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Critical Care Cycling to Improve Lower Extremity Strength (CYCLE): protocol for an international, multicentre randomised clinical trial of early in-bed cycling for mechanically ventilated patients

Michelle E Kho ,[1,2,3] Julie Reid,[1,4] Alexander J Molloy,[2,3] Margaret S Herridge,[5] Andrew J Seely,[6] Jill C Rudkowski,[7,8] Lisa Buckingham,[4] Diane Heels-Ansdell,[4] Tim Karachi,[7] Alison Fox-Robichaud ,[7] Ian M Ball,[9,10] Karen E A Burns,[11,12] Joseph R Pellizzari,[13,14] Christopher Farley,[1] Sue Berney,[15,16] Amy M Pastva,[17] Bram Rochwerg,[4,7] Frédérick D'Aragon,[18,19] Francois Lamontagne,[19,20] Erick H Duan,[7,8,21] Jennifer L Y Tsang ,[7,21] Patrick Archambault,[22,23] Shane W English ,[6,24,25] John Muscedere,[26] Karim Serri,[27] Jean-Eric Tarride,[4,28] Sangeeta Mehta,[29,30] Avelino C Verceles,[31,32] Brenda Reeve,[33] Heather O'Grady,[1] Laurel Kelly,[2] Geoff Strong,[1] Abby H Hurd,[2] Lehana Thabane ,[3,4] Deborah J Cook ,[3,4,8] on behalf of the CYCLE Investigators and the Canadian Critical Care Trials Group

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For numbered affiliations see end of article.

Correspondence to
Dr Michelle E Kho;
khome@mcmaster.ca

ABSTRACT

Introduction In-bed leg cycling with critically ill patients is a promising intervention aimed at minimising immobility, thus improving physical function following intensive care unit (ICU) discharge. We previously completed a pilot randomised controlled trial (RCT) which supported the feasibility of a large RCT. In this report, we describe the protocol for an international, multicentre RCT to determine the effectiveness of early in-bed cycling versus routine physiotherapy (PT) in critically ill, mechanically ventilated adults.

Methods and analysis We report a parallel group RCT of 360 patients in 17 medical-surgical ICUs and three countries. We include adults (≥18 years old), who could ambulate independently before their critical illness (with or without a gait aid), ≤4 days of invasive mechanical ventilation and ≤7 days ICU length of stay, and an expected additional 2-day ICU stay, and who do not fulfil any of the exclusion criteria. After obtaining informed consent, patients are randomised using a web-based, centralised system to either 30 min of in-bed cycling in addition to routine PT, 5 days per week, up to 28 days maximum, or routine PT alone. The primary outcome is the Physical Function ICU Test-scored (PFIT-s) at 3 days post-ICU discharge measured by assessors blinded to treatment allocation. Participants, ICU clinicians and research coordinators are not blinded to group assignment. Our sample size estimate was based on the identification of a 1-point mean difference in PFIT-s between groups.

Ethics and dissemination *C*ritical Care C*ycl*ing to improve *L*ower *E*xtremity (CYCLE) is approved by the Research Ethics Boards of all participating centres and Clinical Trials Ontario (Project 1345). We will disseminate trial results through publications and conference presentations.

Trial registration number NCT03471247 (Full RCT); NCT02377830 (CYCLE Vanguard 46 patient internal pilot).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This protocol describes an open-label, international 17-centre randomised controlled trial of in-bed cycling and routine physiotherapy (PT) versus routine PT alone in critically ill patients.
⇒ The randomised intervention is initiated within 4 days of starting mechanical ventilation, to address the rapid muscle weakness that occurs early in the patient's intensive care unit (ICU) stay.
⇒ The motorised cycle ergometer provides three possible activity modes including passive (no patient initiation, full motor assist), active-assisted (partially initiated, partial motor assist) and active (fully performed by the patient, no motor assist), allowing patients to receive rehabilitation if they cannot participate due to delirium or sedation status.
⇒ The primary outcome is the Physical Function ICU Test-scored at 3 days post-ICU discharge, a reliable and valid measure in this population evaluated by blinded assessors unaware of treatment assignment.
⇒ Our study is limited by offering the intervention 5 days per week and not protocolising routine PT, however, we monitor frequency, time and types of rehabilitation activities.

INTRODUCTION

Advancements in medical care and technology have resulted in higher rates of survival from critical illness than in the past;[1 2] however, many survivors may face important physical disability up to 5 years after their discharge from the intensive care unit (ICU).[3] Muscle atrophy occurs quickly in the ICU. Leg muscles, accounting for 75% of total skeletal muscle mass,[4] are most vulnerable to weakness from immobility.[5] After 10 days, quadriceps size in critically ill patients decreases almost 18% from baseline, with most occurring in the first 72 hours.[6] Therefore, addressing immobility during critical illness represents an important opportunity to optimise patients' physical function.[7]

The Society of Critical Care Medicine guidelines recommends rehabilitation or mobilisation in the ICU for critically ill adults, as the benefits likely outweigh the risks.[8] However, the guidelines did not recommend specific types or timing of rehabilitation activities due to heterogeneous evidence. Documented barriers to physical rehabilitation in the ICU include invasive mechanical ventilation (MV) and receipt of sedative and paralytic medications.[9 10] In-bed cycle ergometry (thereafter termed cycling) is an underused, novel rehabilitation strategy that can address leg weakness. It can safely occur in a hospital bed while a patient is receiving MV and can accommodate patient participation, irrespective of sedation level.[11 12] The motorised cycle ergometer provides three possible activity modes including passive (no patient initiation, full motor assist), active-assisted (partially initiated, partial motor assist) and active (fully performed by the patient, no motor assist).[11] A meta-analysis of three single-centre randomised controlled trials (RCTs) comparing ICU cycling and control groups in 225 patients identified an uncertain effect on physical function at hospital discharge, however this was graded very low certainty evidence due to very serious imprecision.[13] Data on ICU cycling effectiveness are still required. Given a recent multicentre study that may have underestimated the effects of early rehabilitation activities on more proximal outcomes and safety concerns,[14] the need is pressing to identify safe and effective ICU rehabilitation strategies that mitigate post-ICU morbidity.

CYCLE (*C*ritical Care C*y*cling to improve *L*ower *E*xtremity strength) is a research programme studying cycling as a novel early rehabilitation modality in critically ill MV patients. In a cohort study of 33 medical-surgical critically ill patients and 205 cycling sessions, we detected no harm, and found that cycling started within 4 days of MV was feasible.[15] In 66 MV adults in seven centres, we completed the CYCLE Pilot RCT (NCT0237783) which evaluated the feasibility of a future large RCT comparing early cycling and routine physiotherapy (PT) to routine PT alone.[16] After completing the CYCLE Pilot RCT, we conducted CYCLE Vanguard to refine our ability to recruit patients, expand to international sites, and add a measurement timepoint 3 days post-ICU discharge. It was conducted following a protocol amendment to the CYCLE Pilot RCT, under the same trial registration (NCT0237783). CYCLE Vanguard is an internal pilot of the CYCLE RCT.

Objectives of the CYCLE RCT are to determine, in critically ill, MV adults: (1) Whether early in-bed cycling and routine PT compared with routine PT alone improves the primary outcome of physical function at 3 days after ICU discharge, and secondary outcomes of strength, physical function at different timepoints, frailty, psychological distress, quality of life, mortality and healthcare utilisation; and (2) The cost-effectiveness of cycling and routine PT compared with routine PT alone in this population. Here, we report according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)[17] and outcomes extension,[18] Consolidated Standards of Reporting Trials (CONSORT) and SPIRIT Extension for RCTs Revised in Extenuating Circumstances,[19] and Consensus on Exercise Reporting Template (CERT)[20] guidelines. We applied the CERT[20] exercise intervention template rather than the Template for Intervention Description and Replication checklist[21] because CERT explicitly evaluates supervision, tailoring and intervention dosage. A Pragmatic Explanatory Continuum Indicator Summary-2 is included as a online supplemental appendix.[19]

METHODS

Trial design

CYCLE is an international, 360-patient concealed open-label parallel-group RCT conducted in ICUs with blinded outcome assessments 3 days after ICU discharge. After informed consent, research coordinators randomise patients to receive 30 min per day of in-bed cycling (Cycling) with routine PT interventions compared with routine PT interventions alone (Routine) (online supplemental figure 1). Table 1 outlines the schedule for enrolment, interventions and assessments.

Trial setting and participants

CYCLE is enrolling patients in academic and community centres in three countries (Australia, Canada, USA). Our inclusion criteria are: adults (≥18 years old), who could ambulate independently before their critical illness (with or without a gait aid), ≤4 days of invasive MV and ≤7 days ICU length of stay, and an expected additional 2 days ICU stay. Exclusion criteria are any of the following: acute condition impairing patients' ability to cycle (eg, leg fracture), acute, proven or suspected central or peripheral neuromuscular weakness affecting the legs (eg, stroke, Guillain-Barré syndrome, spinal injury), traumatic brain injury, inability to follow commands in local language pre-ICU, severe cognitive impairment pre-ICU, temporary pacemaker (internal or external), suspected or proven pregnancy, expected hospital mortality >90%, equipment unable to fit patient's body dimensions (eg, leg amputation, morbid obesity), specific surgical exclusion as stipulated by surgery or ICU team, palliative goals of care, physician declines, or able to march on the spot at the time of screening. To ensure we start the intervention early, we also exclude patients with cycling therapy

Table 1 Time-events schedule

	Study period							
	Enrolment	Allocation	Postallocation					
Timepoint	ICU admission	0	In ICU	ICU awakening	ICU D/C	3 days post-ICU D/C	Hospital D/C	90 days postrandomisation
Enrolment								
Eligibility screening	X							
Informed consent	X							
Allocation		X						
Interventions								
In-bed cycling + routine PT			X	X	X			
Routine PT			X	X	X			
Assessments								
Severity of illness: APACHE II[52]	X							
Charlson Comorbidity Index[53]	X							
Functional Comorbidity Index[54]	X							
Clinical Frailty Scale[48]	X						X	X
Function: Katz Activities of Daily Living Scale[47]	X				X		X	
Patient-reported functional scale for the ICU[86]					X		X	X
Physical Strength and Function				X	X	X (blinded)	X (blinded)	
Physical Function ICU Test (scored)[31 32]				X	X	X (blinded, primary)	X (blinded)	
Medical Research Council Sum Score[87]				X	X	X (blinded)	X (blinded)	
30 s sit to stand[36]				X	X	X (blinded)	X (blinded)	
2 min walk test[42]					X	X (blinded)	X (blinded)	
Psychological distress: Intensive Care Psychological Assessment Tool[88]				X				
Health-related Quality of Life: EuroQol 5D-5L[44 45]					X		X	X
Hospital Anxiety and Depression Scale[43]								X
Data collection								
Baseline demographics	X							
Co-interventions			Document daily on CRFs					
Study-related serious adverse and adverse events			Document daily on CRFs					
Duration of mechanical ventilation					X			
ICU and hospital length of stay							X	
Mortality					X		X	X

APACHE II, Acute Physiology and Chronic Health Evaluation II; CRF, case report form; D/C, discharge; ICU, intensive care unit; PT, physiotherapy.

exemptions not resolved in the first 4 days of MV described in box 1.

Recruitment and randomisation

The CYCLE RCT registration includes both CYCLE Vanguard (NCT02377830), a 46-patient internal pilot enrolling between 1 November 2017 to 30 March 2018, and the full RCT (NCT03471247), enrolling from 15 October 2018 to 3 May 2023. Critical care research coordinators screen all MV adults in the ICU for trial eligibility. Once a potentially eligible patient is identified, the research coordinator contacts the most responsible physician for their assent to approach the patient or substitute decision-maker (SDM) for a priori written informed consent. In situations where an SDM provides consent,

Box 1 Temporary exemption criteria for in-bed cycling or routine physiotherapy interventions

Cycling or physiotherapy interventions **will not occur** if one or more of the following conditions are present:

1. Increase in vasopressor/inotrope within last 2 hours.
2. Active myocardial ischaemia, or unstable/uncontrolled arrhythmia per intensive care unit team.
3. Mean arterial pressure <60 mm Hg or >110 mm Hg or per treating team within the last 2 hours.
4. Heart rate <40 bpm or >140 bpm within the last 2 hours.
5. Persistent SpO_2<88% or per treating team within the last 2 hours.
6. Neuromuscular blocker within last 4 hours.
7. Severe agitation (Richmond Agitation and Sedation Scale >2 (or equivalent)) within last 2 hours).
8. Uncontrolled pain.
9. Change in goals to palliative care.
10. Team perception that in-bed cycling or therapy is not appropriate for other new reasons (eg, acute peritonitis, new incision/wound, known/suspected muscle inflammation (eg, rhabdomyolysis)).
11. Patient or proxy refusal.

patients are evaluated for capacity once they are alert and consent is requested to continue participation in the trial. Allocation is concealed via centralised randomisation. After informed consent, the research coordinator logs in to the web-based comprehensive, secure randomisation service (http://www.randomize.net/) to register the patient, and receives the randomisation assignment, stratified by centre and age ≥65 years or <65 years.

Procedures

Starting at enrolment, individual participants receive the randomised intervention 5 days per week (excluding weekends and statutory holidays), reflecting current PT staffing models[22] for the duration of their index ICU admission or to a maximum of 28 days, whichever occurs first. ICU physiotherapists or their delegates who have been trained on the protocol including how to use the cycle ergometer deliver the intervention as part of their usual clinical role. Both randomised interventions can occur while a patient is sedated. These interventions can also occur if a patient is delirious and presents with a Richmond Agitation and Sedation Scale[23] of 2 or less (see box 1). If a patient is discharged from the ICU, but is readmitted within 72 hours and is still within the 28-day protocol, the randomised intervention resumes if they still meet the criteria for delivery of the intervention. After 28 days, all patients still in ICU receive routine PT activities for their continued ICU admission as per institutional policy. Patients randomised to routine PT activities will not receive in-bed cycling throughout their entire hospital stay.

We conduct outcomes assessments at ICU awakening, ICU discharge, 3 days post-ICU discharge, hospital discharge and 90 days postrandomisation (further described in online supplemental figure 1). During the randomised intervention sessions, physiotherapists or their delegates review patients for the ability to participate in the ICU awakening assessment. We define readiness for the awakening assessment based on the patient's ability to follow three of five simple commands (open/close your eyes, look at me, open your mouth and stick out your tongue, nod your head, raise your eyebrows when I have counted to 5).[24]

Interventions and comparator

Cycling arm

Patients receive 30 min/day of cycling in addition to routine PT activities, 5 days per week, during their ICU stay. Cycling occurs for a maximum of 28 days as outlined above, or until the patient can march on the spot for two consecutive days, whichever occurs first. We aim for participants to start the cycling intervention within the first 4 days of MV, even if they are receiving sedative infusions, and to complete as much active cycling as possible during each 30 min session. We use a specialised in-bed cycle ergometer (ie, RT300 supine, Restorative Therapies, Baltimore, Maryland, USA), which provides passive, active-assisted and active cycling. Patients are positioned semirecumbently[11] per ventilator-associated pneumonia prevention guidelines.[25 26]

Given the dynamic nature of critical illness, we review enrolled patients daily for temporary PT exemptions precluding cycling described in box 1. For example, we do not offer cycling on a day in which a patient has cardiac or respiratory instability, active major bleeding, severe agitation or a new condition interfering with cycling. During each cycling session, patients are supervised by a physiotherapist or their delegate and continuously monitored for safety (eg, vital signs, catheter or tube dislodgement). We document reasons for terminating a cycling session, including signs of cardiac or respiratory instability, and catheter or tube dislodgement. Box 2 details stopping criteria for the trial intervention sessions. We describe additional details in the accompanying text to the graphical representation in online supplemental figure 1.

Box 2 Indications for terminating cycling or routine physiotherapy sessions

1. Unplanned extubation.
2. Cardiac arrest.
3. Fall to knees during physiotherapy/rehabilitation activities.
4. Concern for myocardial ischaemia or suspected new unstable/uncontrolled arrhythmia.
5. Sustained symptomatic bradycardia (<40 bpm) or tachycardia (>140 bpm).
6. Hypertension (mean arterial pressure >120 mm Hg).
7. O_2 desaturation below baseline.
8. Marked ventilator dyssynchrony.
9. Removal or dysfunction of intravascular catheter (eg, central venous catheter, arterial line).

Routine PT arm

Patients receive PT activities per current institutional practice. In-bed cycling was not part of routine care at any site. Routine PT activities are based on a patient's level of alertness, and include movements to maintain or increase limb range of motion and strength, in-bed and out-of-bed mobility, ambulation, and assistance with optimising airway clearance and respiratory function.[27–30] We use similar criteria as those in cycling to terminate routine PT sessions (box 2).

Outcomes

The primary outcome is the Physical Function ICU test-scored (PFIT-s)[31] measured at 3 days after ICU discharge by assessors blinded to treatment allocation. The PFIT-s is a reliable and valid four-item scale (arm and leg strength, ability to stand, and step cadence) with a score range from 0 to 10; higher scores represent better function. It includes functional items, was developed in an ICU population and can be measured serially over time. We chose the PFIT-s because we expect all ICU patients will be able to complete part of the assessment (eg, arm or leg strength), even if they cannot stand. The PFIT-s has strong psychometric properties (reliability range=0.996 to 1.00;[31 32] convergent validity with the 6 min walk distance and muscle strength).[31] The assessors are hospital physiotherapists, occupational therapists or rehabilitation assistants trained to administer the study assessments by the CYCLE methods centre team. Assessors conduct the outcomes evaluations as part of their usual clinical role.

Primary outcome timing: We revised the primary outcome endpoint from hospital discharge in the Pilot RCT to 3 days after ICU discharge in CYCLE Vanguard and CYCLE RCT, after observing that survivors in the pilot RCT had an additional median 11.5 days hospital stay after ICU discharge.[16] Our main reasons are: (1) 3 days post-ICU discharge is proximal to the intervention; and (2) Prior studies documented variable rehabilitation delivery post-ICU that may contaminate later evaluations.[33] Since muscle strength can decrease quickly due to inactivity and rehabilitation is variable on the wards, any effect of treatment in the ICU may be affected by activities on the ward. We thus adjusted the timing of our primary outcome more proximal to the end of the study intervention.

Secondary outcomes include performance-based measures of muscle strength (Medical Research Council Sum Score)[34 35] and function (30 s sit-to-stand test,[36] 2 min walk test,[37]) each of which have age-based and sex-based reference values, and good reliability in critically ill or frail elderly populations.[38 39] Patient-reported measures include the Patient-Reported Functional Scale-ICU,[40 41] Intensive Care Psychological Assessment Tool,[42] Hospital Anxiety and Depression Scale[43] and health-related quality of life (EuroQol 5D-5L).[44–46] Other measures include the Katz Activities of Daily Living (ADL) Scale,[47] frailty (Clinical Frailty Scale),[48] mortality (ICU, hospital, 90 days postrandomisation), hospital discharge location, and healthcare utilisation (eg, length of MV, ICU and hospital length of stay (LOS)), mortality (ICU, hospital), and information on the intervention use.

Blinding

To protect against detection bias, we trained a core group of assessors (eg, physiotherapists, occupational therapists or rehabilitation assistants) at each hospital—blinded to patients' treatment allocation—to conduct outcome measures 3 days post-ICU discharge and at hospital discharge. If it is not possible to secure a blinded outcomes assessor due to circumstances beyond our control (eg, unexpected patient discharge from hospital, assessor illness), we assess outcomes with an unblinded assessor. In this open-label trial, study participants, patients' family members, ICU physiotherapists, research coordinators, bedside staff, physicians and site investigators are aware of patients' treatment assignment.

Sample size

The sample size of 360 patients (180 patients per group) is based on identifying a 1.0 point mean difference between the Cycling and Routine groups for the PFIT-s 3 days after ICU discharge,[49] corresponding to the minimal clinically important difference identified in psychometric studies.[31 50] By logistic regression, the analysis of patients enrolled in two of our previous pilot studies identified that each 1.0 point increase in PFIT-s at ICU discharge was associated with a 40% reduction in the composite outcome of death, readmission to ICU or need for paid assistance after hospital discharge.[49] Based on a SD of 2.5 points at ICU discharge,[15 51] a 1.0-point difference between groups[31 49 50] and 90% power (0.05 α), we need to randomise and analyse 266 patients (133 per group). Based on pilot data, we anticipate 25% ICU mortality and 1% mortality in the first 3 days post-ICU discharge. Among ICU survivors, we anticipate 5% missed primary outcome assessments at 3 days post-ICU, and 5% unblinded assessments; thus, we will recruit 360 patients overall.

DATA COLLECTION, MANAGEMENT AND ANALYSIS

Data collection

Research coordinators collect baseline data including patient demographics, reason for ICU admission, medical versus surgical status, severity of illness (eg, Acute Physiology and Chronic Health Evaluation II),[52] comorbidity (eg, Charlson Comorbidity Index,[53] Functional Comorbidity Index[54]) and prehospital function (eg, Katz ADL)[47] on CYCLE case report forms. ICU-related variables captured daily from the medical record during the patient's ICU stay include severity of illness (eg, Multiple Organ Dysfunction Score),[55] ICU interventions (eg, MV, vasoactive agents), drug exposure and nutrition. We collect relevant co-interventions that may impair patient function, including receipt of corticosteroids and neuromuscular blocking agents, and duration of bed-rest. We

also record the frequency, type and duration of the PT sessions, and document activities (eg, passive or active range of motion, bed mobility and transfers, ambulation) received in the ICU. For performance-based and patient-reported outcomes, we document reasons for missing assessments.

If a participant withdraws from the trial, we discontinue all trial procedures, however, we use data collected up to the time of withdrawal and include these data in the group to which they were randomised. If a participant withdraws from the trial, we request permission for medical record review to document vital status.

Data management

Completed case report forms are entered into a secure web-based electronic data capture system—iDataFax (DF/Net Research, Seattle, Washington, USA; dfnetresearch.com). The iDataFax server systems are maintained in two separate and secure physical locations providing both data security and redundancy. We limit study data access to the principal investigator, site investigators, site research coordinators, CYCLE RCT Methods Centre staff and biostatistician. Unauthorised access to the system is restricted by means of a firewall and data encryption protection applied to all communications. We retain data for 15 years, or as per institutional requirements. Full data management details will be reported elsewhere.

Statistical data analysis

Trial reporting will follow the CONSORT guideline.[56] For both the intervention and comparator groups, we will measure protocol adherence by determining the total planned randomised intervention days, and sum of days where the patient received the randomised intervention as planned (eg, days where the patient received the randomised intervention or had a temporary exemption).

Primary outcome

We will conduct linear regression to determine if there is a difference in PFIT-s Score at 3 days after ICU discharge between the Cycling and Routine groups. Patients will be analysed according to the group to which they were randomised. We will use multiple imputation to manage missing data.[57] We will conduct sensitivity analyses of the primary outcome to assess the robustness of our findings (eg, per protocol analysis, different methods of handling missing data). We will conduct a per-protocol safety analysis.

We will conduct three subgroup analyses: (1) Age <65 years versus ≥65 years, (2) Frailty pre-ICU admission or not (baseline CFS ≤4 and ≥5), and (3) Sex (male vs female). Since older patients are under-represented in ICU trials,[58] and no trials have specifically studied early cycling in the critically ill older adults,[59] a subgroup analysis will help to identify any age-related differences in response to rehabilitation. Critically ill patients with frailty have worse outcomes,[60] however the effects of exercise on patients with frailty are unclear. Females experience more quadriceps muscle atrophy than men in the ICU[61] and are more likely to develop ICU-acquired weakness.[62] We hypothesise that adults ≥65 years old, patients with baseline frailty and women will have worse outcomes. We will evaluate our findings with the Instrument to assess the Credibility of Effect Modification Analysis.[63]

To conduct the subgroup analyses, we will perform multiple linear regressions including randomised treatment, the subgroup variable, and the interaction between the two as independent variables. The criterion for statistical significance for subgroup analyses will be set at 0.10. We will not be adjusting these for multiple testing since they are exploratory.

Secondary outcomes

For continuous outcomes, we will conduct linear regression analyses, and for dichotomous outcomes (eg, mortality), Cox proportional hazards analyses or simple logistic regression, as appropriate.

For all analyses, we will report estimate of effects, corresponding 95% CI and associated p values. P values will be reported to three decimal places with those less than 0.001 reported as p<0.001. All analyses will be performed using SAS V.9.4 (Cary, North Carolina). We will also perform an economic evaluation, with details reported in a separate paper.

Interim analysis

We conducted one interim analysis after 180 patients[64] (half of our sample) were discharged from hospital, to assess for harm and benefit. We used conservative statistical guidelines for data monitoring based on the modified Haybittle-Peto rule.[64] To maintain the overall type-I error rate (ie, α), we evaluated the primary endpoint using a fixed simple conservative α=0.001 for the interim analyses and will use α=0.05 for the final analysis.

DATA MONITORING

The CYCLE RCT Methods Centre will oversee enrolment rates and conduct periodic central statistical monitoring of cycling adherence and outcome ascertainment. With these data, we provide individualised centre feedback and identify strategies to optimise cycling delivery and cohort retention. The CYCLE Steering Committee is a subgroup of co-investigators including the principal investigator, senior intensivists and trialists, the study biostatistician, selected site leads representing the three countries, two languages, and rehabilitation trial experience, and the Methods Centre coordinator who offers guidance and input on any necessary protocol revisions. An independent Data Safety and Monitoring Board (DSMB) oversees CYCLE, including a senior biostatistician, and two ICU physicians with trial expertise. A DSMB Charter guides their process to assess the progress of the trial.[65]

Box 3 Table of severe and serious adverse events occurring during or immediately after Cycling or Routine physiotherapy (PT)

Severe adverse events
1. Unplanned extubation.
2. Cardiac arrest.

Serious adverse events
3. Fall to knees during routine PT/rehabilitation activities.
4. Concern for myocardial ischaemia or suspected new unstable/uncontrolled arrhythmia.
5. Sustained symptomatic bradycardia (<40 bpm) or tachycardia (>140 bpm) and clinical deterioration attributed to in-bed cycling or routine PT/rehabilitation activities.
6. Sustained hypertension (mean arterial pressure >120 mm Hg) and clinical deterioration attributed to in-bed cycling or routine PT/rehabilitation activities.
7. Sustained O_2 desaturation below baseline and clinical deterioration attributed to in-bed cycling or routine PT/rehabilitation activities.
8. Marked ventilator dyssynchrony.
9. Bleeding at femoral catheter site attributed to in-bed cycling or routine PT/rehabilitation activities.
10. New bruising at femoral catheter site attributed to in-bed cycling or routine PT/rehabilitation activities.
11. Removal or dysfunction of intravascular catheter (eg, central venous catheter, arterial line) attributed to in-bed cycling or routine PT/rehabilitation activities.

Monitoring for harm

ICU rehabilitation interventions have been shown to be safe with an overall low rate of adverse events, however recent studies raised concerns for patients randomised to rehabilitation intervention groups.[14 66] A systematic review of 48 studies and 7456 patients documented a 2.6% cumulative incidence of adverse events during an ICU rehabilitation intervention.[67] We conducted a systematic review of 10 cycling studies, 396 patients and 3117 ICU cycling sessions, and identified five patients each having experienced one adverse event for a 0.16% event rate.[13] In 11 cycling studies, no catheter or endotracheal tube dislodgements occurred.[11 16 68–76] A retrospective chart review of 181 patients and 541 cycling sessions identified 1 patient who experienced one adverse event for a rate of 0.2%.[77] In our 33-patient prospective single-centre study, 3 patients terminated four sessions across 205 cycling sessions due to safety concerns (2.0%; 95% CI 0.8% to 4.9%); no unplanned extubations or device dislodgements occurred.[70] The 66-patient, multicentre CYCLE Pilot RCT documented that only one person experienced early termination across 146 cycling sessions.[16] Based on the literature, and the extensive training we provide to expert physiotherapists, we expect few safety risks to patients.

Box 3 outlines the adverse events we document in this trial. We document adverse events if they occur during or immediately after in-bed cycling or routine PT interventions, are attributable to the randomised intervention, and result in clinical deterioration. Severe adverse events include cardiac arrest and unplanned extubation during cycling or routine PT. Research coordinators record severe adverse events, serious adverse events, and the consequences of these events on the case report forms and immediately report to the patient's clinical team. The DSMB receives notice of severe adverse events from the Methods Centre within 24 hours, and receives safety reports of the events outlined in box 3 every 6 months.

Ethics and dissemination

CYCLE is approved by the Research Ethics Boards (REB) of all participating centres and Clinical Trials Ontario (Project 1345). This paper summarises the REB-approved document (Version 4, date: 3 August 2022). We will disseminate study results regardless of the direction or magnitude of effect to key stakeholders (eg, critical care clinicians, physiotherapists and trialists, research funders, and the public) through local, national and international presentations, and peer-review publications. We will also disseminate information via the CYCLE website (http://www.icucycle.com/). We will follow the International Committee of Medical Journal Editors for authorship,[78] and trial data will be made available, on reasonable request, 1 year after the primary article publication.

Extenuating circumstances due to the COVID-19 pandemic

Like many trials, the global COVID-19 pandemic imposed extenuating circumstances on CYCLE, and ICUs worldwide prioritised COVID-19-related research and clinical care for critically ill patients with COVID-19.[79 80] After 17 March 2020, we paused recruitment in all recruiting centres due to institutional directives prohibiting non-COVID clinical research. Our first site resumed recruitment in June 2020. While no changes were made to the CYCLE protocol, our response to the pandemic is published elsewhere.[81] Patients with COVID-19 were not enrolled in CYCLE due to the high clinical workloads and initial concerns for the need to sterilise the ergometer.

DISCUSSION

Survivors of critical illness often face a long road of physical, cognitive and psychological recovery.[82] Compared to 2011, by 2026, it is estimated that the demand for ICU services will increase by 40%, and more survivors will have post-ICU disability.[83] Systematic reviews of ICU physical rehabilitation trials have reported discordant results for the effectiveness of these interventions.[67 84] Given anticipated increases in required critical care services, the need is pressing to identify effective ICU rehabilitation strategies that mitigate post-ICU morbidity.

There are several strengths of this research. Cycling overcomes some challenges of traditional rehabilitation, as it can occur when patients are in bed and even when they are deeply sedated, unconscious or minimally interactive.[12] By targeting leg muscles, which are most vulnerable to atrophy due to immobility, we are attempting to minimise muscle and strength loss during patients' ICU

stay. Front line, experienced ICU therapists in academic and community settings incorporate this novel technology as part their clinical care, in anticipation of future knowledge translation efforts. We rigorously document PT activities in the comparison group, and we measure our primary outcome proximal to the intervention exposure. By using the SPIRIT[17] and CERT[20] reporting guidance, this research protocol addresses previously documented gaps in ICU rehabilitation intervention reporting.[85]

CYCLE has limitations. Patients were not involved in the development of this research. We exclude patients who have received MV for more than 4 days, and those with persistent exemptions within the first 4 days of MV (eg, respiratory or cardiac instability), acknowledging that these patients are also at risk of developing ICU-acquired weakness. CYCLE uses specialised in-bed ergometers, which are not available in all ICUs, and requires additional therapist time to provide the intervention, limiting the generalisability of results to similarly resourced settings. Our intervention is limited to weekdays, corresponding to models of care in participating centres. We do not protocolise routine care PT at each site, however we incorporate rigorous tracking of the frequency, duration and activity types of usual care.

CYCLE engages the largest number of ICUs to date in a rigorous evaluation of in-bed cycling in the field of critical care rehabilitation. If early cycling during critical illness improves short-term physical and functional outcomes, it could accelerate recovery and reduce long-term disability in ICU survivors. Results from the CYCLE RCT will advance healthcare knowledge by informing the early rehabilitation management of previously ambulatory critically ill patients.

Author affiliations
[1]School of Rehabilitation Science, McMaster University, Hamilton, Ontario, Canada
[2]Physiotherapy, St Joseph's Healthcare Hamilton, Hamilton, Ontario, Canada
[3]Research Institute of St. Joe's, Hamilton, Ontario, Canada
[4]Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada
[5]University Health Network, Toronto General Research Institute, Toronto, Ontario, Canada
[6]Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Ontario, Canada
[7]Department of Medicine, McMaster University, Hamilton, Ontario, Canada
[8]Medicine, St. Joseph's Healthcare Hamilton, Hamilton, ON, Canada
[9]Department of Medicine, Western University, London, Ontario, Canada
[10]Department of Epidemiology and Biostatistics, Western University, London, Ontario, Canada
[11]Li Sha King Knowledge Institute, St Michael's Hospital, Toronto, Ontario, Canada
[12]Interdepartmental Division of Critical Care, Unity Health Toronto, Toronto, Ontario, Canada
[13]Consultation-Liaison Psychiatry Service, St Joseph's Healthcare Hamilton, Hamilton, Ontario, Canada
[14]Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, Ontario, Canada
[15]Department of Physiotherapy, Austin Health, Heidelberg, Victoria, Australia
[16]Department of Physiotherapy, The University of Melbourne, Melbourne, Victoria, Australia
[17]Departments of Medicine and Orthopedic Surgery, Duke University, Durham, North Carolina, USA
[18]Department of Anesthesiology, Universite de Sherbrooke Faculte de medecine et des sciences de la sante, Sherbrooke, Quebec, Canada
[19]Centre de recherche du CHUS, Sherbrooke, Quebec, Canada
[20]Medicine, Universite de Sherbrooke, Sherbrooke, Quebec, Canada
[21]Division of Critical Care Medicine, Niagara Health System, St Catharines, Ontario, Canada
[22]Anesthesiology and Intensive Care, Faculty of Medicine, Université Laval, Quebec, Québec, Canada
[23]Family Medicine and Emergency Medicine, Faculty of Medicine, Université Laval, Quebec, Québec, Canada
[24]Department of Medicine (Critical Care), University of Ottawa, Ottawa, Ontario, Canada
[25]School of Epidemiology and Public Health, University of Ottawa, Ottawa, ON, Canada
[26]Department of Critical Care Medicine, Queen's University, Kingston, Ontario, Canada
[27]Critical Care Division, Department of Medicine, Hôpital du Sacré-Coeur de Montréal, Montreal, Québec, Canada
[28]Programs for the Assessment of Technology in Health, Research Institute of St. Joe's Hamilton, Hamilton, Ontario, Canada
[29]Interdepartmental Division of Critical Care, University of Toronto, Toronto, Ontario, Canada
[30]Sinai Health System, Toronto, Ontario, Canada
[31]Department of Medicine, University of Maryland Medical Center, Baltimore, Maryland, USA
[32]Division of Pulmonary and Critical Care Medicine, University of Maryland School of Medicine, Baltimore, Maryland, USA
[33]Medicine, Brantford General Hospital, Brantford, Ontario, Canada

Twitter Michelle E Kho @khome, Alison Fox-Robichaud @drfoxrob, Ian M Ball @Ball, Patrick Archambault @patarchambault and Heather O'Grady @ogradyhk

Acknowledgements CYCLE Steering Committee Members: Sue Berney, Karen Burns, Deborah Cook, Frederick D'Aragon, Margaret Herridge, Amy Pastva, Andrew Seely, Lehana Thabane, Alexander Molloy (Research Coordinator). CYCLE Data Safety and Monitoring Committee: Eleanor Pullenayegum (Chair), Marc Moss, Nicholas Hart. The authors thank Ms Laurie Lee and the Canadian Critical Care Trials Group Grants and Manuscripts Committee for helpful comments on our manuscript. The authors thank the following participating sites, site principal investigators (PIs), additional co-investigators, physiotherapists (ICU PTs, blinded assessors), research coordinators (RCs), research assistants (RAs), administrative personnel (Admin) and students who have or will contribute to the CYCLE RCT: McMaster University, Hamilton, Ontario, Canada: Diane Heels-Ansdell (Statistician), Quazi Ibrahim (Statistical Analyst), Lisa Buckingham (Database Management), Jean-Eric Tarride (Health Economist), Lehana Thabane (Lead Biostatistician), Julie Reid (RC), Stacy Priest (RA), Marilyn Swinton (RC), Jennifer Hoogenes (Research Associate); St Joseph's Healthcare, Hamilton, Ontario, Canada: Site PI: Michelle Kho; Intensivists: Deborah Cook, Jill Rudkowski; ICU PTs: Daana Ajami, Laura Camposilvan (PT assistant), Magda McCaughan, Kristy Obrovac, Wendy (Perry) Galloway; Blinded assessors: Miranda Prince (PT assistant), Wendy Galloway, Christine Neilson, Tina Memarzadeh, Christina Murphy, Frances Garner, Diana Hatzoglou, Parth Suthar; RCs: France Clarke, Laurel Kelly, Geoff Strong, Laurel Kelly, Abby Hurd, Aileen Costigan, Alex Molloy; RAs: Joanna Semrau, Ayesha Ahamed Sadique, Quincy Hannah, Devin McCaskell, Amy Connell, Selina Chow, Michael Ciancone, Arthi Kunasingam, Vanessa Ng, Daniella Russo, Alyson Takaoka; PT students: Ebuka Osuji, Alli Nikolovski, Natalie Constantin, Alexandra Young, Catherine Hare; Graduate student: Heather O'Grady; Clinical Psychologist: Joseph Pellizzari; Juravinksi Hospital, Hamilton, Ontario, Canada: Site PIs: Tim Karachi, Bram Rochwerg, Joanna Dionne; ICU PTs: Tania Brittain, Leigh-Ann Niven, Andrea Galli, Shivaun Davidson, Chris Farley, Cortney Armstrong, Andrea Galli, Leigh Ann Niven, Jessica Temesy; Blinded assessors: Helen Bishop, Shannon Earl (PT assistant), Chelsea Hale, Gillian Manson, Jesse Coopman; RCs: Tina Millen, Carly DiDonato; RAs: Lauren Locco, Ryan Vaisler, Alia Khalid; Hamilton General Hospital, Hamilton, Ontario, Canada: Site PI: Alison Fox-Robichaud; ICU PTs: Ashley Eves, Elise Loreto, Anastasia Newman, Judi Rajczak, Sarah Lohanyai, Ivone Ivone, Melissa Richardson, Angela Miller, Julie Reid; Blinded assessors: Jennifer Duley, Sue Mahler, Matthew McCaffrey, Jessica Pilon-Bignell, Kristina Saric, Jacqueline Hockridge, Miranda Weins, Lauren VanDerLelie, Randy Nguyen; RCs: Ellen McDonald, Yasmin Sivji, Hassan Kashif, Makena Pook, Lori Hand, Uzma Saeed; RA: Lisa Klotz; Admin: Tracey Reynolds; Brantford General Hospital, Brantford ON, Canada: Site PI: Brenda Reeve; ICU PTs: Charles Landoni, Stephanie Tompkins (PT assistant), Tara Porter (PT assistant), Kelly Cooke (PT assistant); Blinded assessors: Karla Gormen, Stephanie Pedley (PT assistant); RC: Will Dechert; RAs: Mary Copland, Courtney Robb; Niagara

Health St. Catharines, St. Catharines, Ontario, Canada: Site PIs: Erik Duan, Jennifer Tsang; ICU PTs: Angie Dueck, Christina Carile, Daniel Aranda, Kathleen Reardon, Debbie Fenwick, Sylvie LeBlanc, Cassandra Lemieux; Blinded assessors: Jennifer Wagar, Liz Bitzer; RCs: Lisa Patterson, Mercedes Camargo-Penuela; RAs: Diane Nielsen-Smith, Laurie Sadowski, Jane Jomy, Christine Cavers, Aarthy Ehaparaseelan, Fatima Mehmood, Julia Becevel; St. Michael's Hospital, Toronto, Ontario, Canada: Site PIs: Karen Burns, Jan Friedrich, Claudia Dos Santos; ICU PTs: Deanna Feltracco, Christine Leger, Sarah Brown, Caity Heath, Kara Morrison, Olivia So, Kristen Paguiligan, Nikita Gandhi, Siobhan Gallagher; Blinded assessors: Anna Michalski, Meaghan Zsolt, Amber Robertson, Meghan Robson, Diana Horobetz, Natalia Zapata, Verity Tulloch, and Rose Lee, Carina Orschel, Amber Robertson; RCs: Marlene Santos, Gyan Sandhu, Orla Smith, Kurtis Salway; RAs: Imrana Khalid, Jennifer Hodder; Mount Sinai Hospital, Toronto, Ontario, Canada: Site PI: Sangeeta Mehta; ICU PTs: Kristen Baxter, Nick Bradley; Blinded assessor: Celine Nathoo; RC: Sumesh Shah; London Health Sciences Centre – Victoria Hospital, London, Ontario, Canada: Site PI: Ian Ball; ICU PTs: Tania Larsen, Jennifer Curry, Kristen Abercrombie, Erin Blackwell-Knowles; Blinded assessors: Jennifer Jackson, Lori Vantfoort, Christine Smit, Michele Isenor, Kate Neumann, Maciej Prajs; RC: Eileen Campbell; RAs: Rebecca Rondinelli, Athena Ovsenek, Laura Winters; Kingston Health Sciences Centre, Kingston, Ontario, Canada: Site PIs: John Muscedere, Gordon Boyd, John Drover, David Maslove, Stephanie Sibley; ICU PTs: Mimi Anderson, Al MacVicar, Alyssa Whelan, Angela Romero (PT Assistant); Blinded assessors: Ashley Woodroffe-McClintock, Diane Challis, Ashley Bridgen, Stephanie Bryan, Susan Surca, Kathleen Perri; RCs: Miranda Hunt, Tracy Boyd, Michaela Hanley; Managers: Kimberley Smith, Donna Leybourne; The Ottawa Hospital – Civic Campus, Ottawa, Ontario, Canada: Site PI: Shane English; ICU PTs: Kristy Steeves, Josée Lamontagne, Rachel Goard, Jamie Emery, Lyne Marum; Blinded assessors: Karen Saab, Shelley DeRooy, Caroline Rivard, Valerie Reid, Nick Warzee; RCs: Brigette Gomes, Irene Watpool, Jessica Haines; RAs: Heather Langlois, Shelley Acres, Rachel Goard; The Ottawa Hospital – General Campus, Ottawa, Ontario, Canada: Site PI: Andrew Seely; ICU PTs: Sal Patten, Michelle Cummings, Rose Johnston; Blinded assessors: Tanya Forward; RC: Rebecca Porteous, RAs: Liane LeClair, Sydney Miezitis, Nik Altehoefer Hastings, Kaitlyn Montroy; Hôpital du Sacré-Cœur de Montréal, Montreal, Quebec, Canada: Site PIs: Karim Serri, David Wiliiamson; ICU PTs: Xavier Bernet, Jennifer Bessette, Josianne Charbonneau, Vickie Bergeron, Roxanne Martineau, Amilie Langlois, Lysandre Lamontagne-Montminy; Blinded assessors: Genevieve Beauchamp-Vien, Huy-Thanh Bach, Marianne Dénommée, Marie-Carmel Gédéon, Hussein El Maoula, Jeanne Lacombe, Sarah Garant Gignac; RCs: Virginie Williams; RAs: Julia Lainer Palacos, Mathilde Duplaix, Sabrina Araujo de Franca, Patricia Martinez Barrios; Hôpital Fleurimont, Sherbrooke, Quebec, Canada: Site PIs: Frederick D'Aragon, François Lamontagne, Brian Grondin-Beaudoin, Marc-Andre Leclair, Yannick Poulin; ICU/Blinded assessors: Christine Lafond, Pascale Girard, Chantal Guillemette, Cindy Lessard, Jeff Lacouvee; RCs: Marie-Pier Bouchard, Julie Bélisle, Marilene Ladouceur, Joannie Marchand, Line Côté, Elaine Carbonneau, Justine Grégoire; Admin: Marie Michelle-Watt; Hôpital Hôtel-Dieu de Lévis - CISSS Chaudière-Appalaches, Lévis, Quebec, Canada: Site PI: Patrick Archambault; ICU PTs: Karen Bolduc, Mylène Rochon, Phillip Quessy; Blinded assessors: Stephane Guilbault, Claudia Hamel, Isabelle Robitaille, Jessika Giguere RCs: Estel Duquet-Deblois, Julien Le Beller, Annick Jutras, Monia Noel-Hunter, Émilie Côté, Martyne Audet; RAs: Alexandre Pepin, Rosalie Beaudoin, Erik Celikovic, Arianne Boudreault, Lise Lavoie, Veronique Julien, Annie-Julie Belanger, Vanessa Couture, Justine Ruel, William Baron, Andréane Bédard, Mireille Boutin, Bao Tran Tran, Laurie Couture, Coralie Mus, Andréanne Bernatchez; University of Maryland Baltimore, Baltimore, Maryland, USA: Site PI: Avelino Verceles; ICU PTs: Josh Vogel, Mary Hoyt, Chris Wells; Blinded assessors: Suzanne Dunn, Alaina Brescia, Katie DiAnthony, Eileen Connor; RCs: Olga Kolesnik, Thelma Harrington, Anu Varghese, Maura Deeley, Valeriya Rodionova, Francisco Torres; RAs: Harsh Patel, Zain Nagaria, Deana Tran, Hassan Haji, Rohun Dalal; Duke University Hospital, Durham, North Carolina, USA: Site PI: Amy Pastva; Co-I: Paul Wischmeyer; ICU PTs: Karen Bienenstock, Grant Bitzer, Sara Dorn, Michelle Iorio, Brett Koermer, Jessie Poteat, Lane White; ICU OTs: Samantha Hoyle, Kyrsten Spurrier, Meg Williamson; Blinded assessors OTs: Melissa Kandel, Anne Kelly; Blinded Assessors PTs: Tamara Klintworth-Kirk, Karlyn Schiltgen; RCs: Karen Clemmons, Jennifer Kaisen, Brett Koermer, Cara Mariani, Christy Peterson; Andreea Podgoreanu, Hayden Rigsbee, Katherine Sweeney; RA PTs: Amanda Beaty, Grant Bitzer, Summer Collins, Anne Davenport, Grace Ditzenberger, Hannah McHugh, Melissa Minniti, Nicolle Stein; Gabriel Streisfeld; Admin: Alicja Szydlowska; Austin Health, Melbourne, Victoria, Australia: Site PI: Sue Berney; ICU PTs: Joleen Rose, Danielle Dunlop, Hannah Verspey, Nicola Burgess, Luke McDonald, Liv Ramsden, Tony Yuan; Blinded assessors: Estelle Kyriacou, Laura Montgomery, Tessa O'Dea, Chris Ramlu, Caitlin Devanny, Kylie Graham, Laura Lehany, Lexie Mitris, Rebecca Parsons, Stephanie Biffaro, Zoe Bacolas, Celeste Plant; RCs: Ally Macdonell, Steph Jameson, Thomas Rollinson, Sarah Retica, Ashleigh Donavon.

Contributors Conceptualisation: MEK, JCRe, AJM, MSH, AJS, JRu, DH-A, TK, AF-R, IB, KEAB, SB, AMP, BR, FD, FL, EHD, JLT, LT and DJC. Data curation: JCRe, AJM, LB, DH-A, HKO, LK, GS and AHH. Formal analysis: MEK, MSH, AJS, DH-A, KEAB, SB, AMP, BR, FD, FL, JM, J-ET, HKO, LT and DJC. Funding acquisition: MEK, IMB and DJC. Investigation: MEK, JCRe, AJM, AJS, TK, AF-R, IB, KEAB, CF, SB, AMP, BR, FD, FL, EHD, JLT, PA, SWE, JM, KS, ACV, BR, LK, GS, AHH and DJC. Methodology: MEK, JCRe, AJM, MSH, AJS, JCRu, DH-A, TK, AF-R, IB, KEB, SB, AMP, BR, FD, FL, J-ET, LT and DJC. Project administration: MEK, JCRe, AJM, HKO, LK, GS and AHH. Resources: MEK, IMB and DJC. Software: LB, DH-A and GS. Supervision: MEK, MSH, AJS, KEAB, SB, AMP, FL, JM, LT and DJC. Writing (original draft): MEK and JCRe. Writing (review) and editing: MEK, JCRe, AJM, MSH, AJS, JCRu, LB, DH-A, TK, AF-R, IMB, KEAB, JP, CF, SB, AMP, BR, FD, FL, EHD, JLT, PA, SWE, JM, KS, J-ET, SM, ACV, BR, HKO, LK, GS, AHH, LT and DJC.

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ORCID iDs
Michelle E Kho http://orcid.org/0000-0003-3170-031X
Alison Fox-Robichaud http://orcid.org/0000-0001-9912-3606
Jennifer L Y Tsang http://orcid.org/0000-0002-1809-0505
Shane W English http://orcid.org/0000-0002-9477-6146
Lehana Thabane http://orcid.org/0000-0003-0355-9734
Deborah J Cook http://orcid.org/0000-0002-4087-543X

REFERENCES

1 Esteban A, Frutos-Vivar F, Muriel A, *et al*. Evolution of mortality over time in patients receiving mechanical ventilation. *Am J Respir Crit Care Med* 2013;188:220–30.
2 Kaukonen K-M, Bailey M, Suzuki S, *et al*. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012. *JAMA* 2014;311:1308–16.

3 Herridge MS, Tansey CM, Matté A, *et al*. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med* 2011;364:1293–304.
4 Gallagher D, Visser M, De Meersman RE, *et al*. Appendicular Skeletal muscle mass: effects of age, gender, and Ethnicity. *J Appl Physiol (1985)* 1997;83:229–39.
5 Brower RG. Consequences of bed rest. *Crit Care Med* 2009;37:S422–8.
6 Puthucheary ZA, Rawal J, McPhail M, *et al*. Acute Skeletal muscle wasting in critical illness. *JAMA* 2013;310:1591–600.
7 Fan E, Dowdy DW, Colantuoni E, *et al*. Physical complications in acute lung injury survivors: A two-year longitudinal prospective study. *Crit Care Med* 2014;42:849–59.
8 Devlin JW, Skrobik Y, Gélinas C, *et al*. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Critical Care Medicine* 2018;46:e825–73.
9 Berney SC, Harrold M, Webb SA. Intensive care unit mobility practices in Australia and New Zealand: a point prevalence study. *Crit Care Resusc* 2013;15:260–5.
10 Nydahl P, Ruhl AP, Bartoszek G, *et al*. Early mobilization of mechanically ventilated patients: a 1-day point-prevalence study in Germany. *Crit Care Med* 2014;42:1178–86.
11 Burtin C, Clerckx B, Robbeets C, *et al*. Early exercise in critically ill patients enhances short-term functional recovery*. Crit Care Med 2009;37:2499–505.
12 Kho ME, Molloy AJ, Clarke F. Quantifying active in-bed Cycling in medical-surgical critically ill patients. *Am J Respirat* 2014;189.
13 Takaoka A, Utgikar R, Rochwerg B, *et al*. The efficacy and safety of in-intensive care unit leg-cycle Ergometry in critically ill adults: A systematic review and meta-analysis. *Ann Am Thorac Soc* 2020;17:1289–307.
14 Hodgson CL, Bailey M, Bellomo R. Early active mobilization during mechanical ventilation in the ICU. N Engl J Med 2022;387:1747–58.
15 Kho ME, Molloy AJ, Clarke FJ, *et al*. Trycycle: A prospective study of the safety and feasibility of early in-bed Cycling in mechanically ventilated patients. *PLoS One* 2016;11:e0167561.
16 Kho ME, Molloy AJ, Clarke FJ, *et al*. Multicentre pilot randomised clinical trial of early in-bed cycle Ergometry with ventilated patients. *BMJ Open Respir Res* 2019;6:e000383.
17 Chan A-W, Tetzlaff JM, Gøtzsche PC, *et al*. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
18 Butcher NJ, Monsour A, Mew EJ, *et al*. Guidelines for reporting outcomes in trial protocols: the SPIRIT-outcomes 2022 extension. *JAMA* 2022;328:2345–56.
19 Loudon K, Treweek S, Sullivan F, *et al*. The PRECIS-2 tool: designing trials that are fit for purpose. *BMJ* 2015;350:h2147.
20 Slade SC, Dionne CE, Underwood M, *et al*. Consensus on exercise reporting template (CERT): explanation and elaboration statement. *Br J Sports Med* 2016;50:1428–37.
21 Hoffmann TC, Glasziou PP, Boutron I, *et al*. Better reporting of interventions: template for intervention description and replication (Tidier) checklist and guide. *BMJ* 2014;348:bmj.g1687.
22 Koo KKY, Choong K, Cook DJ, *et al*. Early mobilization of critically ill adults: a survey of knowledge, perceptions and practices of Canadian physicians and Physiotherapists. *CMAJ Open* 2016;4:E448–54.
23 Ely EW, Truman B, Shintani A, *et al*. Monitoring sedation status over time in ICU patients: Reliability and validity of the Richmond agitation-sedation scale (RASS). *JAMA* 2003;289:2983–91.
24 De Jonghe B, Sharshar T, Lefaucheur J-P, *et al*. Paresis acquired in the intensive care unit: a prospective multicenter study. *JAMA* 2002;288:2859–67.
25 Muscedere J, Dodek P, Keenan S, *et al*. Comprehensive evidence-based clinical practice guidelines for ventilator-associated pneumonia: prevention. *Journal of Critical Care* 2008;23:126–37.
26 Sinuff T, Muscedere J, Cook D, *et al*. Ventilator-Associated pneumonia: improving outcomes through guideline implementation. *J Crit Care* 2008;23:118–25.
27 Morris PE, Goad A, Thompson C, *et al*. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. *Crit Care Med* 2008;36:2238–43.
28 Schweickert WD, Pohlman MC, Pohlman AS, *et al*. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet 2009;373:1874–82.
29 Koo K. Survey of acute rehabilitation in Canadian intensive care units. McMaster University, 2012.
30 Denehy L, Skinner EH, Edbrooke L, *et al*. Exercise rehabilitation for patients with critical illness: a randomized controlled trial with 12 months of follow-up. *Crit Care* 2013;17:R156.
31 Denehy L, de Morton NA, Skinner EH, *et al*. A physical function test for use in the intensive care unit: validity, responsiveness, and predictive utility of the physical function ICU test (scored). *Phys Ther* 2013;93:1636–45.
32 Skinner EH, Berney S, Warrillow S, *et al*. Development of a physical function outcome measure (PFIT) and a pilot exercise training protocol for use in intensive care. *Crit Care Resusc* 2009;11:110–5.
33 Hopkins RO, Miller RR, Rodriguez L, *et al*. Physical therapy on the wards after early physical activity and mobility in the intensive care unit. *Phys Ther* 2012;92:1518–23.
34 Fan E, Ciesla ND, Truong AD, *et al*. Inter-Rater reliability of manual muscle strength testing in ICU survivors and simulated patients. *Intensive Care Med* 2010;36:1038–43.
35 Hermans G, Clerckx B, Vanhullebusch T, *et al*. Interobserver agreement of medical research Council sum-score and Handgrip strength in the intensive care unit. *Muscle Nerve* 2012;45:18–25.
36 Jones CJ, Rikli RE, Beam WC. A 30-S chair-stand test as a measure of lower body strength in community-residing older adults. Res Q Exerc Sport 1999;70:113–9.
37 Herridge MS, Chu LM, Matte A, *et al*. The recover program: disability risk groups and 1-year outcome after 7 or more days of mechanical ventilation. Am J Respir Crit Care Med 2016;194:831–44.
38 Tveter AT, Dagfinrud H, Moseng T, *et al*. Health-Related physical fitness measures: reference values and reference equations for use in clinical practice. Arch Phys Med Rehabil 2014;95:1366–73.
39 O'Grady HK, Edbrooke L, Farley C, *et al*. The sit-to-stand test as a patient-centered functional outcome for critical care research: a pooled analysis of five International rehabilitation studies. *Crit Care* 2022;26:175.
40 Reid J, Clarke F, Cook D, *et al*. 831: Interrater Reliability and responsiveness of the ICU patient-reported functional scale. *Crit Care Med* 2016;44:284.
41 Reid JC, Clarke F, Cook DJ. Reliability, responsiveness, and validity of the patient-reported functional scale for the intensive care unit (PRFS-ICU): a pilot study. Annals of Intensive Care 2017.
42 Pin TW. Psychometric properties of 2-minute walk test: a systematic review. Arch Phys Med Rehabil 2014;95:1759–75.
43 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–70.
44 Herdman M, Gudex C, Lloyd A, *et al*. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20:1727–36.
45 van Hout B, Janssen MF, Feng Y-S, *et al*. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health* 2012;15:708–15.
46 Xie F, Pullenayegum E, Gaebel K, *et al*. A time trade-off-derived value set of the EQ-5D-5L for Canada. *Med Care* 2016;54:98–105.
47 KATZ S, FORD AB, MOSKOWITZ RW, *et al*. Studies of illness in the aged. The index of Adl: A standardized measure of biological and Psychosocial function. *JAMA* 1963;185:914–9.
48 Bagshaw SM, Stelfox HT, McDermid RC, *et al*. Association between Frailty and Short- and long-term outcomes among critically ill patients: a Multicentre prospective cohort study. *CMAJ* 2014;186:E95–102.
49 Critical Care Canada Forum. *ICU discharge function predicts poor hospital discharge outcomes: lessons from the CYCLE research program; Toronto, ON Canada*, 2017.
50 Parry SM, Denehy L, Beach LJ, *et al*. Functional outcomes in ICU – what should we be using? - an observational study. *Crit Care* 2015;19:127.
51 Nordon-Craft A, Schenkman M, Edbrooke L, *et al*. The physical function intensive care test: implementation in survivors of critical illness. *Phys Ther* 2014;94:1499–507.
52 Knaus WA, Draper EA, Wagner DP. Apache II: a severity of disease classification system. *Crit Care Med* 1985;13:818–29.
53 Charlson ME, Pompei P, Ales KL, *et al*. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic* Dis 1987;40:373–83.
54 Groll DL, To T, Bombardier C, *et al*. The development of a Comorbidity index with physical function as the outcome. *J Clin Epidemiol* 2005;58:595–602.
55 Marshall JC, Cook DJ, Christou NV, *et al*. Multiple organ dysfunction score: a reliable Descriptor of a complex clinical outcome. *Crit Care Med* 1995;23:1638–52.
56 Slade SC, Dionne CE, Underwood M, *et al*. Consensus on exercise reporting template (CERT): explanation and elaboration statement. *Br J Sports Med* 2016;50:1428–37.
57 Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. Hoboken, NJ, USA: Wiley, 1987.

58 Cooke CR, Erickson SE, Watkins TR, *et al*. Age-, sex-, and race-based differences among patients enrolled versus not enrolled in acute lung injury clinical trials. *Crit Care* Med 2010;38:1450–7.
59 Casey CM. The study of activity in older ICU patients: an integrative review. *J Gerontol Nurs* 2013;39:12–25.
60 Brummel NE, Bell SP, Girard TD, *et al*. Frailty and subsequent disability and mortality among patients with critical illness. Am J Respir Crit Care Med 2017;196:64–72.
61 Wu R-Y, Sung W-H, Cheng H-C, *et al*. Investigating the rate of skeletal muscle atrophy in men and women in the intensive care unit: a prospective observational study. Sci Rep 2022;12:16629.
62 De Jonghe B, Sharshar T, Lefaucheur JP. Paresis acquired in the intensive care unit: a prospective multicenter study. JAMA 2002;288:2859–67.
63 Schandelmaier S, Briel M, Varadhan R, *et al*. Development of the instrument to assess the credibility of effect modification analyses (ICEMAN) in randomized controlled trials and meta-analyses. *CMAJ* 2020;192:E901–6.
64 Pocock SJ. When (not) to stop a clinical trial for benefit. JAMA 2005;294:2228–30.
65 DAMOCLES Study Group, NHS Health Technology Assessment Programme. A proposed charter for clinical trial data monitoring committees: helping them to do their job well. *Lancet* 2005;365:711–22.
66 Patel BK, Wolfe KS, Patel SB, *et al*. Effect of early mobilisation on long-term cognitive impairment in critical illness in the USA: a randomised controlled trial. Lancet Respir Med 2023;160.
67 Waldauf P, Jiroutková K, Krajčová A, *et al*. Effects of rehabilitation interventions on clinical outcomes in critically ill patients: systematic review and meta-analysis of randomized controlled trials. *Crit Care Med* 2020;48:1055–65.
68 Parry SM, Berney S, Warrillow S, *et al*. Functional electrical stimulation with Cycling in the critically ill: a pilot case-matched control study. *J Crit Care* 2014;29:695.
69 Camargo Pires-Neto R, Fogaça Kawaguchi YM, Sayuri Hirota A, *et al*. Very early passive cycling exercise in mechanically ventilated critically ill patients: physiological and safety aspects--a case series. PLoS One 2013;8:e74182.
70 Kho ME, Molloy AJ, Clarke FJ, *et al*. TryCYCLE: a prospective study of the safety and feasibility of early in-bed cycling in mechanically ventilated patients. PLoS One 2016;11:e0167561.
71 Pires-Neto RC, Pereira AL, Parente C, *et al*. Characterization of the use of a cycle ergometer to assist in the physical therapy treatment of critically ill patients. Rev Bras Ter Intensiva 2013;25:39–43.
72 Hickmann CE, Roeseler J, Castanares-Zapatero D, *et al*. Energy expenditure in the critically ill performing early physical therapy. Intensive Care Med 2014;40:548–55.
73 Dantas CM, Silva PFDS, Siqueira FHTde, *et al*. Influence of early mobilization on respiratory and peripheral muscle strength in critically ill patients. Rev Bras Ter Intensiva 2012;24:173–8.
74 Thelandersson A, Nellgård B, Ricksten S-E, *et al*. Effects of early bedside cycle exercise on intracranial pressure and systemic hemodynamics in critically ill patients in a neurointensive care unit. Neurocrit Care 2016;25:434–9.
75 Rocca A, Pignat J-M, Berney L, *et al*. Sympathetic activity and early mobilization in patients in intensive and intermediate care with severe brain injuries: a preliminary prospective randomized study. BMC Neurol 2016;16.
76 Maia Coutinho W, Jurema dos Santos L, Fernandes J. n.d. Acute effect of the use of cycle Ergometer during physical therapy treatment in mechanically ventilated critically ill patients. *Fisioterapia e Pesquisa*
77 Kho ME, Martin RA, Toonstra AL. Le tour de ICU: feasibility and safety of routine use of in-bed Cycling for physical rehabilitation in the intensive care unit (ICU). B104 ICU weakness on the run: exercise, electrical stimulation, and Pharmacotherapy. *Am Thor Soc* 2013:A3620–A20.
78 International Committee of Medical Journal Editors. Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical. 2022. Available: https://www.icmje.org/icmje-recommendations.pdf
79 Duffett M, Cook DJ, Strong G, *et al*. n.d. The effect of COVID-19 on critical care research during the first year of the pandemic: a prospective longitudinal multinational survey. *Int Care Crit Care Med*
80 Cook DJ, Kho ME, Duan EH, *et al*. Principles guiding Nonpandemic critical care research during a pandemic. Crit Care Med 2020;48:1403–10.
81 Reid JC, Molloy A, Strong G, *et al*. Research interrupted: applying the conserve 2021 statement to a randomized trial of rehabilitation during critical illness affected by the COVID-19 pandemic. Trials 2022;23:735.
82 Misak CJ. ICU-acquired weakness: obstacles and interventions for rehabilitation. Am J Respir Crit Care Med 2011;183:845–6.
83 Needham DM, Bronskill SE, Calinawan JR, *et al*. Projected incidence of mechanical ventilation in Ontario to 2026: preparing for the aging baby boomers*. *Crit Care Med* 2005;33:574–9.
84 Wang YT, Lang JK, Haines KJ, *et al*. Physical rehabilitation in the ICU: a systematic review and Meta-Analysis*. *Crit Care Med* 2022;50:375–88.
85 Reid JC, Unger J, McCaskell D, *et al*. Physical rehabilitation interventions in the intensive care unit: a Scoping review of 117 studies. *J Intensive Care* 2018;6:80.
86 Reid JC, Clarke F, Cook DJ, *et al*. Feasibility, reliability, responsiveness, and validity of the patient-reported functional scale for the intensive care unit: A pilot study. *J Intensive Care Med* 2020;35:1396–404.
87 Kleyweg RP, van der Meché FG, Schmitz PI. Interobserver agreement in the assessment of muscle strength and functional abilities in Guillain-Barre syndrome. *Muscle Nerve* 1991;14:1103–9.
88 Wade DM, Hankins M, Smyth DA, *et al*. Detecting acute distress and risk of future psychological morbidity in critically ill patients: validation of the intensive care psychological assessment tool. *Crit Care* 2014;18:519.