







# BMJ Open 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

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## 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 ( $\geq 18$  years old), who could ambulate independently before their critical illness (with or without a gait aid),  $\leq 4$  days of invasive mechanical ventilation and  $\leq 7$  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** Critical Care Cycling to improve Lower Extremity (CYCLE) is approved by the Research Ethics Boards of all participating centres and Clinical Trials Ontario

## 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.

(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).



## INTRODUCTION

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

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.<sup>8</sup> 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.<sup>9,10</sup> 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.<sup>11,12</sup> 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).<sup>11</sup> 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.<sup>13</sup> 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,<sup>14</sup> the need is pressing to identify safe and effective ICU rehabilitation strategies that mitigate post-ICU morbidity.

CYCLE (Critical Care Cycling to improve Lower Extremity 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.<sup>15</sup> 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.<sup>16</sup> 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)<sup>17</sup> and outcomes extension,<sup>18</sup> Consolidated Standards of Reporting Trials (CONSORT) and SPIRIT Extension for RCTs Revised in Extenuating Circumstances,<sup>19</sup> and Consensus on Exercise Reporting Template (CERT)<sup>20</sup> guidelines. We applied the CERT<sup>20</sup> exercise intervention template rather than the Template for Intervention Description and Replication checklist<sup>21</sup> because CERT explicitly evaluates supervision, tailoring and intervention dosage. A Pragmatic Explanatory Continuum Indicator Summary-2 is included as a online supplemental appendix.<sup>19</sup>

## 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 ( $\geq 18$  years old), who could ambulate independently before their critical illness (with or without a gait aid),  $\leq 4$  days of invasive MV and  $\leq 7$  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

Timepoint	Study period								
	Enrolment	Allocation	Postallocation					Hospital D/C	90 days postrandomisation
	ICU admission	0	In ICU	ICU awakening	ICU D/C	3 days post-ICU D/C			
<b>Enrolment</b>									
Eligibility screening	X								
Informed consent	X								
Allocation		X							
<b>Interventions</b>									
In-bed cycling + routine PT			X	X	X				
Routine PT			X	X	X				
<b>Assessments</b>									
Severity of illness: APACHE II <sup>52</sup>	X								
Charlson Comorbidity Index <sup>53</sup>	X								
Functional Comorbidity Index <sup>54</sup>	X								
Clinical Frailty Scale <sup>48</sup>	X						X	X	
Function: Katz Activities of Daily Living Scale <sup>47</sup>	X				X		X		
Patient-reported functional scale for the ICU <sup>86</sup>					X		X	X	
<b>Physical Strength and Function</b>									
Physical Function ICU Test (scored) <sup>31 32</sup>			X	X	X (blinded)		X (blinded)		
Medical Research Council Sum Score <sup>87</sup>			X	X	X (blinded)		X (blinded)		
30 s sit to stand <sup>36</sup>			X	X	X (blinded)		X (blinded)		
2 min walk test <sup>42</sup>					X	X (blinded)	X (blinded)		
Psychological distress: Intensive Care Psychological Assessment Tool <sup>88</sup>			X						
Health-related Quality of Life: EuroQol 5D-5L <sup>44 45</sup>					X		X	X	
Hospital Anxiety and Depression Scale <sup>43</sup>								X	
<b>Data collection</b>									
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<sub>2</sub><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<sup>22</sup> 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<sup>23</sup> 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).<sup>24</sup>

#### 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<sup>11</sup> per ventilator-associated pneumonia prevention guidelines.<sup>25 26</sup>

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<sub>2</sub> 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.<sup>27–30</sup> 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)<sup>31</sup> 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,<sup>31 32</sup> convergent validity with the 6 min walk distance and muscle strength).<sup>31</sup> 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.<sup>16</sup> 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.<sup>33</sup> 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)<sup>34 35</sup> and function (30 s sit-to-stand test,<sup>36</sup> 2 min walk test,<sup>37</sup>) each of which have age-based and sex-based reference values, and good reliability in critically ill or frail elderly populations.<sup>38 39</sup> Patient-reported measures include the Patient-Reported Functional Scale-ICU,<sup>40 41</sup> Intensive Care Psychological Assessment Tool,<sup>42</sup> Hospital Anxiety and Depression Scale<sup>43</sup> and health-related quality of life (EuroQol 5D-5L).<sup>44–46</sup> Other measures include the Katz Activities of Daily Living (ADL) Scale,<sup>47</sup> frailty (Clinical Frailty Scale),<sup>48</sup> 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,<sup>49</sup> corresponding to the minimal clinically important difference identified in psychometric studies.<sup>31 50</sup> 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.<sup>49</sup> Based on a SD of 2.5 points at ICU discharge,<sup>15 51</sup> a 1.0-point difference between groups<sup>31 49 50</sup> and 90% power (0.05  $\alpha$ ), 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),<sup>52</sup> comorbidity (eg, Charlson Comorbidity Index,<sup>53</sup> Functional Comorbidity Index<sup>54</sup>) and prehospital function (eg, Katz ADL)<sup>47</sup> 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),<sup>55</sup> 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](http://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.<sup>56</sup> 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.<sup>57</sup> 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  $\geq 65$  years, (2) Frailty pre-ICU admission or not (baseline CFS  $\leq 4$  and  $\geq 5$ ), and (3) Sex (male vs female). Since older patients are under-represented in ICU trials,<sup>58</sup> and no trials have specifically studied early cycling in the critically ill older adults,<sup>59</sup> a subgroup analysis will help to identify any age-related differences in response to rehabilitation. Critically ill patients with frailty have worse outcomes,<sup>60</sup> however the effects of exercise on patients with frailty are unclear. Females experience more

quadriceps muscle atrophy than men in the ICU<sup>61</sup> and are more likely to develop ICU-acquired weakness.<sup>62</sup> We hypothesise that adults  $\geq 65$  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.<sup>63</sup>

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<sup>64</sup> (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.<sup>64</sup> To maintain the overall type-I error rate (ie,  $\alpha$ ), we evaluated the primary endpoint using a fixed simple conservative  $\alpha = 0.001$  for the interim analyses and will use  $\alpha = 0.05$  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.<sup>65</sup>

### 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<sub>2</sub> 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.<sup>14 66</sup> A systematic review of 48 studies and 7456 patients documented a 2.6% cumulative incidence of adverse events during an ICU rehabilitation intervention.<sup>67</sup> 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.<sup>13</sup> In 11 cycling studies, no catheter or endotracheal tube dislodgements occurred.<sup>11 16 68–76</sup> 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%.<sup>77</sup> 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.<sup>70</sup> The 66-patient, multicentre CYCLE Pilot RCT documented that only one person experienced early termination across 146 cycling sessions.<sup>16</sup> 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,<sup>78</sup> 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.<sup>79 80</sup> 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.<sup>81</sup> 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.<sup>82</sup> 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.<sup>83</sup> Systematic reviews of ICU physical rehabilitation trials have reported discordant results for the effectiveness of these interventions.<sup>67 84</sup> 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.<sup>12</sup> 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<sup>17</sup> and CERT<sup>20</sup> reporting guidance, this research protocol addresses previously documented gaps in ICU rehabilitation intervention reporting.<sup>85</sup>

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.

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