

BMJ Open CYCLE pilot: a protocol for a pilot randomised study of early cycle ergometry versus routine physiotherapy in mechanically ventilated patients

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ABSTRACT

Introduction: Early exercise with in-bed cycling as part of an intensive care unit (ICU) rehabilitation programme has the potential to improve physical and functional outcomes following critical illness. The objective of this study is to determine the feasibility of enrolling adults in a multicentre pilot randomised clinical trial (RCT) of early in-bed cycling versus routine physiotherapy to inform a larger RCT.

Methods and analysis: 60-patient parallel group pilot RCT in 7 Canadian medical-surgical ICUs. We will include all previously ambulatory adult patients within the first 0–4 days of mechanical ventilation, without exclusion criteria. After informed consent, patients will be randomised using a web-based, centralised electronic system, to 30 min of in-bed leg cycling in addition to routine physiotherapy, 5 days per week, for the duration of their ICU stay (28 days maximum) or routine physiotherapy alone. We will measure patients' muscle strength (Medical Research Council Sum Score, quadriceps force) and function (Physical Function in ICU Test (scored), 30 s sit-to-stand, 2 min walk test) at ICU awakening, ICU discharge and hospital discharge. Our 4 feasibility outcomes are: (1) patient accrual of 1–2 patients per month per centre, (2) protocol violation rate <20%, (3) outcome measure ascertainment >80% at the 3 time points and (4) blinded outcomes ascertainment >80% at hospital discharge. Hospital outcome assessors are blinded to group assignment, whereas participants, ICU physiotherapists, ICU caregivers, research coordinators and ICU outcome assessors are not blinded to group assignment. We will analyse feasibility outcomes with descriptive statistics.

Ethics and dissemination: Each participating centre will obtain local ethics approval, and results of the study will be published to inform the design and conduct of a future multicentre RCT of in-bed cycling to improve physical outcomes in ICU survivors.

Trial registration number: NCT02377830; Pre-results.

Strengths and limitations of this study

- In-bed cycling is a novel technology that can improve intensive care unit (ICU) patients' function at hospital discharge if started 2 weeks after ICU admission; however, its effects are unknown when started earlier in a patient's ICU stay to address the rapid muscle weakness due to bed rest.
- The CYCLE pilot is a 60-patient parallel group randomised clinical trial (RCT) of early in-bed cycling versus routine physiotherapy in seven Canadian medical-surgical intensive care units
- We will assess the feasibility of patient accrual, in-bed cycling protocol delivery, outcome measure ascertainment at each of three time points, and blinded outcomes ascertainment at hospital discharge.
- This is a feasibility trial, and is not powered to determine treatment effectiveness.
- Results of the CYCLE pilot will inform the design and conduct of a future multicentre RCT of in-bed cycling to improve physical outcomes in ICU survivors.

INTRODUCTION

Surviving critical care is the first step in a long road of physical, cognitive and psychological recovery.¹ While medical advances have reduced the mortality of critical illness,^{2,3} survival comes with substantial residual physical burdens and societal cost. Intensive care unit (ICU) survivors are at risk of important mobility impairments posthospital discharge. At 1-year follow-up, 34% of patients surviving their stay in the ICU were below sex-expected and age-expected norms for the 6 min walk test (6MWT), and 51% had not returned to work.⁴ Although early rehabilitation would benefit survivors if their physical function or

quality of life could be improved, critically ill mechanically ventilated (MV) patients are often perceived as 'too sick' for physiotherapy (PT).⁵ Rehabilitation in the ICU can be infrequent (eg, <6% of all ICU days⁶), and when provided, may occur late in a patient's ICU stay (eg, median 10 days post-ICU admission⁷).

Patients who develop ICU-acquired weakness are at an increased risk of higher mortality, longer duration of MV, ICU, and hospital length of stay (LOS), and higher hospital costs.⁸ Up to 87% of MV ICU patients have electrophysiological evidence of neuromuscular abnormalities,⁹ and 55% have clinically evident weakness. In a study conducted within the first 7 days of ICU admission, patients' quadriceps twitch tension (an involuntary objective measure of muscle force) was four times lower than in healthy controls ($p < 0.001$).¹⁰ After 10 days of ICU admission and MV, quadriceps size decreased almost 18% from baseline.¹¹ Many previously ambulatory patients are unable to walk at ICU discharge due to profound muscle weakness.⁷

A recent systematic review of 14 randomised clinical trials (RCTs) demonstrated that ICU-based exercise studies were most effective to improve long-term physical function in critically ill adults compared with other strategies, including nutrition and different modes of MV.¹² Early mobility interventions started within the first 48 h of MV are feasible and can improve function; however, these studies primarily enrolled young medical ICU patients with acute respiratory failure^{13 14} and may not be generalisable to a medical-surgical population or older adults with multiple comorbidities. Cycle ergometry is a promising early ICU exercise intervention for MV patients because it targets the legs, can occur in bed while patients are sedated¹⁵ or awake, is easily reproducible, and is human resource efficient. In a single-centre, 90-patient RCT, those receiving in-bed leg cycling and usual PT compared with usual PT alone achieved 6MWT distances of 196 vs 143 m ($p < 0.05$), had greater leg strength and had better Short Form 36 (SF-36) physical function scores at hospital discharge.¹⁶ In this study, however, cycling did not start until 2 weeks after ICU admission,¹⁶ which potentially missed an opportunity to address the early rapid muscle atrophy and deconditioning associated with bed rest in the ICU.¹¹

Emerging evidence suggests cycling can occur safely very early in a patient's ICU stay, even while receiving MV.^{17 18} A case series of single in-bed cycling sessions started within the first 72 h of MV showed no increases in cardiac output, oxygen consumption¹⁸ or safety concerns, even while patients received low-dose vasoactive infusions.¹⁸ A case-control study enrolling patients within the first 96 h of MV initiated cycling within 15.3 h of recruitment.^{17 18} Most recently, a retrospective review of 186 patients and 541 in-bed cycling sessions reported use of in-bed cycling within the first 4 days of ICU admission, with patients receiving a median of two cycling sessions of four total PT sessions.¹⁹ However, there has been no systematic evaluation of *early* in-bed leg cycling

on functional outcomes in MV patients. The long-term goal of this research programme is to evaluate whether early exercise with in-bed leg cycling, started within 4 days of MV, improves clinically important outcomes. Before embarking on a large-scale trial, a pilot RCT is needed to determine the feasibility of intervention delivery and outcomes assessment in multiple centres.²⁰ Here, we report our pilot RCT protocol according to SPIRIT²¹ and TIDieR²² guidelines.

OBJECTIVES

Hypothesis

It is feasible to enrol adults (≥ 18 years), execute study procedures and measure functional outcomes in a multi-centre pilot randomised study of early in-bed cycling versus routine PT to inform a larger RCT. Specifically:

1. *Accrual*: The overall average accrual rate will be 1–2 patients per month per site.
2. *Protocol violations*: The in-bed cycling protocol can be successfully implemented with <20% protocol violations.
3. *Outcome measures*: >80% of outcomes will be measured as scheduled at three time points: ICU awakening, ICU discharge and hospital discharge.
4. *Blinded outcome assessment*: >80% of physical strength and function outcomes at hospital discharge will be assessed by personnel blinded to group allocation.

METHODS AND ANALYSIS

Trial design

The CYCLE pilot RCT is an open-label, concealed study in seven Canadian academic medical-surgical ICUs with blinded outcome assessment at hospital discharge. **Table 1** outlines the schedule of enrolment, interventions and assessments.

Participants

Sixty adults in participating medical-surgical ICUs meeting eligibility criteria will be recruited. All participating ICUs will have a dedicated in-bed cycle ergometer, experience contributing to multicentre critical care trials and a site principal investigator (PI) from the Canadian Critical Care Trials Group. *Inclusion criteria*: adults (≥ 18 years old) admitted within the first 4 days of MV and first 7 days of ICU, and able to ambulate independently before hospital admission (with or without a gait aid). We chose this timeframe to address the early and rapid muscle atrophy that occurs within the first week of ICU admission.¹¹ *Exclusion criteria*: acute condition impairing patients' ability to cycle (eg, leg fracture), proven or suspected neuromuscular weakness affecting the legs (eg, stroke or Guillain-Barré syndrome), unable to follow commands in English, temporary pacemaker, expected hospital mortality >90%, body habitus unable to fit the bike, palliative goals of care or persistent therapy exemptions in the first 4 days of MV (see **box 1**). We excluded patients unable to follow commands at

Table 1 CYCLE pilot RCT schedule of enrolment, interventions and assessments

Time point	Study period						
	Enrolment ICU admission	Allocation 0	Postallocation				Close out
			In ICU	ICU awakening	ICU discharge	Hospital discharge	
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	X						
Charlson comorbidity index ⁵⁶	X						
Functional comorbidity index ⁵⁷	X						
Clinical Frailty Scale ⁴³	X				X	X	
Function: Katz activities of daily living scale ⁴⁴	X				X	X	
Physical strength and function*				X	X	X (blinded)	
Psychological distress: Intensive Care Psychological Assessment Tool ⁴⁵				X			
Quality of life: Euro-QOL 5DL ^{47 48}					X	X	
ICU and hospital length of stay						X	X
Mortality					X	X	X

In this table, we outline patient enrolment, interventions and assessments in the CYCLE pilot RCT.

*Strength and function assessments at ICU awakening include Physical Function ICU Test (scored),^{31 32} Medical Research Council Sum Score^{34 35} and 30 s sit-to-stand test,^{37 38} at ICU discharge and hospital discharge, includes all ICU awakening assessments plus the 2 min walk test^{39 40} and quadriceps strength with hand-held dynamometry.³⁶ ICU, intensive care unit; PT, physiotherapy; RCT, randomised clinical trial.

baseline because participants will need to follow simple commands to complete outcome assessments. We excluded patients with conditions associated with muscle weakness to ensure effects of cycling are not confounded by other reasons for persistent muscle weakness.

Recruitment and randomisation

Enrolment began in March 2015, and is anticipated to continue until December 2016. In each centre, an ICU research coordinator will screen the ICU census regularly to identify patients who meet study criteria and will seek written informed consent from patients or their substitute decision makers before randomisation. Once patients are alert, they will be evaluated for capacity and consented for continuation in the trial. We will use a centralised web-based, secure randomisation service for clinical trials (<http://www.randomize.net/>). Following consent, the research coordinator will log in to the website, register the patient and receive the randomised assignment. We will stratify by centre, medical versus surgical admission status and age ≥ 65 or < 65 years.

Procedures

Figure 1 presents the planned flow of participants throughout the study. Individual patients will receive the randomised intervention 5 days per week (excluding weekends and statutory holidays), for the duration of

their index ICU stay (maximum 28 days, whichever occurs first) from ICU physiotherapists as part of their normal role. After 28 days, all patients remaining in the ICU will receive routine PT per institutional standards. Those randomised to routine PT will not receive in-bed cycling. We will conduct outcome assessments at ICU awakening, ICU discharge and hospital discharge (described further below). During PT sessions, physiotherapists will screen participants for readiness for awakening assessments, and will initiate their strength and function assessment once patients successfully answer $\geq 3/5$ standardised questions per previous studies (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 up to 5).²³

Experimental

Patients will receive 30 min of in-bed cycling in addition to routine PT, for the duration of their index ICU stay (maximum of 28 days or when able to march on the spot for 2 consecutive days with assistance, whichever occurs first). We chose to discontinue cycling after marching on the spot for 2 days to allow physiotherapists and patients to focus on progressing mobility and ambulation activities. During in-bed cycling, patients will be positioned semirecumbently¹⁶ as per ventilator-associated pneumonia prevention guidelines.^{24 25}

Box 1 Daily exemption and in-session stopping criteria**A. Daily exemption criteria for in-bed cycling**

Cycling or physiotherapy (PT) sessions *will not occur* if any of the following conditions are present:

1. Any increase in vasopressor/inotrope within past 2 h
2. Active myocardial ischaemia, or unstable/uncontrolled arrhythmia per intensive care unit (ICU) team
3. Mean arterial pressure (MAP) <60 or >110 mm Hg or out of range for this patient within the past 2 h
4. Heart rate <40 or >140 bpm within the past 2 h
5. Persistent SpO₂ <88% or out of range for this patient within the past 2 h
6. Neuromuscular blocker within past 4 h
7. Severe agitation (Richmond Agitation and Sedation Scale >2 (or equivalent)) within past 2 h
8. Uncontrolled pain
9. Change in goals to palliative care
10. Team perception that in-bed cycling or therapy is not appropriate despite absence of above criteria (eg, active major haemorrhage from any site, acute peritonitis, new incision or wound precluding cycling, new known/suspected muscle inflammation (eg, rhabdomyolysis))
11. Patient or proxy refusal

B. Criteria to terminate in-bed cycling or routine PT

Cycling or routine PT will *stop* if the following occurs:

- ▶ Concern for myocardial ischaemia or suspected new unstable/uncontrolled arrhythmia
- ▶ Unplanned extubation
- ▶ Physiotherapist perceives continuing cycling or routine PT is not appropriate, for example,
 - *Respiratory*—sustained O₂ desaturation <88%; marked ventilator dysynchrony
 - *Cardiovascular*—sustained symptomatic bradycardia (<40 bpm), tachycardia (>140 bpm), hypotension (MAP <60 mm Hg) or hypertension (MAP >120 mm Hg)
 - Catheter or tube dislodgement or severe patient agitation
- ▶ ICU physician, patient or proxy requests termination of session

We will use a specialised in-bed cycle ergometer (eg, RT300 supine cycle), which provides three possible cycling modes: passive (ie, no patient initiation), active-assisted (ie, partially initiated by the patient) or active (ie, fully initiated by the patient).¹⁶ Our aim is for participants to complete as much active cycling as possible during each 30 min session. Each patient will receive a pre-programmed standardised treatment template. Each session will start with a 1 min motor-driven passive cycling warm-up at a rate of 5 revolutions per minute (RPM). We chose 5 RPM based on clinical experience with comatose patients who demonstrated some active cycling above the set motor rate. Patients will continue with passive, active-assisted or active cycling for the next 29 min, according to their level of participation. The session will finish with a 30 s motor-driven cool-down (30:30 total). Since ICU patients' level of consciousness may vary throughout their stay, we will allow patients to cycle at a self-selected RPM and will not change the

resistance. If the patients stop cycling actively, the ergometer will revert to passive cycling. Therapists will titrate the motor speed to provide sufficient support to promote as much active cycling as possible.

Because of the dynamic nature of critical illness, we will screen participants daily for criteria precluding in-bed cycling (**box 1**). For example, we will not cycle on a day where a patient has cardiac or respiratory instability, active major bleeding, or severe agitation. During every cycling session, patients will be carefully monitored for safety and indications for termination of cycling, including signs of cardiac or respiratory instability, and catheter or tube dislodgement. We will record vital signs (eg, heart rate), physiological parameters (eg, minute ventilation) and cycling achievements (eg, active cycling, distance) every session. **Box 1** outlines cycling session termination criteria.

For centres with no experience with in-bed cycling or with the study bike, we will provide all ICU PTs with a 1-day (approximately 8 h) training session on use of the in-bed cycle ergometer from the study PI (MEK) and equipment vendor. This training session includes didactic lectures and use of the cycle with both simulated and critically ill patients. The PTs receive a binder including key ICU rehabilitation trials, specialised ICU bike instruction manuals, a laminated bike quick start pocket card and a computer tablet in a military-grade protective case compliant with hospital infection-control requirements preloaded with electronic versions of all paper materials. Centres will gain clinical experience with routine use of the in-bed cycle with critically ill patients before enrolling patients in the CYCLE pilot RCT. All PTs will receive in-service training on the in-bed biking protocol. At each site, we will train multiple PTs to bike to ensure a trained therapist is always available despite vacation time or unplanned absences. The Methods Centre will also assist each site with trouble-shooting equipment problems and outcome measure questions.

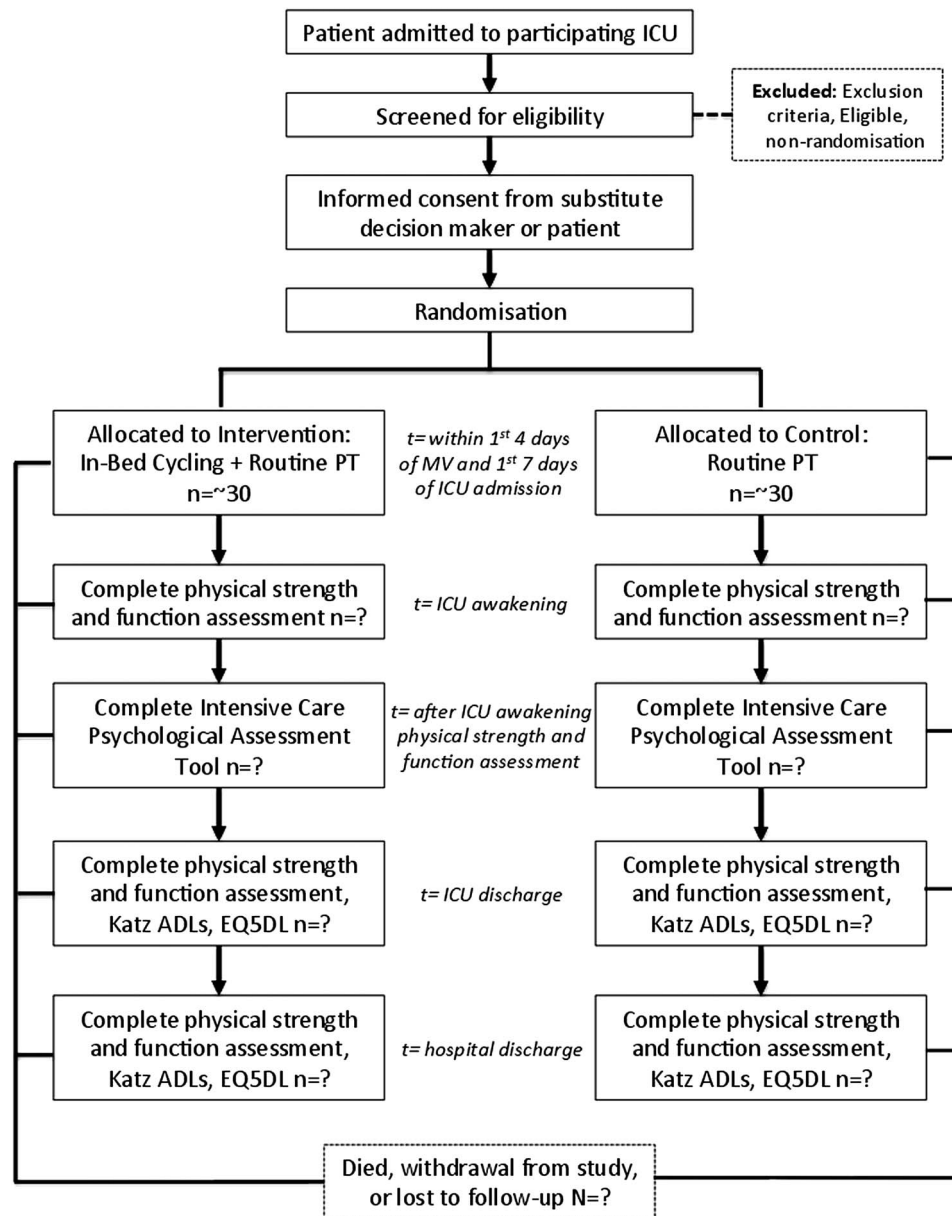
Control: routine PT

Patients will receive routine PT per current institutional practice as part of their normal role. Routine PT may include activities to assist with optimising airway clearance and respiratory function, and, based on the patient's alertness and medical stability, activities to maintain or increase limb range of motion and strength, in and out of bed mobility, and ambulation.^{13 14 26 27} We expect some interinstitutional variation in routine PT interventions. To date, there are no Canadian data documenting routine PT interventions; two point prevalence studies^{28 29} and a multicentre prospective cohort study documented inconsistent mobilisation practices in different countries, across centres.³⁰ We will use the same criteria to terminate routine PT sessions (**box 1**).

Outcome measures

The four feasibility outcomes are outlined above. Below, we describe the planned primary and secondary

Figure 1 Planned flow of participants throughout the CYCLE pilot RCT. ADL, activities of daily living; ICU, intensive care unit; MV, mechanically ventilated; PT, physiotherapy; RCT, randomised clinical trial.



outcome measures for the full CYCLE RCT. We will measure all of the outcomes described below in the CYCLE pilot RCT.

Outcome measures for the full CYCLE RCT: The primary outcome for the full RCT will be the Physical Function ICU Test—scored (PFIT-s) measured at hospital discharge.^{31 32} It 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=better function).^{31 32} We chose the PFIT-s because we expect all ICU patients will be able to complete part of the assessment even if they cannot stand (eg, arm or leg strength), limiting floor effects,³³ and its strong psychometric properties (reliability intraclass correlation coefficient range=0.996–1.00³²; convergent validity with the 6MWT and manual muscle strength testing³¹).

Secondary outcomes in the full CYCLE RCT include muscle strength (Medical Research Council manual muscle strength,^{34 35} quadriceps strength³⁶) and function

(eg, 30 s sit-to-stand,^{37 38} and 2 min walk test).^{39 40} These measures have normative values, good reliability in critically ill or frail elderly populations and are included in other ongoing ICU rehabilitation studies.^{41 42} We will also collect hospital discharge location, frailty,⁴³ length of MV, LOS (ICU, hospital) and mortality (ICU, hospital), patients' perception of physical function, Katz activities of daily living (ADLs) scale,⁴⁴ critical care-related psychological distress (Intensive Care Psychological Assessment Tool (IPAT)^{45 46}), and health-related quality of life (EQ-5DL).^{47–49} table 2 describes the outcome measures.

We will follow all patients throughout their ICU and hospital stay until death, transfer to another hospital or hospital discharge. At each site, a research coordinator will track each patient's location in hospital and liaise with hospital staff to identify anticipated hospital discharge date. At ICU discharge and at hospital discharge, the research coordinator will assess patients' perceptions

Table 2 Description of outcome measures for the CYCLE pilot and full RCT

Outcome measure	Description
Physical strength and function measures	
1. Outcome for full RCT (anticipated): PFIT-s ^{31 32}	Patients complete four activities: arm and leg strength, ability to stand, and step cadence. Scores range from 0 to 10, with higher score=better function.
2. Outcomes	
Medical Research Council muscle strength ^{34 35}	Standardised physical examination of six muscle groups (three upper, three lower), using a six-point scale (0=no contraction; 5=contraction sustained against maximal resistance), summed to a total score (range 0–60), higher score=better strength.
30 s sit-to-stand ^{37 38}	Patient completes as many full sit-to-stand repetitions within 30 s, with higher score=better strength.
2 min walk test ^{39 40}	Patient walks as far as possible over 2 min, with farther distance=better endurance.
Quadriceps strength ³⁶	Standardised physical examination using a small device that fits into the palm of the examiner's hand, and quantifies force (in Newtons) on a continuous scale when the patient's leg pushes against the device, higher score=better strength.
Other measures	
Clinical Frailty Scale ⁴³	Nine-point scale evaluating physical function, activities of daily living, instrumental activities of daily living and assistance for personal care; higher score=more frailty and poorer function.
Katz activities of daily living scale ⁴⁴	Six-question survey evaluating dependence or independence in bathing, dressing, toileting, transferring, continence and feeding. Each item rated dependent or independent; higher score=more independence.
Intensive Care Psychological Assessment Tool ⁴⁵	Ten-item interviewer-administered questionnaire to identify acute distress and risk of future psychological distress. Score ranges from 0 to 20; score of 7 or more represents higher risk of psychological distress.
Quality of Life: EuroQOL 5DL ^{47 48}	Five-question interviewer or self-administered, preference-based instrument to measure mobility, self-care, usual activities, pain and anxiety/depression, and a global assessment of health; higher score=better quality of life.

In this table, we describe the outcome measures included in the CYCLE pilot RCT and the future full CYCLE RCT. ICU, intensive care unit; RCT, randomised clinical trial; PFIT, Physical Function Test for ICU; QOL, quality of life.

of physical function, Katz ADL scale,⁴⁴ IPAT^{45 46} and EQ-5DL.^{47 48}

All strength and physical function outcome assessors will receive a 3 h in-person training session and support materials. At each site, we will train multiple assessors to ensure a blinded outcomes assessor is always available despite planned or unplanned absences. This interactive training session includes didactic lectures, and use of the strength and physical function outcome measures with simulated patients. The PTs will receive paper copies of each outcome measure, administration instructions and normative values (where available).

Harms

We expect few risks to the safety of participants involved in either arm of the CYCLE Pilot RCT. Routine PT in the ICU, including in-bed cycling, is safe. A comprehensive review of 2.5 years of PT in a critical care rehabilitation programme in 1110 patients and over 5267 rehabilitation sessions identified physiological abnormalities or potential adverse events in 2.5 per 1000 patients and 6 per 1000 therapy sessions, respectively.⁵⁰ Of these, patients received 628 in-bed cycling sessions as part of routine PT, and experienced 1 safety event (1.6 safety events per 1000 PT treatment days). In a focused retrospective review of a subset of the critical care rehabilitation programme described above, of 541 cycling sessions, patients experienced one radial arterial

catheter dislodgement, no unplanned extubations and no predefined cardiorespiratory physiological abnormalities.⁵¹ Authors reported no catheter or tube dislodgements in six ICU cycling studies.^{16–18 52–54} Similarly, in the RCT of cycling started 2 weeks into the patient's ICU stay, no severe physiological adverse events occurred (eg, arrhythmias, myocardial ischaemia); 16 sessions (4%) stopped early due to low oxygen saturation (<90%; n=8) or blood pressure concerns (n=8, systolic >180 mm Hg; n=6, >20% decrease in diastolic; n=2); all variables returned to baseline within 2 min of activity cessation.¹⁶ Three patients in the cycling group withdrew: two due to cardiac instability, and one due to an Achilles tendon rupture.¹⁶ **Box 1** outlines termination criteria and safety events recorded in the CYCLE pilot RCT. We will also record the consequences of the safety events.

Blinding

Given the nature of the intervention, patients, ICU PTs, ICU caregivers, family members and research coordinators will not be blinded to intervention allocation. However, outcomes assessors will be blinded to the allocation, as they will be assessed by a core group of PTs who did not care for patients in the ICU. We will ask patients and their family members not to disclose the patient's assigned treatment to PTs involved in assessing hospital outcomes to protect against performance bias.

DATA COLLECTION, MANAGEMENT AND ANALYSIS PLAN

In both groups, we will collect baseline data including patient demographics, ICU admission reason, medical versus surgical status, severity of illness,⁵⁵ comorbidity^{56 57} and prehospital function.⁴⁴ ICU-related variables captured daily during the patient's ICU stay will include illness severity,⁵⁵ other life supports, drug exposure and nutrition. We will collect relevant cointerventions that may impair patient function, including receipt of corticosteroids⁵⁸ and neuromuscular blocking agents,⁵⁹ and duration of bed rest.⁵⁹ We will also record the type and duration of all PT interventions (eg, passive or active range of motion, bed mobility and transfers, ambulation) received in the ICU.

STATISTICS

Sample size calculation

We will recruit 60 patients for this pilot RCT. Our sample size calculation is based on identifying a 0.25 standardised effect size for the full RCT for the PFIT-s at hospital discharge.³¹ Assuming a baseline SD of 3.06 points at ICU awakening,³¹ we hypothesise that 0.75 points in the final PFIT-s score at hospital discharge is clinically important for the main trial. Using a CI approach for continuous outcomes, we require 504 participants with outcomes at hospital discharge to detect a difference in the main trial ($\alpha=0.05$).⁶⁰ For the pilot RCT, we will recruit 9% of the sample size for the planned main trial to have an 80% power to detect such a difference.⁶⁰ Thus, we need to recruit, randomise and analyse 46 patients (23 per group) to produce a

one-sided 80% confidence limit, which would exclude a 0.75 difference on the PFIT if the point estimate from the pilot study were 0. Assuming 25% in-hospital mortality, we plan to include 60 patients in the pilot RCT.

STATISTICAL ANALYSIS

For all feasibility analyses, we will include all patients randomised, regardless of protocol adherence. We will conduct a subgroup analysis of patients ≥ 65 years old. Since elderly patients are under-represented in critical care trials,⁶¹ and no studies have specifically studied early cycling in the elderly critically ill,⁶² subgroup analysis of these patients for our four primary objectives will help to identify barriers and facilitators to conducting the research protocol in this population. We will have no formal interim analysis in this pilot trial. We will use data from the CYCLE pilot RCT in the full CYCLE RCT and will consider public access to data and statistical code after the full RCT. Table 3 outlines the variables, hypotheses, outcome measures and analytic methods for our four feasibility outcome measures.

Trial management

The Methods Centre, coordinated by St Joseph's Healthcare and McMaster University, will oversee all contracts, research ethics board preparation, site initiation and training, screening log and data submission, data quality assurance, study close-out, and finances at each site. It will develop and prepare all study materials (eg, standard operation procedures, operations manuals, data collection forms) for participating sites, be the

Table 3 CYCLE pilot RCT variables, measures and methods of analysis for the four feasibility objectives

Variable/outcome	Hypothesis	Outcome measure	Methods of analysis
Feasibility outcomes			
1. Accrual	The overall average accrual rate will be 1–2 patients per month per site.	Average monthly patient enrolment per site	Descriptive statistics (mean, SD) by site
2. Protocol violations	The in-bed cycling protocol can be successfully implemented with <20% protocol violations.	(1) Patients with no cycling exemptions from box 1 who did not receive cycling, and (2) Patients with cycling exemptions from box 1 and did receive cycling	Descriptive statistics (n, %, 95% CI)
3. Outcome measures	>80% of outcomes (described above) will be measured as scheduled at ICU awakening, ICU discharge, and hospital discharge.	Whether the measurement occurred, the result, and any barriers to data collection	Descriptive statistics (n, %, 95% CI)
4. Blinded outcome assessments	>80% of physical strength and function outcomes at hospital discharge will be assessed by personnel blinded to group allocation.	Whether the measurement occurred, the result, and any barriers to data collection	Descriptive statistics (n, %, 95% CI)
Subgroup analysis			
≥ 65 years old and <65 years old	There is no difference in any of the above four feasibility objectives between those ≥ 65 years old and those <65 years old	As outlined above	χ^2 test

In this table, we outline the variables, measures and methods of analysis for the four feasibility outcomes in the CYCLE pilot RCT. ICU, intensive care unit; RCT, randomised clinical trial.

point contact for study questions, and will communicate important protocol amendments electronically to relevant parties. To protect confidentiality, all data will be anonymised and entered into iDataFax, a password-protected encrypted server that runs on Red Hat Enterprise Linux. All PIs will have access to the clean data set and their local data after the full CYCLE RCT.

Steering committee

The CYCLE pilot RCT steering committee will be a subgroup of co-investigators, including MEK, DJC, all site leads, and the Methods Centre research coordinator. This group will provide input on any necessary protocol revisions, and offer clinical guidance. We will have a formal Data Monitoring Committee for the full CYCLE RCT.

ETHICS AND DISSEMINATION

We will disseminate study results regardless of the magnitude or direction of effect. We will disseminate results to key stakeholders (eg, critical care clinicians, critical care trialists, research funders and the public) through conference presentations, peer-review journal publications, trial registry (clinicaltrials.gov) and the CYCLE trial website (<http://www.icucycle.ca>). We will submit trial progress summaries to our sponsors as required. We will not use professional writers and will follow the International Committee of Medical Journal Editors for authorship.⁶³

DISCUSSION

Limitations and strengths of the CYCLE multicentre pilot RCT

The CYCLE pilot RCT is designed as a feasibility study, and is therefore not powered to determine treatment effectiveness. In-bed cycle ergometry only targets the lower extremities, whereas the upper extremities and torso also weaken with bed rest.⁶⁴ Implementing this cycling protocol as part of their normal role will add to the workload of participating physiotherapists; however, we expect that efficiency with the cycling protocol will improve over time in participating centres, as recorded in our pilot study. Cycling is not necessarily a functionally oriented therapy; however, once patients can march on the spot, therapists will transition from cycling to help patients focus on advancing other mobility activities. Moreover, cycling allows both passive and active activity, which is easily adaptable to a patient's current physical status. Our pilot trial is modest in size but is a foundational step in this research programme.

This study will engage the largest number of ICUs to date in the field of critical care rehabilitation. Numerous strengths of this proposed research include the innovative, portable and publically familiar intervention of cycling. In-bed cycling can occur while patients are deeply sedated, unconscious or are minimally interactive.¹⁵ Our intervention targets the leg muscles, which account for 75% of total skeletal muscle mass,⁶⁵ and are

most vulnerable to loss of muscle size and strength during bed rest.^{64 66} Unlike ambulation during MV, which can require up to four clinicians,⁶⁷ cycling only requires the assistance of one clinician.¹⁶ Our pilot data support the safety and feasibility of early cycling in critically ill patients receiving MV⁶⁸ and we are engaging front-line PTs to provide the cycling intervention as part of normal care, in anticipation of future knowledge translation efforts. To reduce detection bias, we will conduct blinded functional outcome assessments at hospital discharge. We will collect key feasibility data to inform a future larger RCT.

Results from the CYCLE pilot RCT will inform the future large-scale multicentre CYCLE RCT. Consistent with the four primary objectives of our pilot RCT, we will identify barriers and facilitators to accrual, including occasions to revise inclusion and exclusion criteria, and improve the informed consent process, if needed. We will systematically collect protocol violations to identify opportunities to optimise and streamline the delivery of in-bed cycling in other centres by seeking direct feedback from the front-line physiotherapists at each site. We will assess our ability to conduct outcome measures at ICU awakening, ICU discharge and hospital discharge, and blinded outcome measures at hospital discharge. Finally, results from our pilot RCT will document the nature and frequency of routine PT interventions in multiple centres in the new era of early mobility activities in critically ill patients.

We anticipate the primary outcome for the full CYCLE RCT will be the PFIT-s,³¹ powered to detect a difference in patients' function at hospital discharge. Thus, our ability to successfully measure outcomes with minimal losses to follow-up is critical. We will collate and synthesise strategies from outcome assessors to maximise our outcome measures. Observed hospital mortality and loss to follow-up data will inform the number of patients we will need to recruit for the full CYCLE RCT to achieve our target sample size at hospital discharge.

By 2026, the number of patients aged >60 years requiring MV is expected to increase by 105%.⁶⁹ This presents an urgent need to proactively address ICU rehabilitation needs, since more of these survivors will be at risk for post-ICU disability. If effective, early in-bed leg cycling could decrease disability and may represent a cost-effective healthcare intervention.

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