



CYCLE RCT:

**An international, multi-centre, randomized clinical trial of
early in-bed cycling for mechanically ventilated patients**

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Investigator's Statement and Signature:

I have reviewed this protocol and comprehend the study design. I accept to participate as a Principal Investigator and to abide to the protocol as outlined. The trial shall be conducted according to GCP and all applicable regulatory requirements.

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Abstract

Title of the Study: CYCLE RCT: An international, multi-centre, randomized clinical trial of early in-bed cycling for mechanically ventilated patients

Background: Survivors of critical illness have a long road of physical, cognitive, and psychological recovery.¹ Although medical advances have reduced the mortality of critical illness,^{2,3} survival often comes with substantial long-term morbidity and societal cost. At 1-year follow-up, ~35% of intensive care unit (ICU) survivors had sub-normal 6-minute walk distance, and ~50% had not returned to work.⁴ Rehabilitation interventions started in the ICU may reduce this morbidity. In-bed cycling is a novel technology that may help critically ill, mechanically ventilated (MV) patients receive exercise very early to prevent or attenuate muscle weakness. Patients on MV typically receive prolonged bedrest and are often perceived as ‘too sick’ for physiotherapy (PT) interventions.⁵ However expert consensus and our previous multicenter pilot work suggest these interventions are safe.⁶ The CYCLE RCT will evaluate whether early in-bed leg cycling compared to usual PT interventions improves patient- important outcomes.

Objectives:

1. **CYCLE RCT:** To determine if early in-bed cycling and routine PT compared to routine PT alone in critically ill, mechanically ventilated adults improves the primary outcome of physical function at 3 days after ICU discharge and secondary outcomes of strength, physical function, frailty, psychological distress, quality of life, mortality, and healthcare utilization.
2. **Economic Evaluation:** To determine the cost-effectiveness of cycling and routine PT compared to routine PT alone among critically ill, mechanically ventilated adults.

Design: 360-patient concealed open-label RCT with blinded outcome assessment.

Population: Critically ill adults receiving MV in a medical-surgical ICU.

Major inclusion/ exclusion criteria: Inclusion: Adults within the first 4 days of MV and within the first 7 days of their ICU stay who walked independently before hospitalization.

Exclusion: Patients who could not follow simple commands at baseline, could not receive cycling (e.g., did not fit equipment, acute leg fracture), had confirmed or suspected central or peripheral neuromuscular weakness, had a temporary pacemaker, were not likely to survive their hospital stay, had palliative goals of care, or could not march on the spot at screening.

Methods: After *a priori* informed consent, patients will be randomized to receive 30 minutes/day of cycling and routine PT interventions or routine PT interventions alone. Assessors, blinded to treatment allocation, will measure the primary outcome of patients’ physical function at 3 days post-ICU.

Relevance: By 2026, demand for ICU services is estimated to increase by 40% and more survivors will be at risk for post-ICU disability. 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.

2. List of Abbreviations

Abbreviation	Term
6MWT	6 minute walk test
ADL	Activity of daily living
APACHE II	Acute physiology and chronic health evaluation II
CEAC	Cost-effectiveness acceptability curves
CHEERS	Consolidated health economic evaluation reporting standards
CI	Confidence interval
CIHR	Canadian Institutes of Health Research
CCCTG	Canadian Critical Care Trials Group
CONSORT	Consolidated standards of reporting trials
CRF	Case report form
D/C	Discharge
DSMB	Data safety and monitoring board
HADS	Hospital anxiety and depression scale
EQ-5DL	European quality of life – 5 dimensions
HR	Hazard ratio
HRQoL	Health-related quality of life
ICU	Intensive care unit
IPAT	Intensive care psychological assessment tool
IQR	Interquartile range
LOS	Length of stay
MV	Mechanically ventilated
PFIT-s	Physical function test for ICU – scored
PI	Principal Investigator
PRFS-ICU	Patient-reported functional scale - ICU
PT	Physiotherapy
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
RPM	Revolutions per minute
SC	Steering committee
SD	Standard deviation
SDM	Substitute decision maker
US	United States

3. Introduction

3.1 Background and Summary

Patients who survive critical illness usually experience long-lasting physical and psychological impairments, which are often debilitating.⁷⁻⁹ Demand for critical care resources is increasing in Canada and world-wide due to aging baby boomers.^{10,11} More patients are surviving their ICU stay due to medical advances,^{2,3} and these ICU survivors have diminished quality of life, with physical function impairments lasting up to 5-8 years.^{4,12} Recently, landmark Canadian research reported that patients' age and physical function at 7 days after ICU discharge predicted physical function 1 year later.¹³ Thus, optimizing patients' physical function early during their critical illness could potentially alter their recovery trajectory to improve their function 1 year later. Creative solutions to improve the physical function of ICU survivors are urgently needed.

One promising solution is early structured rehabilitation interventions in the ICU, which can reduce ICU and hospital length of stay¹⁴ (LOS), and improve physical function.^{15,16} In a quality improvement study, PT interventions during MV decreased ICU and hospital LOS by 30% and 18%, respectively.¹⁴ A systematic review of 14 RCTs showed that compared to nutrition and various modes of MV, ICU-based exercise was the most effective strategy to improve physical function in critically ill adults.¹⁷ In a 2-centre, 104 patient RCT, 59% of those who received early PT and occupational therapy interventions within 1.5 days of MV returned to independent function at hospital discharge, compared to 35% who started at 7.4 days and received none during MV ($p=0.02$).¹⁶

Leg cycle ergometry is an attractive early intervention for MV patients because it targets the lower limbs, can occur in bed while patients are sedated¹⁸ or are awake, and is easily reproducible. However, cycle ergometry in the ICU is very uncommon, with only 3% of Canadian ICU clinicians reporting frequent or occasional use.¹⁹ Cycle ergometry involves specialized portable equipment that attaches to a patient's hospital bed (*Appendix A*). It provides 3 possible activity modes to accommodate fluctuations in ICU patient participation: passive (no patient initiation), active-assisted (partially initiated by the patient), and active (fully performed by the patient).¹⁵ In a single-centre, 90 patient RCT, in-bed leg cycling starting 14 days after ICU admission in addition to usual care resulted in greater 6 minute walk test (6MWT) distances at hospital discharge compared to usual care (196m vs 143m, $p<0.05$).¹⁵ However, there are no multicenter RCTs completed, and the effect of early in-bed cycling is unknown.

3.2. Rationale for CYCLE RCT

3.2.1 The Problem: Muscle weakness that develops in the ICU is common and is associated with increased mortality, morbidity, and health care costs. Up to 87% of MV ICU patients have electrophysiological evidence of neuromuscular abnormalities,²⁰ and 55% have clinically evident weakness.²¹ Patients who develop weakness in the ICU have an increased risk of mortality, longer duration of MV, ICU, and hospital LOS, and higher hospital costs.²¹

Muscle weakness occurs quickly in the ICU, and the legs are most vulnerable to weakness with immobility. Critically ill patients who are admitted to ICU are typically exposed to prolonged bed rest, which contributes to muscle weakness, muscle atrophy, and cardiovascular deconditioning.²² Weakness and atrophy occur quickly in leg muscles, which account for 75% of total skeletal muscle mass.²³ After 7 days in ICU, quadriceps twitch tension (an involuntary objective measure of muscle force) was 4 times lower than healthy people (p

<0.001).²⁴ After 10 days, ICU patients' quadriceps size decreased almost 18% from baseline, with most atrophy occurring in the first 72 hours.²⁵ By ICU discharge, 60% of patients need to learn to walk again due to profound muscle weakness.¹³

In-bed leg cycle ergometry is a promising early ICU exercise intervention. Emerging evidence suggests that cycling can start very early. In a case-control study enrolling 16 patients within the first 96 hours of MV, cycling started within 15.3 hours of recruitment.²⁶ There were no increases in cardiac output, oxygen consumption²⁷, or safety concerns, even while patients received low-dose vasopressors.²⁷ Unlike ambulation during MV, which can require the assistance of up to 4 clinicians,²⁸ cycling only requires only 1 clinician.¹⁵ The effect of early in-bed cycling in critically ill, MV patients has not been evaluated in a multicenter RCT.

3.2.2 Principal research question(s) to be addressed:

1. **CYCLE RCT:** Among critically ill, mechanically ventilated adults, does early in-bed cycling and routine PT compared to routine PT alone improve the primary outcome of physical function at 3 days after ICU discharge and secondary outcomes of strength, physical function, frailty, psychological distress, quality of life, mortality, and healthcare utilization?
2. **Economic Evaluation:** Among critically ill, mechanically ventilated adults, what is the cost-effectiveness of cycling and routine PT compared to routine PT alone?

3.2.3 Why is a trial needed now? Current clinical practice guidelines related to PT interventions are adduced from a modest literature base, and recommendations for early rehabilitation in critically ill patients have not been implemented in practice.^{29,30} For example, the Society of Critical Care Medicine recommends early mobilization to improve outcomes in critically ill patients³¹ based on a single 104-patient RCT done in a single ICU in the United States (US). The European Society of Intensive Care Medicine recommends early active or passive mobilization based on a single centre, 85-patient study in a single ICU in the US.⁵ In spite of this limited evidence, continuing educational events targeting clinicians, researchers, and decision makers promote early rehabilitation interventions in the ICU. A recent editorial questioned the readiness of the evidence for widespread implementation of early mobilization and rehabilitation in the ICU.³² More research is required to confirm or refute these recommendations.

Recent RCTs in this field have not replicated the results of earlier promising research. Highly cited research reported positive effects of early mobility on heterogeneous outcomes.^{14,33-36} However, a systematic review identified that the majority of these reports were non-randomized, quality improvement studies,³⁷ reflecting low quality evidence that may be prone to selection bias. Challenges to conducting exercise trials with critically ill patients include low consent rates (<60%)^{26,38,39} slow recruitment, early study closure,^{39,40} difficulty delivering the intervention,^{40,41} and large losses to follow up.^{41,42} The role of in-bed cycling is not clear.

3.3 Literature Review

Physical activity is feasible and safe with MV patients. A systematic review examined 17 studies of exercise with MV patients, including interventions such as in-bed range of motion and strengthening, bed mobility (e.g., rolling, sitting at the edge of the bed), transfers (e.g., sit to stand, bed to chair), and ambulation.⁴³ Of 10 studies reporting adverse events, none occurred in 824 patients.⁴³

Exercise-based interventions could improve long-term physical function in critically ill patients. A systematic review of 14 RCTs demonstrated that ICU-based exercise studies versus non-exercise interventions (e.g., nutrition, different modes of MV) were most effective to

improve long-term physical function in critically ill adults.¹⁷ Similarly, a more specific systematic review of 17 exercise studies during MV reported that patients had better walking ability, activities of daily living (ADLs), and health-related quality of life (HRQoL).⁴³ However, 2 more recent systematic reviews documented discordant effects of ICU rehabilitation interventions on function.^{44,45} And recently, an RCT of more versus less intensive rehabilitation therapy in the ICU demonstrated no difference in function at 6 months post-ICU.⁴¹ Overall, these studies are very heterogeneous, including the population (medical vs. medical-surgical), intervention (different types, timing, and doses), comparators (variance in usual care), and outcomes (different types and timing of primary outcome). Of the RCTs to-date, the most promising signal of benefit occurs in 2 trials initiating rehabilitation within the first week of ICU admission.^{16,46} Thus, based on the rapid muscle atrophy and weakness occurring within the first 7 days of ICU, and the best available evidence, early intervention is needed.

3.4 Use of Study Results

Recent point prevalence and cohort studies document that patients receive little to no rehabilitation interventions early in their ICU stay.^{29,30,47} Results from the CYCLE RCT will advance healthcare knowledge by informing the early rehabilitation management of previously ambulatory, critically ill, MV patients. Our economic evaluation will provide justification for equipment purchase and additional personnel time required to implement cycling in the ICU.

4. Study Objectives

1. **CYCLE RCT:** To determine if early in-bed cycling and routine PT compared to routine PT alone in critically ill, mechanically ventilated adults improves the primary outcome of physical function at 3 days after ICU discharge and secondary outcomes of strength, physical function, frailty, psychological distress, quality of life, mortality, and healthcare utilization.
2. **Economic Evaluation:** To determine the cost-effectiveness of cycling and routine PT compared to routine PT alone among critically ill, mechanically ventilated adults.

4.1 Primary Outcome:

The primary outcome will be the Physical Function Test for ICU-scored (PFIT-s) measured at 3 days after ICU discharge by assessors blinded to treatment allocation.

4.2 Secondary Outcomes:

Secondary outcomes include muscle strength^{48,49} and function (e.g., 30-second sit to stand,^{50,51} 2 minute walk test).⁵² These measures have age- and sex- based reference values, and good reliability in critically ill or frail elderly populations.^{51,52} We will also collect patients' perception of physical function (Patient-reported functional scale- ICU, PRFS-ICU),^{53,54} Katz activities of daily living (ADL) scale,⁵⁵ frailty,⁵⁶ critical care-related psychological distress (Intensive Care Psychological Assessment Tool (IPAT))^{57,58}, Hospital Anxiety and Depression Scale (HADS))⁵⁹, HRQoL (EQ-5DLTM),⁶⁰⁻⁶² Quality-Adjusted Life Years (QALYs), mortality, hospital discharge location, healthcare utilization (e.g., length of MV, LOS and mortality (ICU, hospital)), and intervention and healthcare costs.

5. The Proposed Trial

5.1 Overall Trial Design

Trial design: International, 360-patient concealed open-label RCT in 17 medical-surgical ICUs with blinded outcome assessment at 3 days after ICU discharge. After informed consent, patients will be randomized to receive 30 minutes/day of in-bed cycling (Cycling) in addition to routine physiotherapy interventions, or routine physiotherapy interventions alone (Routine). (Figure 1).

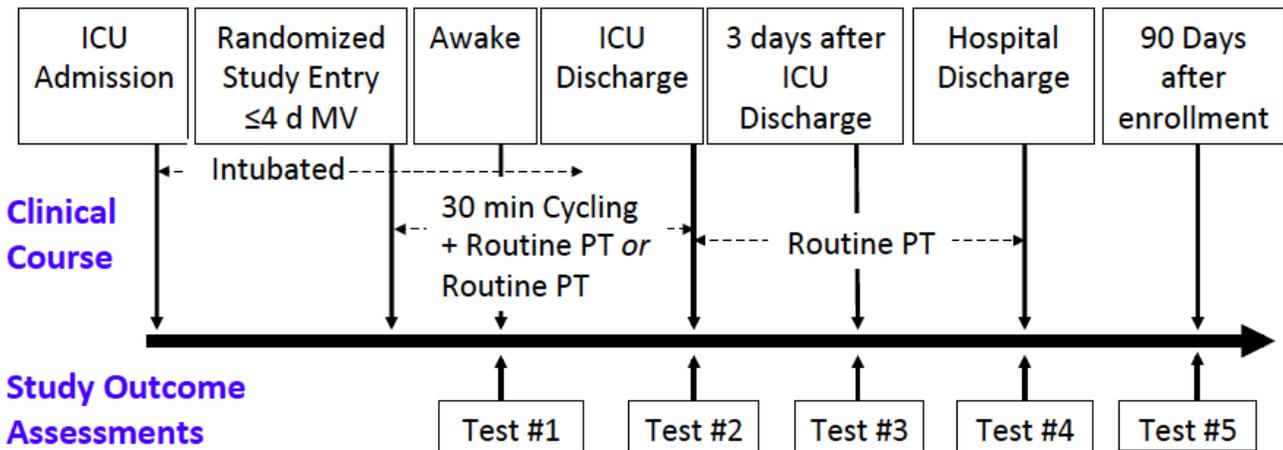


Figure 1: Study schema (not to scale). Legend: ICU=intensive care unit; MV=Mechanical ventilation; PT=physiotherapy interventions; Tests include strength and physical function, psychological distress, and health-related quality of life.

5.2 Study Population: Critically ill adult patients admitted to a medical-surgical ICU.

5.2.1 Inclusion Criteria: Eligible patients must be admitted to a participating medical-surgical ICU and must meet all of the following 4 inclusion criteria: adults (≥ 18 years old) within the first 4 days of MV and first 7 days of ICU, and who could ambulate independently before hospital admission (with or without a gait aid).

5.2.2 Exclusion Criteria:

We will exclude patients who have any one of the following criteria at the time of enrolment: acute condition impairing patients' ability to cycle (e.g., leg fracture), proven or suspected neuromuscular weakness affecting the legs (e.g., stroke or Guillain-Barré syndrome), traumatic brain injury, inability to follow commands in local language pre-ICU, severe cognitive impairment pre-ICU, temporary pacemaker, pregnant (or suspected pregnancy), expected hospital mortality $>90\%$, body habitus unable to fit the bike, palliative goals of care or able to march on the spot at the time of screening.

We will exclude patients with the following persistent therapy exemptions in the 1st 4 days of MV (*Table 1*) to ensure we start the intervention early:

5.2.3 Eligible Non-Randomized Exclusion Criteria:

1. Enrolled previously in CYCLE RCT or related study
2. Patient unable to give consent and no SDM identified
3. Patient or substitute decision maker (SDM) declines consent
4. ICU Physician declines patient or SDM to be approached
5. Other, specify

Once the research coordinator identifies potential study participants, the eligibility of every patient admitted to specified medical-surgical ICUs at participating centres will be determined by the investigator. Study participants eligible for the CYCLE RCT will fulfil all inclusion criteria, meet no exclusion criteria and provide informed consent.

5.3 Time Window for Inclusion

Following ICU admission and initiation of mechanical ventilation, research coordinators have approximately 24 hours to complete study enrollment. Initiation of the randomized intervention must occur within the first 4 days of mechanical ventilation.

5.4 Randomization and Stratification Methods

Randomization will occur after informed consent is obtained. We will conceal allocation and utilize a central randomization process. We will use a web-based, comprehensive and secure randomization service (<http://www.randomize.net/>). After consent, the site research coordinator will log in to the website, register the patient, and receive the randomized assignment, ensuring allocation concealment. We will stratify by center and age ≥ 65 or < 65 years.

5.5 Trial Interventions

Experimental - Cycling: Patients will be randomized to receive 30 minutes/ day of in-bed cycling in addition to routine physiotherapy interventions, 5 days per week, during their ICU stay. Cycling will occur for a maximum of 28 days or when the patient is able to march on the spot for 2 consecutive days, whichever occurs first (*see Section 5.7*).

To ensure we start the intervention early, we will screen patients for temporary exemptions before enrolment (*Table 1*). Because of the dynamic nature of critical illness, we will also review participants daily for temporary exemptions precluding cycling. For example, we will not cycle on a day where a patient has cardiac or respiratory instability, active major bleeding, severe agitation, or a new condition interfering with cycling. During every cycling session, patients will be carefully monitored for safety and we will document any indications for termination of cycling, including signs of cardiac or respiratory instability, and catheter or tube dislodgement (*see Section 6.2*).

We aim for participants to start the cycling intervention as early as possible, even if they are receiving MV and/ or sedative infusions. We also aim for patients to complete as much active cycling as possible during each 30-minute session. We will use a specialized in-bed cycle ergometer (e.g., RT300 supine), which provides passive, active- assisted, and active cycling (see above).¹⁵ Patients will be positioned semi-recumbently¹⁵ per ventilator-associated pneumonia prevention guidelines.^{63,64} The physiotherapist will place the patient's legs in the cycle ergometer, starting with passive cycling at a rate of 5 revolutions per minute (RPM) with 0.6 Newton-meters of resistance. If patients initiate active cycling, the physiotherapist will use standardized verbal encouragement for patients to continue active cycling. Since level of

consciousness may vary throughout the ICU stay, we will allow patients to cycle at a self-selected RPM. If the patients stop cycling actively, the ergometer will revert to passive cycling. If patients re-start active cycling, we will provide standardized verbal encouragement.

Control – Routine: Patients will receive routine PT interventions per current institutional practice. Routine PT includes, 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, ambulation, and assistance with optimizing airway clearance and respiratory function.^{16,19,34,39} We will use similar criteria to terminate routine PT sessions (See Section 6.2).

5.6 Blinding of Outcome Assessors

To protect against detection bias, at each hospital we will identify and train a core group of assessors (e.g., physiotherapists or occupational therapists), unaware of the patient’s treatment assignment to conduct blinded outcome measures at 3 days after ICU discharge and at hospital discharge. In this open-label trial, study participants, patients’ family members, research coordinators, bedside staff, physicians, and site investigators will be aware of patients’ treatment allocation.

5.7 Duration of Treatment Period

Patients will receive cycling 5 days per week, for the duration of their index ICU stay (maximum of 28 days or when able to march on the spot for 2 consecutive days, whichever occurs first). We discontinue in-bed cycling after a patient can march on the spot for 2 consecutive days to allow the patient to focus on higher yield progressive mobility activities. To ensure some exposure to the cycling intervention, patients will receive a minimum of 2 consecutive cycling sessions even if they can march on the spot for 2 consecutive days. If, after discontinuing cycling, a patient is no longer able to march on the spot, we will resume cycling up to a maximum of 28 days of their index ICU stay or when able to march on the spot for 2 consecutive days. For safety, patients will not receive cycling on days where we identify temporary exemptions (*Table 1*). After 28 days, all patients will receive routine PT interventions per institutional standards. Those randomized to routine PT interventions will not be permitted to receive in-bed cycling.

5.8 Frequency and Duration of Follow-Up

We will follow all patients throughout their ICU and hospital stay until discharge from the index hospital, death in the index hospital, or transfer to another hospital. To capture the short-term benefits of the intervention, we will conduct a follow-up call at 90-days after study enrolment to measure HRQoL, any psychological distress, and healthcare resource utilization after discharge for participants alive at hospital discharge. This time horizon of 90 days was deemed appropriate based on the CYCLE Pilot RCT data⁶⁵ (e.g., a median 26 day hospital LOS, maximum of 46 days) and the expected duration of the benefits associated with cycling.

5.9 Participating Center(s)

We anticipate the CYCLE RCT will occur in 17 academic medical-surgical ICUs (# sites): Ontario (11): Hamilton (3), Toronto (2), London (2), Ottawa (2), Kingston (1), St. Catharines (1); British Columbia (1); Quebec (2); International (3): Australia, United States, Brazil. Each ICU has or will have a dedicated in-bed cycle ergometer, and have experience leading or contributing to multi-centre critical care trials.

5.10 Eliminating Bias

We will conceal allocation and utilize a central randomization process. Randomization will occur after informed consent is obtained. We will collect relevant co-interventions that may impair patient function, including receipt of corticosteroids⁶⁶ and neuromuscular blocking agents,⁶⁷ duration of bedrest,⁶⁷ and concurrent physiotherapy interventions. To protect against detection bias, at each hospital, we will identify a core group of assessors (e.g., physiotherapists or occupational therapists), unaware of the patient's treatment assignment to conduct blinded outcome measures at 3 days after ICU discharge and at hospital discharge. We will ask patients and their family members not to disclose the patient's assigned treatment to blinded assessors to protect against performance bias. Our sample size calculation accounts for mortality to protect against survivor bias (See Section 10.1).

5.11 Recruitment Rate

We will enrol from 7/2018 to 3/2021 (Table 3). Nine sites from CYCLE Pilot and CYCLE Vanguard will receive re-orientation to the study. New sites will receive in-bed cycling training and orientation to the research protocol. We anticipate all sites will be active by Year 2, Q3.

6. Patient Safety

6.1 Risks to the Safety of Participants Involved in the Trial

In a systematic review of 48 studies and 7,546 patients, the cumulative incidence of potential adverse events during any ICU rehabilitation was only 2.6%.⁶⁸ A systematic review of 14 ICU rehabilitation RCTs demonstrated no differences in safety events or mortality at ICU and hospital discharge, and 6 months after hospital discharge.⁴⁴ In the RCT of cycling starting after 14 days in the patient's ICU stay, no severe physiologic adverse events occurred (e.g., arrhythmias, myocardial ischemia), however 1 patient withdrew due to Achilles tendon rupture.¹⁵ Our retrospective chart review documented a low adverse event rate (0.2%) in 181 patients and 541 cycling sessions.⁶⁹ Our prospective TryCYCLE study documented only infrequent termination of 205 cycling sessions due to safety concerns (2.0%, 95% CI 0.8% to 4.9%) and no device dislodgements.⁷⁰ Of all 7 cycling studies, no catheter or tube dislodgements occurred.^{15,26,27,70-73} Based on the literature, our previous experiences, the extensive training we provide, and clinical expertise of our ICU physiotherapists, we expect few safety risks to patients in the CYCLE RCT.

6.2 Serious Adverse Events

We will consider the following adverse events if they occur during or immediately after in-bed cycling or routine physiotherapy interventions, are attributable to the randomized intervention, and result in a clinical deterioration of the patient's status^{15,37,68,70,74}:

- Concern for myocardial ischaemia or suspected new unstable/ uncontrolled arrhythmia
- Sustained O₂ desaturation below baseline
- Marked ventilator dysynchrony
- Sustained symptomatic bradycardia (<40 bpm) or tachycardia (>140 bpm)
- Sustained hypertension (mean arterial pressure >120 mmHg)
- Removal or dysfunction of intravascular catheter (e.g., central venous catheter, arterial line)

We will consider the following severe adverse events:

- Unplanned extubation
- Cardiac arrest
- Fall to knees (very uncommon, and more likely during routine physiotherapy)

Adverse events, serious adverse events, and the consequences of these events will be recorded on the case report form, and will be immediately reported to the patient's clinical team. We will follow the patient until 90 days post- randomization or hospital discharge, whichever occurs first.

6.3 Removal of Study Participant and Unblinding

If a participant withdraws from the trials, we will discontinue the trial procedures. We will use information collected up to the time of withdrawal, and request permission for medical record review for safety data.

As an open-label trial, physicians, nurses, physiotherapists, patients, families and healthcare team members will be aware of patients' randomized intervention. Those assessing physical function outcomes at 3 days post-ICU and at hospital discharge will be blinded to the randomized intervention.

6.4 Pregnancy

Pregnant females will not be knowingly be enrolled in the trial. If a study participant is confirmed to be pregnant during the trial, the participating site will notify the methods centre to report of the pregnancy follow-up information regarding the peri-natal and neonatal outcome.

7. Data Collection

7.1 Data Collection

We will collect baseline data including patient demographics, ICU admission reason, medical vs. surgical status, severity of illness,⁷⁵ comorbidity,^{76,77} and pre-hospital function.⁵⁵ ICU-related variables captured daily during the patient's ICU stay will include illness severity,⁷⁵ other life supports, drug exposure, and nutrition. We will collect relevant co-interventions that may impair patient function, including receipt of corticosteroids⁶⁶ and neuromuscular blocking agents,⁶⁷ and duration of bedrest.⁶⁷ We will also record the type and duration of all physiotherapy interventions (e.g., passive or active range of motion, bed mobility and transfers, ambulation) received in the ICU. *Table 2* outlines the timeline for the CYCLE RCT trial data collection.

7.2 Monitoring of the Trial

The CYCLE RCT Methods Centre, led by the principal investigator, will oversee enrollment rates and will conduct routine central statistical monitoring of cycling adherence and outcome measure ascertainment.

7.3 Storing and Archiving Data

We will use iDataFax which is used by the CLARITY research group at McMaster University. iDataFax has been used for many local, national, and international studies. The DataFax server runs on Red Hat Enterprise Linux within a high-availability virtualized server infrastructure. The systems are maintained in 2 separate and secure physical locations providing data security and redundancy. Snapshots of the data are stored for a period of 30 days at both locations. Unauthorized access to the system is restricted by means of a firewall and data encryption protection applied to all communications.

We will limit study data access to the principal applicant, site investigators, site research coordinators, CYCLE RCT Methods Centre Study Staff, and biostatistician. We will retain data for 15 years as per institutional requirements.

8. Management of Study Device

8.1 Training

For centres with no experience with in-bed cycling or with the study bike, we will provide all those providing in-bed cycling (typically ICU PTs) with a 1-day (approximately 8 hour) training session on use of the in-bed cycle ergometer from the study PI and equipment vendor. This training session includes didactic lectures, bike resource material, and use of the cycle with both simulated and critically ill patients. Centres will gain clinical experience with routine use of the in-bed cycle with critically ill patients before enrolling patients in the CYCLE RCT.

8.2 Storage

Each centre will identify a secure location for the study bike and will be responsible for its routine maintenance.

9. Outcome Measurement

9.1 Primary Outcome: The primary outcome will be the Physical Function Test for ICU-scored (PFIT-s) measured at 3 days after ICU discharge by assessors blinded to treatment allocation. PFIT-s is a reliable and valid 4-item scale (arm and leg strength, ability to stand, and step cadence) with a score range from 0 to 10 (higher scores = better function).^{78,79} It was developed in an ICU population, includes functional items, and, unlike the 6MWT, can be measured serially over time (as few patients can walk at ICU awakening).⁸⁰ We chose the PFIT-s because we expect all ICU patients will be able to complete part of the assessment if they cannot stand (e.g., arm or leg strength), limiting floor effects, and strong psychometric properties (reliability range = 0.996 to 1.00;⁷⁹ convergent validity with the 6MWT and muscle strength⁷⁸). We selected 3 days after ICU discharge because it is proximal to the intervention, and some patients may be discharged before 7 days. Also, prior studies documented variable delivery of rehabilitation post-ICU⁸¹ that may contaminate later evaluations.

9.2 Secondary Outcomes: Secondary outcomes include muscle strength^{48,49} and function (e.g., 30-second sit to stand,^{50,51} 2 minute walk test).⁵² These measures have age- and sex-based reference values, and good reliability in critically ill or frail elderly populations.^{51,52} We will also collect patients' perception of physical function (Patient-reported functional scale- ICU, PRFS-ICU),^{53,54} Katz activities of daily living (ADL) scale,⁵⁵ frailty,⁵⁶ critical care-related

psychological distress (Intensive Care Psychological Assessment Tool (IPAT)^{57,58}, Hospital Anxiety and Depression Scale (HADS))⁵⁹, HRQoL (EQ-5DLTM),⁶⁰⁻⁶² Quality-Adjusted Life Years (QALYs), mortality, hospital discharge location, healthcare utilization (e.g., length of MV, LOS and mortality (ICU, hospital)), and intervention and healthcare costs.

All strength and physical function outcomes assessors will receive a 3-hour 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 assessors will receive paper copies of each outcome measure, administration instructions, and normative values (where available).

10. Statistical Analysis

10.1 Sample Size Calculation

Our sample size of 360 patients is based on identifying a 1.0 point mean difference⁸² between the Cycling and Routine groups for the PFIT-s 3 days after ICU discharge. Psychometric studies of the PFIT identified the minimal clinically important difference was 1.0 points.^{78,83} By logistic regression, our analysis of patients enrolled in TryCYCLE and CYCLE pilot studies identified that each 1.0 point increase in PFIT-s at ICU discharge (representing better function) was associated with a 40% reduction in the composite outcome of death, readmission to ICU, or need for paid assistance after hospital discharge.⁸² Based on a standard deviation of 2.5 points at ICU discharge^{70,84} (from our CYCLE pilot RCT, since we do not have data at 3 days after ICU), a 1.0 point difference between groups,^{78,82,83} and 90% power (0.05 alpha), we need to randomize and analyze 266 patients (133 per group). Based on pilot data, we anticipate approximately 35% total attrition (See Section 10.1), and will recruit 360 patients overall.

10.2 Statistical and Analytical Plan

CYCLE RCT: The trial will be reported in accordance with the CONSORT criteria.⁸⁵ We will adopt the intention-to-treat principle for analysis of all outcomes and will use multiple imputation to handle missing data. We will summarize baseline characteristics by group reported as mean (SD) or median (first quartile, third quartile) for continuous variables and count (percent) for categorical variables. We will use chi-squared test for analysis of binary outcomes. The criterion for statistical significance will be set at $\alpha = 0.05$. The results will be reported as estimates of hazard ratios [HR] (corresponding 95% (CI)) and associated p-values, reported to 3 decimal places with those < 0.001 reported as $p < 0.001$. All analyses will be performed using SAS 9.2 (Cary, NC).

For our **Primary outcome**, we will conduct an independent t-test (normal distribution) or Mann-Whitney U test (non-normal distribution) to determine if there is a difference in PFIT-s score at 3 days after ICU discharge between the Cycling and Routine groups. We consider a 1-point difference in score clinically and statistically important (Section 2.10).

Economic Evaluation: The base case analysis will use the Canadian algorithm to derive the EQ-5D utility scores.⁶² QALYs will be calculated by weighting the EQ-5D utility scores by time spent in health state using an area under the curve approach. From a cost

perspective, we will amortize the cost of the cycle based on site-specific information (e.g. amortization rules, annual ICU days associated with therapy services) and patients eligible to receive cycling (from screening logs). Based on our pilot data we estimate the cost of the bike per patient to be \$100, assuming a bike cost of Cdn\$25,000, an amortization over 5 years and that 50 patients will use the bike per year ($\$25,000/5/50 = \100); this may vary by site. Inpatient (e.g., therapist time, ICU and hospital LOS) and post-hospital resources during the 90-day follow-up (e.g. # rehabilitation therapy sessions since discharge) will be multiplied by their respective unit costs (e.g. therapist hourly wage, average cost/day in ICU and general ward). The base case analysis will use unit costs from Ontario, since 11 of 17 sites are in Ontario (*Section 5.9*).

We will compare the Cycling and Routine groups by mean differences in costs and effects using parametric or non-parametric tests as described above. To deal with sampling uncertainty, bootstrap techniques will be used by drawing a random sample from the original dataset (with replacement) and then calculate the mean costs and effects associated with each treatment group.^{86,87} The sampling process will be repeated 1,000 times to create a sampling distribution and generate 95% CIs around the costs and the effects associated with each intervention. Cost-effectiveness acceptability curves (CEACs) will be used to present the probability of the intervention to be cost-effective at different willingness-to-pay thresholds (\$50,000/QALY gained; \$100,000/QALY gained). Several sensitivity analyses will be conducted to explore variation between sites or countries or sub-groups or to check the impact of certain assumptions (e.g. bike cost per patient, unit costs, baseline utility). Net benefit regressions will be used to adjust for covariates if required.⁸⁸ The economic evaluation will be conducted according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS)⁸⁹ and good practices.^{87,89-93}

10.3 Frequency of Analyses

We will conduct one interim analysis after 180 patients (half of our sample) are discharged from hospital to assess for harm and benefit. We will use conservative statistical guidelines for data monitoring based on the modified Haybittle-Peto rule.⁹⁴ To maintain the overall type-I error rate (i.e., α), we will evaluate the primary endpoint using a fixed simple conservative $\alpha=0.001$ for the interim analyses and $\alpha=0.05$ for the final analysis.

10.4 Subgroup Analyses

We will conduct a subgroup analysis of patients <65 and ≥ 65 years old, frailty or not (baseline clinical frailty score⁵⁶ ≤ 4 and > 4), and sex (male vs. female). Since older patients are underrepresented in ICU trials,⁹⁵ and no trials have specifically studied early cycling in the elderly critically ill,⁹⁶ a subgroup analysis will help to identify any age-related differences in response to rehabilitation. Critically ill patients with frailty have worse outcomes,⁹⁷ however the effects of frailty on exercise are not known. To support the Government of Canada's Health Portfolio, we will conduct an analysis by sex.⁹⁸ Given the exploratory nature of these analyses, we will use tests for interactions between the subgroup and treatment group variables in the regression analysis.

10.5 Loss to Follow-Up Rate

Our ICU mortality was 27% (18/66) in the CYCLE Pilot RCT.⁶⁵ Based on preliminary data from CYCLE Vanguard, 1 person died between ICU discharge and 3 days post-ICU. In

CYCLE Vanguard, we added the assessment 3 days post-ICU, and our primary outcome ascertainment rate was 95% (20/21); 90% (18/20) of these occurred with blinded assessors. Based on these data, we estimate 35% attrition (25% ICU mortality, 1% mortality in the first 3 days post-ICU discharge, 5% missed primary outcome assessments at 3 days post-ICU, and 5% unblinded).

If a study participant, SDM, clinician, or investigator discontinues participation in the trial, data from the study participant will be included in the group to which they were randomized. We will replace any patients withdrawn from the study. We will use information collected up to the time of withdrawal, and request permission for medical record review for safety data.

10.6 CYCLE RCT Compliance

We successfully delivered the early in-bed cycling protocol in 7 Canadian centres in the CYCLE Pilot RCT.⁶⁵ Our median (IQR) time from ICU admission to cycling was 3 (2 to 5) days, and cycling occurred on 146 (79%) of all eligible days, representing a mean (SD) delivery of 78% (27) per patient and mean (SD) session duration of 27.4 (7.0) minutes. Of 39 eligible days, physiotherapist availability (56%) and patient declines (49%) were the most common reasons that cycling did not occur. In the CYCLE RCT, we will regularly monitor compliance with the cycling protocol, provide individualized centre feedback, and identify strategies to optimize cycling delivery.^{99,100}

11. Pilot results

The CYCLE Program of Research: Critical Care Cycling to Improve Lower Extremity Strength

CYCLE is an interdisciplinary, multi-method, 5-phase research program to investigate the use of early in-bed cycling in critically ill patients who are receiving MV. Extensive pilot work from our team demonstrated that protocolized in-bed cycling can start within 3 days of MV, even if patients are deeply sedated.^{65,70} It is safe and feasible in multiple ICUs, and we can accurately record patient functional outcomes.^{65,70,101,102} **Preparation Phase:** UniCYCLE was a retrospective chart audit of in-bed cycling.¹⁰³ **Phase 1:** TryCYCLE (NCT01885442, CIHR funded) prospectively evaluated safety and feasibility in 33 patients, had a high consent rate (92%), and low rate of cycling termination for safety (2.0%).^{70,104} **Phase 2:** a) CYCLE Pilot RCT (NCT02377830, CIHR funded) enrolled 66 patients in 7 Canadian centres, with 85% consent, 79% cycling delivery, and 82% blinded outcome ascertainment, illustrating the ability and commitment of the critical care community to address this research question.^{65,101,102} b) CYCLE Vanguard (CIHR funded) enrolled 40 patients, added 2 international sites (US, Australia), added a physical function assessment at 3 days after ICU discharge, and refined enrolment and cycling strategies. **Phase 3 (current application):** a) **CYCLE RCT**; b) **CYCLE\$** economic evaluation; **Phase 4 (future):** BICYCLE, a behavioural knowledge translation intervention.

We have conducted extensive preparatory work. We can deliver early in-bed cycling safely within the first 4 days of MV and throughout a patient's ICU stay.^{65,70} In 7 centres, we taught 36 ICU physiotherapists to cycle, 58 to conduct outcome measures, and completed enrolment in 15 months.¹⁰⁵ We can initiate the randomized protocol in multiple international centres, achieve a high consent rate, deliver the cycling intervention, and measure blinded

outcomes.^{65,101,102} We identified potential barriers to enrolment and addressed them with additional pilot work in CYCLE Vanguard. Our 9 pilot sites are prepared to participate in the full RCT, we are ready to train and initiate 8 new sites, and poised to enrol the 320 patients in 32 months.

12. Trial Management

12.1 CYCLE RCT Methods Centre

Methods Centre: The CYCLE RCT will be organized and administered through McMaster University by a critical care research coordinator under the leadership of Dr. Kho. The Methods Centre will oversee all contracts, ethics 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 (e.g., standard operation procedures, operations manuals, data collection forms) for participating sites and be the point contact for study questions. Dr. Kho and the Methods Centre will lead monthly teleconferences among participating sites to provide study updates, offer opportunities to clarify protocol-related questions, and share strategies to optimize study delivery.

12.2 Principal Applicant and Co-applicant Roles

Principal Applicant (20 h/wk): Dr. Kho holds a Tier II Canada Research Chair, is a new investigator, has 75% protected time for research, and successfully led the 3 CIHR-funded studies in preparation for the CYCLE RCT. She will be responsible for the overall design, conduct, analysis, coordination, and financial management of the study, will lead the Methods Centre (*Section 12.1*) and communicate regularly with Site Leads.

Co-Applicants: Site Leads (3-5 h/wk;): Responsible for the implementation of the research protocol in their respective ICUs. Working closely with Dr. Kho and the Methods Centre, the Site Leads will be responsible for engaging local research personnel to prepare ethics review, negotiate contracts, screen, recruit and enrol patients, deliver the randomized intervention, and resolve local barriers to protocol implementation.

Biostatistician (1h/wk): Sample size calculation, statistical advice, and statistical analyses.

Health Economist (1h/wk): Design and conduct of economic analysis.

Each member of our multidisciplinary team will provide contributions to study design, implementation, and analysis (1h/wk): **Clinical:** physiotherapy, internal medicine, surgery, critical care, and psychology. **Methodologic:** Advanced training in clinical epidemiology or public health, health economics, biostatistics, clinical trials, and knowledge translation. Senior members will share their multicenter trial experience with protocol implementation. **All:** Interpretation of analyses, manuscript development.

All of our Canadian site leads are members of the CCCTG, a multidisciplinary national organization with research commitment to improving the outcomes of critically ill patients. The CCCTG also provides training and workshops for research personnel responsible for patient recruitment, and access to trial-related documentation (e.g., standard operating procedures, regulatory guidance documents, etc.).

12.3 Steering Committee

The CYCLE **Steering Committee** (SC) will be a subgroup of co-investigators, including Dr. Kho, Dr. Cook (senior intensivist and trialist), all site leads (*Section 12.2*), and the Methods

Centre coordinator who will offer clinical guidance and input on any necessary protocol revisions.

12.4 Data Safety and Monitoring Board

An independent **Data Safety and Monitoring Board** (DSMB) will oversee CYCLE, including a senior biostatistician (e.g., Dr. E Pullenayegum, Canada), and 2 ICU physicians with trial expertise (e.g., Dr. M Moss, US; Dr. N Hart, UK). A DSMB Charter¹⁰⁶ will guide their process to assess the progress of the trial. The DSMB will review the protocol, adherence, efficacy and safety reports, and the full analysis. They will make their recommendations to the SC after considering all of the available efficacy and safety study data and external data from relevant studies. The DSMB will maintain written records of all its meetings.

12.5 Publication Policy and Dissemination of Results

We will disseminate our research through local and national presentations, international scientific conferences (e.g., American Thoracic Society, Canadian Frailty Network), and peer-review publications.

13. Ethical Issues

13.1 Selection of Participants

In each centre, an ICU research coordinator will screen the ICU census regularly to identify patients who meet study criteria. Once their research coordinator identifies a potentially eligible patient, he or she will contact the most responsible physician for his or her assent to approach the patient or their substitute decision maker for consent. Given that most ICU patients are unable to provide informed consent, consent will be obtained from SDMs when necessary. Once patients are alert, they will be evaluated for capacity and consented for continuation in the trial.

13.2 Consent Process

The trial will be conducted in concordance with the Ethical Conduct for Research Involving Human Tri-Council Policy Statement 2 (<http://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/Default/>). A research coordinator will approach the patient or substitute decision maker to explain the trial objectives. The research coordinator will explain to the patient or substitute decision maker that their decision regarding participation in this trial will not impact the care they receive in the ICU. To minimize coercion, the research coordinator will not be responsible for clinical care of the patient in the ICU.

If a substitute decision maker is not available in person, we will contact them by phone to describe the study objectives and determine their interest in learning more about the research study. If interested, we will follow-up with further information about the study and seek verbal consent, verification of consent by a second party, and follow-up of written consent.

Throughout the study participants' intensive care unit (ICU) stay, we will maintain contact with the study participant and their SDM. We will periodically assess participants for their capacity to engage in decision-making. If informed consent was originally provided by an SDM, we will evaluate capacity for providing first-party consent from the patient. If the study participant declines continued participation, we will respect their wishes.

13.3 Confidentiality

We will safeguard study participant information by assigning each participant a unique code for the study. The participant will be identified by this code for the study, and the case report forms will not include the study participant's name or any other personal identifiable data. At each participating site, the site investigator will retain a list that links the participants' code names with their actual name so data can be re-linked if necessary. The study code and identifiable personal health information will be isolated from the study data and stored in a secure manner at each site (e.g., locked cabinet in locked institutional office, password-protected computer on a secure network).

We will use iDataFax which is used by the CLARITY research group at McMaster University. iDataFax has been used for many local, national, and international studies. The DataFax server runs on Red Hat Enterprise Linux within a high-availability virtualized server infrastructure. The systems are maintained in 2 separate and secure physical locations providing data security and redundancy. Snapshots of the data are stored for a period of 30 days at both locations. Unauthorized access to the system is restricted by means of a firewall and data encryption protection applied to all communications

13.4 Co-Enrollment

Co-enrollment will be permitted with the CYCLE RCT. The Steering Committee will review potential trials to determine if the trial in question is suitable or not for co-enrollment.

14. Tables

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

Cycling or physiotherapy interventions **will not occur** if 1 or more of the following conditions are present:

1. Increase in vasopressor/ inotrope within last 2 hours
 2. Active myocardial ischemia, or unstable/ uncontrolled arrhythmia per ICU team
 3. Mean arterial pressure <60 or >110 mmHg or per treating team within the last 2 hours
 4. Heart Rate <40 or >140 bpm within the last 2 hours
 5. Persistent SpO₂ <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 (e.g., acute peritonitis, new incision/wound, known/suspected muscle inflammation (e.g., rhabdomyolysis))
 11. Patient or proxy refusal
-

Table 2: Time-Events Schedule

	Study Period							
	Enrolment	Allocation	Post-allocation					
Timepoint	ICU admission	0	In ICU	ICU awakening	ICU D/C	3 days post-ICU D/C	Hospital D/C	90 days post-enrolment
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 ⁷⁵	X							
Charlson comorbidity index ⁷⁶	X							
Functional comorbidity index ⁷⁷	X							
Clinical Frailty Scale ⁵⁶	X						X	
Function: Katz Activities of Daily Living scale ⁵⁵	X				X		X	
Physical Strength and Function*				X	X	X (blinded)	X (blinded)	
Psychological distress: Intensive Care Psychological Assessment Tool ⁵⁷				X				
Quality of life: Euro-QOL 5DL ^{60,61}					X		X	X
Hospital Anxiety and Depression Scale ⁵⁹								X
Data Collection:								
Baseline demographics	X							
Co-interventions			Document daily on CRFs					
Study-related Serious Adverse Events			Document daily on CRFs					
ICU and Hospital Length of Stay							X	
Mortality					X		X	X

Legend: In this table, we outline patient enrolment, interventions, and assessments in the CYCLE RCT. *Strength and function assessments at ICU awakening include Physical Function ICU Test (scored)^{78,79}, Medical Research Council Sum Score^{48,49}, and 30 second sit to stand test^{50,51}; at ICU discharge, 3 days post-ICU discharge, and hospital discharge, includes all ICU awakening assessments plus the 2 minute walk test^{52,107}. Abbreviations: ICU = intensive care unit; D/C = discharge; PT = physiotherapy; CRF = case report form.

Table 3: Gantt Chart of Planned Recruitment

Activity by Quarter	Pre	Year 1				Year 2				Year 3				Year 4	
		1	2	3	4	1	2	3	4	1	2	3	4	1/2	3/4
Start-up and enrolment															
Previous sites (n=9)	40	-	6	6	16	23	18	18	23	23	18	18	18	-	
New sites (n=8)		-	-	-	-	2	8	16	23	23	16	16	16	13	
Randomized patients		-	6	6	16	25	26	34	46	46	34	34	34	13	
Cumulative total*	40	40	46	52	68	93	119	153	199	245	279	313	347	360	

Legend: Quarter 1= April / May / June; Quarter 2= July / August / September; Quarter 3= October / November / December; Quarter 4= January / February / March; #= number of patients enrolled; *Cumulative total includes 40 patients from CYCLE Vanguard Pilot RCT.

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