BMJ Open

Trajectories of Recovery after ACutE and cRitical illness (TRACER): a prospective observational study protocol

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To cite: González-Seguel F, Summers LA, Fresenko LE, *et al*. Trajectories of Recovery after ACutE and cRitical illness (TRACER): a prospective observational study protocol. *BMJ Open* 2025;**15**:e108885. doi:10.1136/bmjopen-2025-108885

► Prepublication history for this paper is available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2025-108885).

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Received 04 August 2025
Accepted 04 November 2025

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ABSTRACT

Introduction Patients who survive admission to intensive care unit (ICU) for critical illness are at high risk of developing muscle atrophy and weakness, commonly diagnosed as ICU-acquired weakness (ICUAW). The development of ICUAW is closely linked to long-term symptoms and impairments known as post-intensive care syndrome (PICS). Despite heightened recognition of impairments, there is limited research supporting effective interventions to improve muscle and physical outcomes after hospital discharge. Prior to developing and testing interventions for ICU survivors, it is imperative to understand the trajectory of muscle and physical function recovery following an ICU stay. The purpose of this study is to longitudinally investigate skeletal muscle health and physical function outcomes after ICU admission.

Methods and analysis This protocol describes a single site, prospective, observational study in adult patients who have survived a critical illness (ie, sepsis or acute respiratory failure). Patients will participate in a battery of testing including primary outcomes: muscle power and physical function; and secondary outcomes: muscle strength, muscle size, endurance and physical activity (by accelerometry) at hospital discharge and 3, 6, and 12 months post-discharge. A subset of patients will participate in muscle biopsy and venipuncture. To examine if the trajectory of recovery predicts primary outcomes, we will perform multivariate linear regression models in 150 evaluable patients. To examine differences in molecular and cellular outcomes in plasma and muscle tissue, a control group of community-dwelling adults without history of an ICU stay will be enrolled as a comparator group. Enrolment started on 18 October 2022 with an estimated completion date of 1 August 2027.

Ethics and dissemination This protocol was approved by the University of Kentucky Office of Research Integrity Medical Internal Review Board (# 77407), with patients providing informed written consent. We anticipate our findings to establish recovery trajectories, improving the classification of patients who experience sustained physical disability. Improved identification of recovery trajectories of muscle and physical function enables future studies to employ an individually targeted rehabilitation approach, that is, precision medicine, with the goal of improving patient outcomes. The cellular findings will support the development of novel interventions specifically designed for detecting underlying mechanisms. We intend to disseminate findings to patients, healthcare professionals, the public and other relevant groups via conference presentations and manuscripts without publication restrictions.

Trial registration number NCT05537298.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The Trajectories of Recovery after ACutE and cRitical illness (TRACER) study is a prospective, observational cohort study examining long-term physical recovery after intensive care unit admission for critical illness.
⇒ By integrating clinical assessments with molecular and cellular analyses from muscle tissue, TRACER is designed to capture the complex relationship between biological mechanisms and functional recovery.
⇒ As major strength, this study will include detailed characterisation of skeletal muscle using validated, reproducible measures—including ultrasonography, dynamometry, accelerometry—paired with functional tests and a subset of patients undertaking muscle biopsy.
⇒ Although the depth of characteristics is a strength, the study is single-site which may limit generalisability.
⇒ Attrition remains a potential challenge in longitudinal studies of patients with critical illness; although retention strategies have been built into the design, differential non-random loss to follow-up could influence observed trajectories.

INTRODUCTION

Nearly 5 million Americans survive an admission to the intensive care unit (ICU) for critical care every year in the USA.[1 2] Of those survivors, roughly 70%–80% will develop

muscle weakness, and 40%–50% will meet diagnostic criteria for ICU acquired weakness (ICUAW).[3 4] ICUAW is an umbrella term that encompasses muscle impairments including neuromuscular dysfunction, myopathy and/or atrophy that develop as a direct result of critical illness.[5] Impairments in skeletal muscle are known contributors to physical disability and prevent the performance of simple daily life activities like standing up from a chair. The occurrence of ICUAW is an independent predictor of mortality and closely linked to post-intensive care syndrome (PICS).[5–8] The term PICS was developed to raise awareness for the long-term symptoms and impairments in emotional, cognitive and physical health following critical illness,[9] also including falls,[10] return to work[11] and driving.[12] Despite heightened awareness of functional deficits after critical illness, there is a scarcity of evidence elucidating the molecular and cellular mechanisms of muscle and physical dysfunction in patients surviving critical illness.[13 14]

The trajectory (timing and degree) of physical recovery after hospital discharge is not fully understood.[15 16] Distinct recovery phenotypes exist based on age, comorbidities and severity of illness in the ICU,[17 18] but the relationship between cellular alterations and physical function recovery remains mostly unexplored. Research from three patient pools of seven published articles[19–25] of skeletal muscle tissue from biopsies of ICU survivors demonstrates varied outcomes including sustained muscle fibre atrophy, reduced satellite cell content, increased collagen deposition and downregulated mitochondrial biogenesis gene expression. Thus, there is a significant gap in the literature connecting the cellular, demographic and clinical factors that drive physical function recovery after critical illness.

Studying muscle at the cellular level and integrating findings with physical function enhance our understanding of the different phenotypes of recovery. Improved classification of recovery of physical impairment provides new opportunities to develop and test targeted interventional strategies based on the underlying pathophysiology instead of the historical rehabilitation approach of one-size-fits-all protocols. Identification of the recovery trajectories also enhances clinical decision making to prescribe interventions individualised to the patient.[15] Thus, the overarching goal of the proposed study is to determine the trajectories of muscle and physical recovery with carefully aligned measures of cellular and molecular biology to determine the underlying rate of muscle recovery after critical illness. Secondarily, this study aims to elucidate patient, clinical and biologic factors that associate or predict risk for sustained physical disability.

METHODS

Study design

The TRACER (Trajectories of Recovery after ACutE and cRitical illness) is a single-site, prospective, observational study assessing the recovery of muscle and physical function in patients surviving critical illness at hospital discharge (ie, baseline recovery) with repeated assessments at 3, 6, and 12 months following hospital discharge. The time points were selected based on two rationales: (1) comparability with previous studies examining long-term outcomes after critical illness[26] and (2) standard of care follow-ups from the ICU Recovery Clinic at the University of Kentucky.[27] Thus, time points use a pragmatic design to enhance adherence and follow-up. A summary of the procedural timeline is presented in figure 1. Patients will be approached for enrolment near the time of ICU discharge after life-saving modalities and sedative medications have been weaned. Patients or their legally authorised representative will provide written informed consent prior to participation in research activities. The TRACER study enrolment started on 18 October 2022 with an estimated completion date of 1 August 2027.

Study setting

The setting is an academic medical centre consisting of two hospitals with a 1025 acute care and 158 ICU bed capacity. UK Healthcare includes Chandler Medical Center, a level-one trauma centre with 850 acute care and up to 142 ICU level beds in conjunction with Good Samaritan Hospital that can provide 175 acute care and 16 ICU level bed capacity. UK Healthcare houses the ICU Recovery Clinic, a specialised clinic providing care to survivors of critical illness.[27] Study assessments will be performed in the hospital room of the patient at or near discharge with follow-ups occurring in a research laboratory or within the patient's home. Muscle biopsies will be performed in a procedural room in the Center for Clinical and Translational Science.

Eligibility criteria

Adult patients (≥18 years of age) who are admitted to the ICU for at least 72 hours at the University of Kentucky with a diagnosis of sepsis or acute respiratory failure are eligible (box 1). We defined sepsis according to the Sepsis-3 consensus.[28] We considered a patient with respiratory failure if they received any of the following support: invasive mechanical ventilation, non-invasive ventilation, continuous positive airway pressure, high-flow nasal cannula, or any supplemental oxygen therapy. Patients will be excluded if they were not ambulatory prior to the hospital admission, not expected to survive at least 6 months after hospital discharge, have a new or pre-existing neurological infarct or condition with deficits preventing participation in physical testing, or have recurrent critical illness (defined by >2 previous ICU hospitalisations during the last year). Patients who enrol in the study will have the opportunity to consent to an optional muscle biopsy with additional exclusion criteria related to safety of the procedure. A group of community-dwelling adults (≥18 years of age) without a history of ICU admission will be recruited through advertisements to participate as a comparator group performing the battery of functional tests, muscle assessments and muscle biopsy.

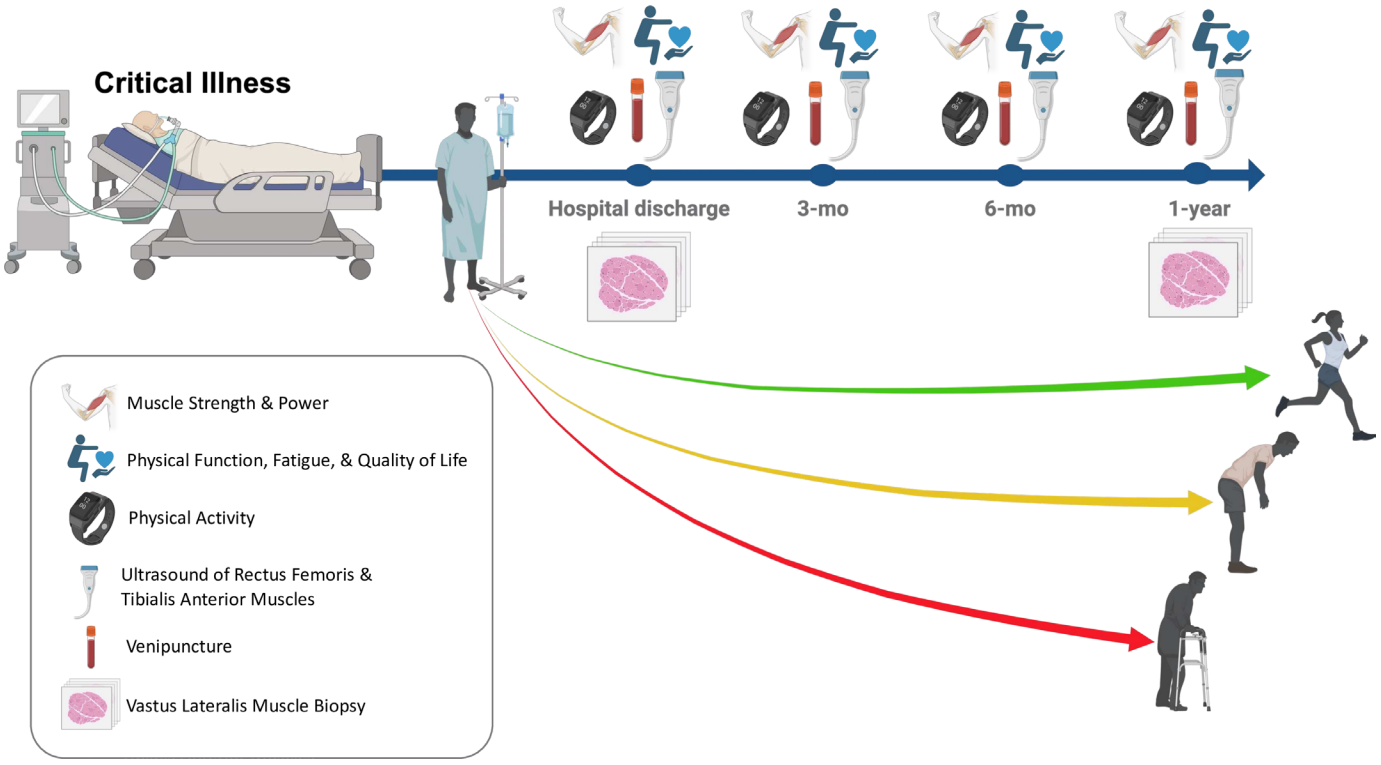

Figure 1 Procedural timeline of TRACER study. Screening will initiate at or near ICU discharge and may continue until the first ICU Recovery Clinic visit. The study window to complete the baseline (hospital discharge) visit will be within 30 days of returning home from the hospital or secondary facility. Part of the figure was created in BioRender (https://app.biorender.com/illustrations/68838b0cb8116ecd54499b5f). 3-mo, 3 months follow-up; 6-mo, 6 months follow-up; ICU, intensive care unit; TRACER, trajectories of recovery after acute and critical illness.

Box 1 Eligibility criteria of TRACER study

Inclusion criteria

1. Age ≥18 years.
2. Survived an ICU admission of 72 hours.
3. Diagnosis of sepsis or acute respiratory failure.

Exclusion criteria

1. Not ambulating independently prior to illness (use of gait aid permitted).
2. Experienced >2 ICU admissions in the past year, that is, chronic critical illness.
3. Not expected to survive 6 months after hospital discharge.
4. Have a pre-existing or acute neurological infarct or condition that precluded functional testing.
5. Orthopaedic or traumatic injury with weight-bearing restrictions precluding participation in functional testing.
6. BMI >50 kg/m^2 that distort muscle ultrasonography images and preclude performance of functional testing.

Additional exclusion criteria for optional muscle biopsy

1. Bleeding condition, that is, 'free bleeder' such as unexplained epistaxis or prolonged bleeding after minor procedures.
2. Medications that increase the risk of bleeding that cannot be temporarily paused including clopidogrel, non-steroidal anti-inflammatory drugs and anticoagulation therapy.
3. History of allergic reaction to lidocaine.
4. History or high risk of cerebrovascular accident.

BMI, Body Mass Index; ICU, intensive care unit; TRACER, Trajectories of Recovery after ACutE and cRitical illness.

Patients from the comparator group will be excluded based on the same criteria for the ICU survivors and will perform the measures of muscle and physical function with the muscle biopsy at one time-point.

Screening and Recruitment

The TRACER study will initiate screening at or near ICU discharge and may continue until the first ICU Recovery Clinic visit. The study window to complete the baseline (hospital discharge) visit will be within 30 days of returning home from the hospital or secondary facility (ie, rehabilitation facility). Our team will employ previously successful recruitment strategies to ensure retention, including frequent contact with patients and Internal Review Board (IRB)-approved incentives.

Outcomes

A summary of primary and secondary outcomes is listed in table 1.

Primary Outcomes

The primary outcomes are muscle power and physical function followed for 12 months after hospital discharge. For the subset of patients undertaking the muscle biopsy, the primary outcome is muscle mitochondrial function measured 12 months after hospital discharge.

Muscle power. Lower-extremity muscle power will be assessed with a linear potentiometer (GymAware Power Tool, Kinetic Performance Technologies, Canberra,

Table 1 Schedule of enrolment and follow-up of the TRACER study

		Enrolment baseline recovery	Follow-up		
		Hospital discharge	3 months	6 months	12 months
Patient & clinical data	Informed consent	X			
	Demographics	X			
	ICU data (ie, length of stay)	X			
Pre-hospital function	Pre-hospital ADLs, exercise routine, & falls, driving & employment status	X			
	Pre-hospital WHODAS 2.0	X			
Patient & symptomology	Current symptoms & Falls	X	X	X	X
	Current ADLs, exercise routine, & falls, driving & employment status		X	X	X
	Community-based rehabilitation receipt		X	X	X
Muscle strength & power	MRC Sum Score	X	X	X	X
	Handgrip dynamometry	X	X	X	X
	Handheld dynamometry	X	X	X	X
	Muscle power		X	X	X
Muscle ultrasound	Rectus femoris & tibialis anterior	X	X	X	X
Physical frailty	Clinical frailty scale & fried frailty phenotype	X	X	X	X
Physical function	SPPB, TUG & TUG-cog	X	X	X	X
	Sit to stand 30 s	X	X	X	X
	6MWT		X	X	X
Activity	Physical activity tracker (step counts)	X	X	X	X
Self-report questionnaires	EQ-5D-5L and VAS	X	X	X	X
	FACIT-fatigue	X	X	X	X
	Physical Activity Questionnaire (IPAQ)	X	X	X	X
	Social determinants of health		X		
	Optimism & Resilience Questionnaire			X	
	Sleep Questionnaires (STOP-Bang & PSQI)		X	X	X
Biological testing	Venipuncture	X	X	X	X
	Muscle biopsy sample	X			X

ADLs, activities of daily living; BMI, Body Mass Index; EQ-5D-5L, EuroQol 5-dimensions 5-levels; FACIT, Functional Assessment of Chronic Illness Therapy; ICU, intensive care unit; IPAQ, International Physical Activity Questionnaire; LOS, length of stay; MRC, Medical Research Council; MV, mechanical ventilation; 6MWT, 6-Minute Walk Test; PSQI, Pittsburgh Sleep Quality Index; SPPB, Short Physical Performance Battery; TRACER, trajectories of recovery after acute and critical illness; TUG, Timed Up and Go; TUG-cog, Timed Up and Go with cognitive task; VAS, Visual Analogue Scale; WHODAS 2.0, World Health Organization Disability Assessment Schedule 2.0.

Australia) to record the mean/peak power and velocity of a unilateral lower-extremity press using a Shuttle MiniPress as previously described by our team.[29] After a familiarisation period, patients will perform three repetitions of the leg press at three levels of resistance: 2 lbs, 14 lbs and 21 lbs.

Physical function. The Short Physical Performance Battery (SPPB), Timed-Up and Go (TUG) and 6-Minute Walk Test (6MWT) will be assessed at the defined time points. SPPB is a performance-based test with components of balance, repetitive sit-to-stand for time and 4-m habitual gait speed.[30 31] Higher scores on SPPB indicate better physical function. The 6MWT assesses the distance a patient can walk in 6 min, providing a general marker of overall physical function and exercise capacity.[26 32 33] The TUG test is a measure of mobility used to assess functionality, frailty and risk of falling.[34] Patients will also perform the dual-task TUG to examine concurrent performance of physical and cognitive tasks, which is significantly impaired in ICU survivors.[35]

Muscle biopsy. Primary outcomes for this subset of patients are mitochondrial function and protein synthesis. Secondary outcomes are defined in table 2. Patients will be labelled for 7 days with deuterium oxide (D_2O)

Table 2 Skeletal muscle biopsy outcomes

Parameter	Description and approach	Outcome
Mitochondrial respiration[58 59]	High-resolution respirometry will be assessed from permeabilised muscle fibres using Oroboros O2K.	Primary
Muscle protein synthesis[19 36 60]	Deuterium oxide (D_2O) is ingested daily for 7 days prior to muscle biopsy procedure (150 mL on days 1 and 2; 100 mL days 3–7). Muscle tissue is then fractionated into myofibrillar, mitochondrial and collagen protein fractions using differential centrifugation as previously described. Myofibrillar, mitochondrial and collagen protein fractions will be used derivatised for analysis of deuterium enrichment in alanine using Gas Chromatography-Mass Spectroscopy (7890A GC-Agilent 5975C). For precursor pool enrichment, serum will be prepared for analysis of deuterium enrichment on a liquid water isotope analyser (Los Gatos Research, Los Gatos, CA, USA), which is then adjusted for equilibration with alanine using mass isotopomer distribution analysis. The deuterium enrichments of both the protein (product) and the precursor will be used to calculate fraction new: Fraction new=Eproduct/Eprecursor, where the Eproduct is the enrichment (E) of protein-bound alanine and Eprecursor is the calculated maximum alanine enrichment from equilibration of the body water pool.	Primary
Mitochondria enzyme activity[19]	Histochemical staining of muscle fibres will include (a) succinate dehydrogenase, a marker of oxidative capacity per myofibre type; (b) citrate synthase, a general marker of mitochondrial content; and (c) cytochrome c oxidase, a general marker of mitochondrial activity. Citrate synthase and cytochrome c oxidase activity will be measured in lysates as proxy measures of mitochondria content and Complex IV activity.	Secondary
Myofibre size & type[19 61]	Immunohistochemistry will be performed with antibodies directed against myosin heavy chain (MyHC) isoforms: I, IIA and IIX as well as laminin (fibre borders) to examine myofibre type and size using MyoVision.[61]	Secondary
Myogenic progenitor cells, myonuclear number and centronucleation[62]	Quantification of satellite cell abundance using Pax7 antibody. Dystrophin antibody to identify muscle fibre borders, and DAPI for nuclei localised inside cell membrane and centrally in muscle fibre will be counted.	Secondary
Muscle collagen content[19 20]	We will quantify picrosirius red staining for collagen; we will further characterise collagen content by specific staining for types I and III collagen (fibrillar collagens, the major structural components of the extracellular matrix) and for basal laminar collagen type IV.	Secondary

DAPI, 4′,6-diamidino-2-phenylindole.

administered through drinking water. After 7 days, patients will undertake a muscle biopsy as previously described.[19 36] In brief, muscle tissue is obtained from the vastus lateralis after administration of local anaesthetic (1% lidocaine premixed with bicarbonate) using a 5-mm Bergström needle with suction apparatus. The vastus lateralis muscle was selected for its crucial involvement in gait and sit-to-stand performance. The technique yields 150–250 mg of skeletal muscle tissue for experiments described in table 2. Muscle tissues are coded to blinded laboratory personnel during experiments.

Secondary Outcomes

Secondary outcomes include muscle strength, cardiorespiratory fitness estimated from the 6MWT, dual-task ability on TUG – cognitive test, actual and self-reported physical activity, emotional health, and self-reported quality of life. For Spanish-speaking patients, we will use the available Spanish cross-culturally adapted versions for each self-report questionnaire and test.

Muscle strength: Muscle strength will be assessed using three different approaches: (1) the ICUAW standard of care clinical diagnosis Medical Research Council Sum Score (MRC-SS) to examine limb muscle strength of six major muscle groups that is standard of care for the clinical diagnosis of ICUAW.[37 38] (2) Knee extension muscle strength including peak force production and rate of force development will be recorded using a Lafayette digital hand-held dynamometer (HHD) (Lafayette Instrument Company, Lafayette, Lafayette, LA, USA). HHD to assess isometric muscle strength is reliable, validated and strongly associated with gold standard of isokinetic dynamometry.[39] (3) Bilateral handgrip dynamometry (HGD) will be used to measure grip strength with a portable hydraulic hand dynamometer (5030J1, Jamar, Sammons Preston, Inc., Nottinghamshire, UK).[37]

Muscle fatigue and endurance: Patients will self-report fatigue on the Functional Assessment of Chronic Illness Therapy-fatigue subscale[19] and perform the 30 s sit-to-stand test (30STS), a valid and reliable measure of lower-extremity muscle performance.[40 41]

Physical activity: Patients will wear an accelerometer (Garmin, Vivofit 4 or Oura ring Gen 4, depending on

preference) to record daily physical activity specifically focused on the number of steps ambulated per day.[42] Patients will also self-report physical activity on the International Physical Activity Questionnaire (IPAQ).[43 44]

Muscle ultrasound: Ultrasound images will be obtained using the SonoSite iViz (FUJIFILM SonoSite Inc. Bothell, WA) to assess muscle size (muscle thickness and anatomical cross-sectional area) and echo-intensity (quality), as described previously.[45 46] We will assess rectus femoris (RF), measured two-thirds the distance from anterior superior iliac spine to superior border of the patella, and tibialis anterior (TA) muscle, measured at one-third the distance from tibial plateau to the superior border of lateral malleolus. We will also assess the vastus lateralis muscle prior to any biopsy. Previous data demonstrate that muscle ultrasound has high reproducibility and reliability.[45 46] Echo intensity has been previously used in critical illness with changes in muscle correlated to myofiber necrosis and increased fibrosis suggesting high construct validity.[20 47]

Cognitive function and quality of life: We will use instruments recommended by the Core Outcome Measurement Set for critical illness survivors,[48 49] including the Montreal Cognitive Assessment (cognitive function), and the European Quality of Life Health 5D-5L questionnaire (self-reported quality of life).

Social Determinants of Health (SDOH): An SDOH screener based on the Kaiser Permanente "Your Current Life Situation" will assess unmet social needs such as food insecurity, financial difficulties, stress, transportation, support and isolation.[50] SDOH are factors that influence critical illness recovery from the patient's perspective.[51 52]

Venipuncture: Standard venipuncture may be performed at all time points to collect three tubes of blood: (a) Becton Dickinson vacutainer for separation of plasma to examine circulating cytokine levels[53]; (b) RNA PAXgene tube to assess RNA abundance; and (c) DNA PAXgene tube for downstream sequencing and genotyping.

Rigor and Quality Assurance

Physical therapists and exercise physiologists will perform the physical testing (muscle strength, muscle power, physical function and ultrasonography) in one of three locations described above. To ensure rigour and standardisation, research personnel will participate in training with online videos and protocols, as well as dedicated in-person training led by senior physical therapist-scientist (KPM). Training and quality assurance (QA) will occur at the start of the study and be repeated annually. Quality assurance testing includes performance of the assessment protocols with standardised patients to confirm competency. Data collection will occur using standardised case report forms (CRF) in the REDCap (Research Electronic Data Capture) Database hosted at the University of Kentucky with data validation, user access control and quality queries to ensure accuracy of the data. Ultrasound images obtained on Sonosite will be transferred to MyoVision-US using a hard drive to prevent image compression. Ultrasound images will be automatically examined with artificial intelligence software previously validated.[54]

A Priori Sample Size Calculation

Using data from the previously published study[29] and a finite mixture model, two distinct patterns of change in muscle power from 1-month post-discharge to 3 months post-discharge were observed, p=0.02, with group membership of 60%:40%. For lower-extremity muscle power, 150 survivors of critical illness will provide over 99% power to see the difference of 6.9 Watts seen in our pilot data.[29] To see the 4.3 s difference in the sit-stand time, assuming SD of 9.2 s as seen in pilot data, 150 survivors of critical illness will provide 92.9% power. In the 6-min walk distance, assuming the SD of 95 m from our pilot data, we will have 80.5% power to see the pilot difference of 44.9 m with 150 survivors of critical illness. To allow for 28% attrition over the 1 year of follow-up for survivors of critical illness, 209 patients with critical illness will be enrolled.

Statistical Approach

We will perform descriptive statistics at each time point using frequencies and proportions for categorical variables and means, and SD or medians and (interquartile range), as appropriate, for continuous variables. To examine the change in muscle strength and power during recovery trajectory, analyses will be conducted. Although we predict two distinct patterns of recovery, analyses will consider the appropriate number of groups. Once appropriate group membership is determined, demographic variables will be analysed for prediction of membership. To determine how changes in muscle power and strength based on our grouping predict long-term physical function, we will perform multivariate regression modelling with demographic (age and sex) and clinical variables (severity of illness, comorbid index) as potential confounders. All outcomes will be assessed for normality and transformations, or non-parametric analyses, will be used as needed. To assess the change over time for each outcome measure, a generalised mixed model will be fit using time as a random repeated effect and the baseline (post-discharge) measure as a covariate. The appropriate covariance structure will be determined by reviewing the data. In addition, to assess the group differences between survivors of critical illness and community dwelling adults, t-tests or Wilcoxon rank sum tests will be used as appropriate. Demographic characteristics (age, sex, Body Mass Index, and comorbid status) will be compared between the subset of patients with critical illness and the controls, and any imbalance will be adjusted in analyses using analysis of covariance models. Patterns of missing data will be examined and established methods for handling missing data will be employed if needed.

Patient and public involvement

Qualitative data[55] and engagement with patients in the ICU Recovery Clinic strongly support that physical function recovery is a primary outcome for ICU survivors. Although patients and caregivers were not directly involved with the design of the study, two former patients provided oversight from the patient's perspective and may participate in dissemination of findings in public and medical formats.

DISCUSSION

The TRACER study is a comprehensive, prospective study into the long-term trajectories of muscle and physical function recovery among survivors of critical illness. By integrating clinical and functional assessments, molecular and cellular analyses of muscle tissue, and patient-reported outcomes over a 12-month period, this protocol is designed to capture the complex relationship between biological mechanisms and functional recovery. Unlike prior studies that have primarily relied on cross-sectional or single-domain evaluations,[15 17 21 53 56] this study's longitudinal and multimodal design provides an opportunity to identify recovery trajectories and the cellular underpinnings of sustained disability. This foundational knowledge is critical to informing future intervention trials that are tailored to individual risk profiles, aligning with emerging models of precision and individualised rehabilitation.[57]

A major strength of the protocol lies in its detailed characterisation of skeletal muscle using validated, reproducible measures—including ultrasonography, dynamometry and parameters derived from muscle biopsy—paired with functional tests and accelerometry. The inclusion of a comparator group of community-dwelling adults allows for more rigorous interpretation of molecular findings. In addition, the study incorporates social determinants of health, recognising their potential influence on recovery outcomes.[51 52]

Limitations

This study has limitations that need to be acknowledged. First, as a single-site study conducted at an academic medical centre, generalisability may be limited. Second, sample sizes were based on a preliminary sample with change from baseline to 3 months, and thus, may not be representative of a 12-month change. Moreover, while the sample size is powered for key physical outcomes, the subset of patients who consent to muscle biopsy may introduce selection bias due to the invasiveness of the procedure. Third, attrition remains a potential challenge in longitudinal studies of patients with critical illness; although retention strategies have been built into the design, differential non-random loss to follow-up could influence observed trajectories. Fourth, although the study assesses multiple biologic, clinical and psychosocial domains, causality cannot be inferred from this observational design. Finally, as this is a study focused on trajectories of recovery in survivors of critical illness, we are not capturing baseline measures during the ICU stay (eg, muscle ultrasound at ICU admission).

ETHICS AND DISSEMINATION

This protocol was approved by the University of Kentucky Office of Research Integrity Medical Internal Review Board (IRB) under full review (# 77407 with initial approval 3 May 2022). Patients provide informed written consent. Significant protocol revisions are communicated and approved by the IRB; any changes to protocol are updated on the ClinicalTrials.gov registry. Since the study is not a clinical trial by definition, a Data Monitoring Safety Board is not required. Due to the vulnerable population with invasive procedures, an independent safety officer will provide oversight on patient safety, supplied by the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

We intend to disseminate results to patients, healthcare professionals, the public and other relevant groups via conference presentations, poster presentations, and manuscripts.

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Contributors KPM, EEDV, BFM and PEM contributed to the conception and design of the study. FGS, LS, DEL and KPM drafted the manuscript; KPM and EEDV obtained funding for the project; all authors performed revisions and approved the final version of the manuscript. EEDV is the guarantor, who accepts full responsibility for the integrity of the work.

Funding The project was supported by the NIH National Center for Advancing Translational Sciences through grant number UL1TR001998. Dr. Kirby Mayer was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institute of Health K23-AR079583. The TRACER study team was supported by NIGMS and NIAMS on the 5R01AR081002. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Competing interests YW is the founder of MyoAnalytics LLC. The remaining authors have no conflicts of interest.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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