternatives that are reasonably available that may be of benefit to the potential subject and include in the consent form as well.*

	Not Applicable

There are few alternative treatments to participating in this RCT. The standard of care at all participating centers is a traditional soft wrist restraint. Use of the *Exersides™* restraint device is not standard of ICU care at any clinical center. However, this study will not alter clinical care that occurs with regard to other aspects of critical illness. Specifically, only patients whose physicians have already written an order requiring physical restraints will be considered for the study.

Data Safety and Monitoring: *The specific design of a Data and Safety Monitoring Plan (DSMP) for a protocol may vary extensively depending on the potential risks, size, and complexity of the research study. For a minimal risk study, a DSMP could be as simple as a description of the Principal Investigator's plan for monitoring the data and performance of safety reviews or it could be as complex as the initiation of an external, independent Data Safety and Monitoring Board (DSMB). The UVM/UVM Medical Center process for review of adverse events should be included in the DSMP.*

DATA SAFETY MONITORING PLAN

The STTR Phase I Cohort Study will be monitored locally by the Principle Investigator who will assess participant safety, efficacy of the study intervention, benefit/risk, recruitment of participants, adequacy of measured and collected data, and adherence to the protocol. At the conclusion of the Phase I cohort study, we will convene a Data and Safety Monitoring Board (DSMB) that will oversee the RCT in STTR Phase II. Below, we outline the responsibilities, membership, and organization of the DSMB:

1. Responsibility: As per NIH policy, the responsibility of the DSMB will be to advise and make recommendations regarding participant safety; efficacy of the study intervention; benefit/risk ratio of procedures and participant burden; selection, retention, and recruitment of participants; adherence to protocol requirements; data and statistical analysis plan; adequacy of measured and collected data; and possible amendments to the study protocol and consent forms. As this proposal includes a small clinical trial, the main charge of the DSMB will to focus on safety, and there will be no stopping rules for efficacy or futility.

2. Membership: We will convene 4 independent voting members (3 members will constitute a quorum) who are not study investigators, and have no financial, scientific, or other conflict of interest with the trial. All members will provide written documentation of competing interests. We will include expertise in the following fields: 2 members from key subject areas involved in the research (clinical experts in critical care medicine, mobility and/or delirium/cognitive impairment), 1 from biostatistics, and 1 from clinical investigation/ trials. The group will designate a chair and an executive secretary from the group membership; the chair will be responsible for overseeing meetings, developing agendas, generating reports, and being the contact person for the DSMB. Because committee members will likely be located at various sites, the committee meetings may be conducted by teleconference.

3. Organization: The group will meet during the course of the trial as follows

a. Meeting coordination: All meetings will occur in 3 parts:

i. An open meeting with principal investigators, project coordinators, and statistician to review accrual and outcomes as per below.

ii. A partially closed meeting with the DSMB and study statistician only to review the study outcomes per below.

iii. A closed session for DSMB members only to discuss oversight issues, emerging results, comments, and recommendations, which will be discussed until consensus among members. The chair would reserve the right to break a tie, if needed.

b. RCT in STTR Phase II

i. Initial meeting for RCT

1. Protocol, consent, and data quality review: The DSMB will meet again before start of the RCT in Phase II. They will review data from Phase I. They will also review the entire IRB-approved RCT protocol with regard to participant safety, recruitment, randomization, intervention, data management, quality control, and statistical analysis. Additionally, they

will review the informed consent documents for applicability and readability, and standard operating procedures for data management and control.
2. Safety review: The DSMB will review information for recruitment, subject retention, protocol adherence, intervention effects, gender and minority inclusion, and participant safety. The DSMB will review, discuss, and approve the plan for identifying, assessing, and transmitting serious adverse event (SAE) and adverse (AE) information to the DSMB.
3. The DSMB will also approve the DSMB Charter and review any conflicts of interest that have bene disclosed.
4. Recommendations: Voting in closed session, the DSMB can recommend that the trial continue with no modifications, continue with modifications, or stop for safety concerns. The chair or designate will summarize major points of discussion, decisions, actions, and reasons, and additional information needed for future meetings. The report will be provided to study's Principal Investigators for submission to the study sites' IRBs.

ii. Interim meetings:
Meetings will occur after 1/2 (n=27) of the total participant sample (n=54) have completed all study procedures. Ad hoc meetings can be requested by the PI or DSMB if an unanticipated safety signal is identified. The DSMB will evaluate all of the items outlined above in the safety review (3b(ii)). Recommendations from the DSMB will also be summarized as outlined above (3b(iii)). During this interim meeting, the DSMB will review data for recruitment, randomization, subject retention, protocol adherence, intervention effects, gender and minority inclusion, and participant safety. The DSMB will receive cumulative data, including safety events that are reported to the IRB (as described below) and major clinical outcome variables prepared by the trial biostatistician. They may perform its own statistical analysis of these data and can request additional data if necessary. All data will initially be provided to the DSMB without indication of treatment group allocation.

Safety monitoring also will occur via the PIs and co-Is being involved in the conduct of the clinical trials including supervising the screening for patient eligibility. The PIs will have knowledge of any adverse events that may arise and will report them according to IRB and NIH/NIA guidelines and to the description provided below. All potential participants will be provided contact information for the IRB of record (University of Vermont, Johns Hopkins University, University of California) to register complaints or other problems. The DSMB will modify or stop the study if any such complaints represent a legitimate concern about the study procedures or methods. The design of the proposed studies and the proposed *Exersides*^{TM} restraint intervention are not complex and have very low potential risk to the patient. Our preliminary data demonstrate that the *Exersides*^{TM} restraint is safe, as we experienced no adverse events in the pilot study already completed with the prototype device. The physical restraint device proposed for this trial is a Class I medical device under US Food & Drug Administration regulation 21 C.F.R. § 880.6760 subject to general controls and is exempt from Federal Drug Administration (FDA) approval. The relatively low risks will be further minimized as described in the above Human Subjects section entitled "Protection Against Risks."
Confidentiality of participants' data will be protected by having all identifying participant-information removed from databases before analysis. Electronic data storage will be password protected with daily back-up and storage. Only research associates who directly interact with research subjects will have access to participant identifying information. All filing cabinets and storage facilities that contain sensitive patient information will be locked when not used. All computers and storage cabinets will be located within secure office locations.

Adverse Event and Unanticipated Problem (UAP) Reporting: *Describe how events and UAPs will be evaluated and reported to the IRB. All protocols should specify that, in the absence of more stringent reporting requirements, the guidelines established in the Committees on Human Research "Adverse Event and Unanticipated Problems Reporting Policy" will be followed. The UVM/UVM Medical Center process for review of adverse events and UAPs to subjects or others should be included in the DSMP.*

1. *Events of Interest*
The novel restraint device being tested in the FREEDOM Trial is considered so low-risk that it is exempt

from FDA IDE regulations. Nevertheless, participants will be monitored for medical events of interest including skin laceration, upper extremity joint pain, and equipment damage that may not be serious but may be related to the novel restraint intervention. These data will be collected daily while the subject is on study (through day 3 for the pilot study and day 7 for the RCT). These data will be recorded in the electronic database.

2. *Adverse Event (AE) Reporting*
Given the high acuity of diseases and morbidity related to critical illness in the patient population under study (over age 60 years old receiving invasive or non-invasive mechanical ventilation and requiring restraint), it is difficult to identify an adverse event (AE) within the constellation of symptoms related to the normal evolution of critical illness. Therefore, expected AEs (e.g. abnormal laboratory values, aberrant physiology such as fever or tachycardia or hypotension, etc.) consistent with the underlying pathophysiology or progression of underlying illness will neither be collected nor reported. Only AEs that are both unexpected and felt to be related (to any degree) to the novel restraint device will be collected and reported, the majority of which will be considered "events of interest" as above. The investigator will use his/her judgment to determine whether an AE is considered to be definitely related, probably related, possibly related, unlikely related, or not related (see table below in 5.a.). These unexpected and related (to any degree) AEs will be documented in the participant medical record and/or study file. It is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory results, diagnostic reports, etc.) regarding each event. This reporting process is outlined below.

3. *Serious Adverse Event (SAE) Reporting*
Similar to AEs, given the high acuity of diseases and morbidity related to critical illness in the patient population under study (over age 65 years old receiving invasive or non-invasive mechanical ventilation and requiring restraint), it is difficult to identify an SAE within the constellation of symptoms related to the normal evolution of critical illness. Only 'unexpected' SAEs (inconsistent with underlying pathophysiology or progression of underlying disease) will be collected and reported. Expected SAEs will not be reported (see description below). The investigator will use his/her judgment in determining whether an event is considered to be reportable per guidelines. SAEs will be documented in the participant medical record and/or study file. It is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory results, diagnostic reports, etc.) regarding each event. This reporting process is outlined below.

3.A. DEFINITION OF SERIOUS ADVERSE EVENTS (SAES)

An event will be considered an SAE if it meets any one or more of the following criteria:

A. Results in death
B. Is life-threatening - an event where a participant is at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it was more severe.
C. Prolongation of hospitalization - any substantial extension of an inpatient hospitalization beyond the stay anticipated/required in relation to participant's condition prior to the SAE, as determined by the investigator or treating physician.
D. Results in Disability or Incapacity - is defined as a substantial disruption of a person's ability to conduct normal life functions.
E. Led to fetal distress, fetal death or a congenital abnormality or birth defect
F. Important medical event - are those that may not be immediately life-threatening, but may jeopardize the participant and may require intervention to prevent one of the other serious outcomes listed above.

3.B. EXPECTED SAES

As the patient population under study are hospitalized and critically ill at baseline, care must be taken to determine if an event is outside of what would be expected given the degree and nature of the critical

illness prior to the serious adverse event. In the population under study, some examples of potential expected SAEs include:

- Abnormalities in oxygenation and/or ventilation expected for the degree of injuries sustained.
- Fluctuations in hemodynamic measures expected for the degree of injuries sustained.
- Agitation and/or pain responses expected for the degree of injuries sustained.
- Complications directly related to sustained injuries.
- Use of medications, blood products, support devices and other therapies expected for the degree of injuries sustained.

3.c. Expected Deaths

Importantly, as approximately 15-25% of participants will die from their critical illness, we anticipate that deaths in this study will be expected and occur as a result of the patients' underlying illness, with associated mortality data recorded in the CRF. Please note that reporting an expected death as an SAE via the electronic database report form is not required. However, it is left to each individual site to determine whether it meets local requirements for reporting to the IRB. Unexpected deaths should be reported as described below.

3.D. UNEXPECTED SAES

All unexpected SAEs must be reported to the PIs and Project Manager using the appropriate form as outlined below.

3.e. Definition of Unexpected SAE

Any SAE occurring in a subject participating in this Trial where the nature, severity, or frequency of the event is not consistent with the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event (e.g. sudden death from MI in a person with ARDS and sepsis without known heart disease).

4. Reporting Period

Participants should be monitored for related AEs (to any degree) and unexpected SAEs from the time of randomization until the day after the on-study period is complete (study day 7 for multi-site RCT as participants will be on study for maximum of 6 days, or 24 hours after removal of restraint device under study, whichever is earlier).

5. Reporting Timelines

Related AEs (to any degree – definitely, probably, possibly, or unlikely) and unexpected SAEs should be reported to the PIs and Project Manager (Dr Stapleton, Dr. Needham, and Ms. Ardren) **within 24h of knowledge of the occurrence of the event**. The site is expected to notify the PIs or Project Manager by phone or email and complete the Related AE and Unexpected SAE report form to submit the initial report, as well as any follow-up reports.

5.a. Initial Report

If the investigator does not have all information regarding an unexpected SAE, he/she will not wait to receive additional information before notifying the PIs and Project Manager of the event and completing the appropriate report.

Initial reports, at a minimum, should include the following information:

- Date (if available, time) of event onset
- Individual reporting the event (i.e. investigator, sub-investigator)
- Assessment of causality (i.e. relationship of event to participation in the study)
- As much information regarding the event as possible (i.e. if the event is still ongoing and the participant is still undergoing investigations and/or treatments, any preliminary information)

Assessment of Causality

The investigator is responsible for assessing the relationship of all unexpected SAEs to study participation. The following categories should be used to make the causality determination.

Definitely related	Suggests that a temporal sequence of this SAE is associated with study participation, and there is no doubt that the event is associated with participation in this study.
Probably related	Suggests that a reasonable temporal sequence of this SAE with study participation exists and the association of the event with participation in the study seems likely.
Possibly related	Suggests that the association of this SAE with study participation is unknown and the event is not reasonably supported by other conditions.
Unlikely related	A serious adverse event that is more likely due to other causes than study participation.
Not related	A serious adverse event that is clearly due to extraneous causes (disease, environment, etc.) and does not meet the criteria for a study participation relationship listed under possibly, probably, or definitely related.

There may be instances when an event has occurred and the investigator has minimal information at hand to include in the initial SAE report to the central study team. In these cases, it is important that the investigator make an assessment using their best judgement or opinion at the time of the initial report. The investigator would then reassess when the necessary information becomes available and may opt to update their causality assessment.

5.b. Follow-up

After the initial report, the investigator is required to monitor and treat the participant until the event is resolved, stabilizes, or otherwise explained. New or updated information will be recorded until the event information is considered complete.

5.c. Expedited Reporting

Safety events that fulfill the following criteria require specific expedited reporting timelines to the DSMB And NIA: Unexpected SAE **and** definitely related, probably related, possibly related, or unlikely related to study participation.

Once the site submits the event report to the PIs and Project Manager, the SC will review the report and determine whether it meets the criteria for expedited reporting. If the unexpected SAE is considered definitely related, probably related, possibly related, or unlikely related to study participation, the study leadership will generate an expedited event report that will be submitted to the DSMB and the NIA within 3 working days of receiving the site's report.

5.c. General Event Reporting to the Safety Officer and the DSMB

Any safety event that is an unexpected SAE and related (to any degree) to study participation will be reported to the DSMB and to the Safety Officer in expedited fashion, as described above in 5.c.

Withdrawal Procedures: *Define the precise criteria for withdrawing subjects from the study. Include a description of study requirements for when a subject withdraws him or herself from the study (if applicable).*

Once patients who did not have decisional capacity at the time of initial consent regain that capacity, they will be re-consented for ongoing participation in the study. A patient's decisional capacity will be determined by his or her treating physician using accepted standards for determining decisional capacity and will be confirmed, in

a similar manner, by the research staff, as part of the informed consent process. For all participants, it will be emphasized that participation is voluntary, that all steps involved with participation are voluntary, and that they are allowed to decline to complete any activity or to answer any question they are asked. For all participants, it will be emphasized that they may withdraw from the study or any study procedures at any time without any loss of rights or benefits to which they are otherwise entitled and without losing status or standing within the institution.

Sources of Materials: *Identify sources of research material obtained from individually identifiable human subjects in the form of specimens, records or data. Indicate whether the material or data will be obtained specifically for research purposes or whether use will be made of existing specimens, records or data.*

Sources of Materials

Via electronic and physical safeguards, all data will be secure in accordance with the Office of Management and Budget, and accessible only to those directly involved with this project. Throughout the study, research staff will have access to individually identifiable information available in the medical record. Patient identifying information only will be known to the research team members who are required to directly interact with the participant. All research staff who are not directly involved with patient evaluation (e.g. Data Manager and Analyst) will not have access to the linkage between the unique ID number and participant-identifying information.

a) Critically ill older patients recruited into cohort study in STTR Phase I and multi-site RCT in STTR Phase II : Screening data to identify eligible critically ill older patients will be viewed from the medical record. Data collected for these studies will come from patient or proxy interviews, chart review, clinical assessment and physical examination (using validated and reliable measurement instruments). At enrollment and during their ICU stay, research personnel will collect data, such as comorbid conditions, demographic information, physical functioning, severity of illness, and organ failure data. Research staff will also assess agitation/sedation, delirium, sedative medications received as part of clinical care, with these assessments done in person via direct observation/interaction or by medical record review. Additionally, we will also collect information from satisfaction questionnaires and semi-structured interviews, which will be done in person.

b) Family members, nurses and physicians caring for patients enrolled into Phase I or Phase II studies : Information collected from satisfaction questionnaires and semi-structured interviews will be done in person.

DRUG AND DEVICE INFORMATION

Investigators are encouraged to consult the UVM Medical Center Investigational Pharmacy Drug Service (847-4863) prior to finalizing study drug/substance procedures.

Drug (s) [X] ***Not applicable***

Drug name – generic followed by brand name and common abbreviations. Availability – Source and pharmacology; vial or product sizes and supplier. If a placebo will be used, identify its contents and source. (attach investigational drug brochure)

Preparation: Reconstitution instructions; preparation of a sterile product, compounded dosage form; mixing guidelines, including fluid and volume required. Identify who will prepare.

Storage and stability – for both intact and mixed products.

Administration – Describe acceptable routes and methods of administration and any associated risks of administration.

Toxicity – Accurate but concise listings of major toxicities. Rare toxicities, which may be severe, should be included by indicated incidence. Also adverse interactions with other drugs used in the protocol regimen as well as specific foods should be noted. Address significant drug or drug/food interactions in the consent form as well. List all with above details.

Is it FDA approved: (include FDA IND Number)

1. *in the dosage form specified? If no, provide justification for proposed use and source of the study drug in that form.*
2. *for the route of administration specified? If no, provide justification for route and describe the method to accomplish.*

3. for the intended action?

Device (s) ☐ ***Not applicable***

Device name and indications (attach investigational device brochure)

Exersides™ Restraint

Is it FDA approved: (include FDA IDE Number)

1. for indication specified? If no, provide justification for proposed use and source of the device.

The device is 510k exempt and IDE exempt.

Risk assessment (non-significant/significant risk) - PI or sponsor needs to assess risk of a device based upon the use of the device with human subjects in a research environment.

Risk assessment is deemed to be non-significant and potential risks from the *Exersides™* restraint device are considered to be very low. Our own preliminary data demonstrate safety in that no adverse or severe adverse events (i.e. no self-removal of endotracheal tubes, feeding tubes, intravenous lines, etc.) – these preliminary data are from a pilot study that has already taken place that enrolled critically ill patients in a single intensive care unit. Although self-removal of tubes and lines is a risk, as occurs with any existing currently available restraint device, we anticipate that this risk is very low due to the design of the *Exersides™* restraint that intentionally was created to further reduce this risk in comparison to traditional restraints. Other potential risks include skin breakdown from the *Exersides™* restraint device, and a theoretical increased risk of increased removal of upper extremity peripheral IVs, but we did not observe any of these events in our pilot study.

SUBJECT CHARACTERISTICS, IDENTIFICATION AND RECRUITMENT

Subject Selection: *Provide rationale for subject selection in terms of the scientific objectives and proposed study design.*

Critically ill older patients recruited into cohort study in STTR Phase I and multisite
RCT in STTR Phase II Eligible patients will be those who are 60 years of age or older, requiring invasive or non-invasive mechanical ventilation with actual or expected duration of mechanical ventilation >48 hours, cared for in an ICU with an expected ICU length of stay of >3 days after enrollment, and who are not deeply sedated (i.e. have a Richmond Agitation Sedation Scale (RASS) score > -2). No individuals 65 years and older will be excluded from the proposed study based on sex, race, or ethnicity. We anticipate that enrolled patients will have a wide range of health status, including potentially ranging from no prior comorbid disease and high prior health status to patients with many comorbidities and low prior health status.

Patients will be excluded if they meet any of the following criteria:

1. Upper extremity impairments that prevent use of novel restraint device (e.g. amputation, arm injury)
2. Severe skin breakdown preventing securing of Exersides™ restraint
3. Limited mobility of either upper extremity prior to admission (e.g. frozen shoulder, severe arthritis)
4. Pre-existing primary systemic neuromuscular disease (e.g. Guillain Barre)
5. Neuromuscular blocker infusion (eligible once infusion discontinued if other inclusion criteria met)
6. Pre-existing severe cognitive impairment or language barrier prohibiting outcome assessment
7. Expected death or withdrawal of life-sustaining treatments within 6 days from enrollment
8. Treating clinicians disagree with participation
9. Incarcerated

Subject selection aligns with the project's goal of studying intubated senior patients requiring restraint.

Vulnerable Populations: *Explain the rationale for involvement of special classes of subjects, if any. Discuss what procedures or practices will be used in the protocol to minimize their susceptibility to undue influences and unnecessary risk (physical, psychological, etc.).*

X ***Not applicable***

Number of Subjects: *What is the anticipated number of subjects to be enrolled at UVM/UVM Medical Center and in the case of a multi-center study, with UVM/UVM Medical Center as the lead, the total number of subjects for the entire study.*

Phase I study: 8; Phase II study: 54

Inclusion/Exclusion Criteria: *Eligibility and ineligibility criteria should be specific. Describe how eligibility will be determined and by whom. Changes to the eligibility criteria at a later phase of the research have the potential to invalidate the research.*

Table 5: Inclusion and Exclusion Criteria for Study Entry into STTR Phase I and Phase II Studies

Inclusion Criteria	Exclusion Criteria	Rationale for Exclusion
1. ≥65 years old **2.** Physician order for use of bilateral wrist restraints **3.** Requiring invasive or non-invasive mechanical ventilation with actual or expected total duration of ≥48 hours **4.** Expected ICU stay ≥3 days after enrollment (to permit adequate exposure to proposed intervention) **5.** Not deeply sedated (Richmond Agitation Sedation Scale [RASS] score ≥ -2)[186]	1. Upper extremity impairments that prevent use of novel restraint device (e.g. amputation, arm injury)	Unable to receive proposed intervention
	2. Limited mobility of either upper extremity prior to admission (e.g. frozen shoulder, severe arthritis)	Inaccurate data for primary outcome assessment during RCT (i.e. actigraphy)
	3. Pre-existing primary systemic neuromuscular disease (e.g. Guillain Barre)	
	4. Neuromuscular blocker infusion (eligible once infusion discontinued if other inclusion criteria met)	
	5. Pre-existing severe cognitive impairment or language barrier prohibiting outcome assessment	Unable to perform outcome assessments
	6. Expected death or withdrawal of life-sustaining treatments within 6 days from enrollment	Patients unlikely to complete proposed outcome assessment protocol
	7. Incarcerated	Vulnerable population; ethical issues
	8. Severe skin breakdown on either upper extremity	Unable to receive proposed intervention

Using the electronic medical record and daily ICU rounds, study staff will identify consecutive patients admitted to the ICU who meet eligibility criteria. After this initial screen for eligibility, study personnel will contact the patient's ICU physician to confirm appropriateness for the study. The PI will confirm that a patient is eligible for the study prior to enrollment and this will be documented on a case report form.

Inclusion of Minorities and Women: *Describe efforts to include minorities and women. If either minorities or women are excluded, include a justification for the exclusion.*

INCLUSION OF WOMEN AND MINORITIES

Targeted/planned distribution and rationale:

Persons of either sex and of all race and ethnicity categories, who meet the eligibility criteria, will be eligible to enroll in the clinical study. The eligibility criteria do not exclude any specific sex, race or ethnic category. More specifically, no individual will be excluded from this study based on sex or race/ethnicity. Based on past similar studies at all study sites, we estimate the proportion of women among patients in the proposed study will be approximately 40-50% and reflects the population of critically ill patients. We anticipate that minority representation of the patient sample will reflect the demographics in the regions where each of the 3 study sites is located (Vermont/Upstate New York; Baltimore, Maryland; and Los Angeles, California) (see Table 1).

Please see our Planned Enrollment Table for details. Overall, we estimate that approximately 35% of the study population will be comprised of racial or ethnic minorities. Based on existing data, we do not expect differences in our outcomes due to minority status but we are collecting sex/gender and race/ethnicity data and will include them as covariates in our multivariate analyses if needed.

Table1: Race/ethnicity in Vermont, Washington, and South Carolina (%)*

Race/Ethnicity	Vermont	Baltimore, MD	Los Angeles, CA	Total for Critically Ill Patients Enrolled in this Research
White/Caucasian	94.9	29.6	71.0	65.2
Black/African-American	1.3	63.7	9.1	24.7
Native American/Alaskan Native	0.4	0.4	1.5	0.8
Asian	1.8	2.3	15.1	6.4
Native Hawaiian/Pacific Islander	<0.1	<0.1	0.4	0.1
Two or more races	1.9	2.1	3.0	2.3
Hispanic (separate data category)	1.9	4.2	48.5	18.2

* https://www.census.gov/quickfacts/fact/table/US/PST045216

Inclusion of Children: *Describe efforts to include children. Inclusion is required unless a clear and compelling rationale shows that inclusion is inappropriate with respect to the health of the subjects or that inclusion is inappropriate for the purpose of the study. If children are included, the description of the plan should include a rationale for selecting or excluding a specific age range of children. When included, the plan must also describe the expertise of the investigative team in working with children, the appropriateness of the available facilities to accommodate children, and the inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose of the study.* ***If children are excluded*** *then provide appropriate justification. Provide target accrual for this population.*

INCLUSION OF CHILDREN

The Program Announcement (PAS-17-065) to which this proposal is responding to is to "conduct research leading to the development of innovative products and/or services that may advance progress in preventing and treating Alzheimer's disease (AD) and Alzheimer's-disease-related dementias (ADRD)." Hence, we are specifically including only patients ≥65 years old in the proposed study, as previously discussed with a program officer at the National Institute on Aging. This population (i.e. adult >65 years old) is suitable to the topic of this study since the prevalence of restraint use and the risk of ICU-associated delirium and long-term cognitive impairment are much higher in older than in younger patients (see Significance section within the proposal). Study subjects will therefore not include children, as defined by NIH, since the target area of investigation involves older critically ill adults. Children have unique age-related mobility and cognitive development issues that would need separate study from the proposed research. Moreover, the developing brain of children makes them markedly different from the target patient population needed for investigating ADRD issues for this Program Announcement and the Aims of the proposed study.

For protocols including the use of an investigational drug, indicate whether women of childbearing potential have been included and, if not, include appropriate justification.

N/A

If HIV testing is included specifically for research purposes explain how the test results will be protected against unauthorized disclosure. Include if the subjects are to be informed of the test results. If yes, include the process and provision for counseling. If no, a rationale for not informing the subjects should be included.

X | ***Not applicable***

Recruitment: *Describe plans for identifying and recruitment of subjects. All recruitment materials (flyers, ads, letters, etc) need to be IRB approved prior to use.*

Using the electronic medical record and daily ICU rounds, study staff will identify consecutive patients admitted to the ICU who meet eligibility criteria. After this initial screen for eligibility, study personnel will contact the patient's ICU physician to confirm appropriateness for the study and permission to contact patient/proxy for discussion of study and informed consent process in compliance with local IRB procedures. If the physicians agree, study staff will contact the patient in-person; if the patient does not have decision-making capacity at the time of enrollment, a legal next of kin in-person will be approached for informed consent. If patients regain capacity, patients will be asked to re-consent for continued participation.

FINANCIAL CONSIDERATIONS

Expense to Subject: *If the investigation involves the possibility of added expense to the subject (longer hospitalization, extra studies, etc.) indicate in detail how this will be handled. In cases where the FDA has authorized the drug or device company to charge the patient for the experimental drug or device,* ***a copy of the authorization letter from the FDA or sponsor must accompany the application. Final approval will not be granted until the IRB receives this documentation.***

There are very limited circumstances under which study participants may be responsible (either directly or via their insurance) for covering some study-related expenses. If the study participant or their insurer(s) will be billed for any portion of the research study, provide a justification as to why this is appropriate and acceptable. For example, if the study involves treatment that is documented standard of care and not investigational, state so. In these cases, the protocol and the consent should clearly define what is standard of care and what is research.

There is no charge to patients.

Payment for participation: *Describe all plans to pay subjects, either in cash, a gift or gift certificate. Please note that all payments must be prorated throughout the life of the study. The IRB will not approve a study where there is only a lump sum payment at the end of the study because this can be considered coercive. The amount of payment must be justified. Clarify if subjects will be reimbursed for travel or other expenses.*

X | ***Not applicable***

Collaborating Sites*. When research involving human subjects will take place at collaborating sites or other performance sites when UVM/UVM Medical Center is the lead site, the principal investigator must provide in this section a list of the collaborating sites and their Federalwide Assurance numbers when applicable. (agreements may be necessary)*

| ***Not applicable***

Johns Hopkins University, FWA00005834
University of California Los Angeles, FWA00004642
Rutland Regional Medical Center, FWA00003554

INFORMED CONSENT

***Consent Procedures**: Describe the consent procedures to be followed, including the circumstances under which consent will be obtained, who will seek it, and the methods of documenting consent. Specify the form(s) that will be used e.g. consent (if multiple forms explain and place identifier on each form), assent form and/or HIPAA authorization (if PHI is included). These form(s) must accompany the protocol as an appendix or attachment.*

Note: Only those individuals authorized to solicit consent may sign the consent form confirming that the prospective subject was provided the necessary information and that any questions asked were answered.

As most eligible patients will be unable to make decisions, written informed consent will most often occur via legally authorized representatives (LARs) with participant re-consent upon regaining capacity.
All patients who meet inclusion and exclusion criteria will be invited to participate in this study. Using observation/review of the electronic medical record and daily hospital rounds, study staff will identify consecutive patients admitted to the ICU who meet the basic eligibility criteria. In order to conduct the screening, the research team will obtain: 1) an IRB waiver of consent for screening; 2) an IRB waiver of HIPAA authorization; and 3) all necessary institutional confidentiality agreements. After this initial screen for eligibility, study personnel will proceed as per local IRB requirements, including contacting the patient's ICU physicians to confirm appropriateness for the study and obtain permission to approach the patient/legal next of kin for discussion of the study and to undertake the informed consent process. If the physicians agree, study staff will approach the patient in-person or, if the patient doesn't have decisional capacity at the time of enrollment, a legal next of kin in-person (via in-person meeting).
Most patients participating in this study will require mechanical ventilation and will therefore be receiving some amount of sedative medications at the time of enrollment. Hence, we anticipate that a large proportion of patients will lack the capacity to provide informed consent at the time of study eligibility and therefore, we expect that study staff will go through the process of informed consent and review the consent materials with the legal next of kin. Consent will be documented, in writing, on an IRB-approved consent form. No minors will be considered in the proposed research; therefore, parental permission and child assent is not applicable to this application. All conversations with the patient/legal next-of-kin regarding the study will be held in a private setting; study staff will allow for patients' desire to have family present and/or to confer with family, and to make participation decisions according to his or her own time. Once patients who did not have decisional capacity at the time of initial consent regain that capacity, they will be re-consented for ongoing participation in the study.

Family members may be the Legally Authorized Representatives (LARs) who provide consent for the patient to participate in the RCT, but additional family members beyond the LARs also may be asked to participate, and they will be identified via observation of them visiting the consented participant while in the ICU. Only family members >18 years of age will be included. Family members will undergo informed consent, but no identifiable information will be obtained from them. Nurses and physicians caring for the patients in the RCT (study (C) from above) also will be asked to complete the satisfaction questionnaire and semi structured interview with their enrollment and consent in accordance with institutional IRB policy.

***Information Withheld From Subjects:** Will any information about the research purpose and design be withheld from potential or participating subjects? If so, explain and justify the non-disclosure and describe plans for post-study debriefing.*

[X] ***Not applicable***

Attach full grant application, including budget information and/or any contract or draft contract associated with this application.

All materials must be submitted electronically to the IRB via InfoEd. Proper security access is needed to make electronic submissions. Visit the InfoEd Resource Materials page for more information.