Early in-bed cycle ergometry with critically ill, mechanically ventilated patients - Statistical Analysis Plan for CYCLE (Critical care cycling to improve lower extremity strength), an international, multi-centre, randomized clinical trial

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Abstract

Background: Survivors of critical illness are at risk of developing physical dysfunction following intensive care unit (ICU) discharge. ICU-based rehabilitation interventions, such as early-in bed cycle ergometry, may improve patients' short-term physical function. CYCLE (Critical care cycling to improve lower extremity strength) is a 360-patient, international, multi-center, open-label, parallel group randomized control trial (1:1 ratio) with blinded primary outcome assessment at 3 days post-ICU discharge.

Objective: Before unblinding and trial database lock, we describe a prespecified statistical analysis plan (SAP) for the CYCLE RCT.

Methods: The CYCLE principal investigator and statisticians prepared this SAP with approval by the steering committee and coinvestigators. The SAP defines the primary and secondary outcomes (including adverse events), and describes the planned, primary, secondary, and subgroup analyses.

Results: The primary outcome for the CYCLE trial is the Physical Function Intensive Care Unit Test-scored (PFIT-s) at 3 days post-ICU discharge. The PFIT-s is a reliable and valid performance-based measure. We plan to use a frequentist statistical framework for all analyses. We will conduct a linear regression to analyze the primary outcome, including randomization as an independent variable, adjusting for age (? 65 years versus <65 years) and center. We will report the regression results as mean difference in PFIT-s with corresponding 95% confidence intervals (CIs) and p-values. We consider a 1-point difference in PFIT-s score as clinically important. We plan 3 subgroup analyses including age (?65 versus <65 years), frailty (Baseline Clinical Frailty Scale ?5 versus <5) and sex (male versus female).

Conclusions: We developed and present an SAP for the CYCLE RCT and will adhere to it for all analyses. This study will add to the growing body of evidence evaluating the efficacy and safety of ICU-based rehabilitation interventions. Clinical Trial: NCT03471247 (Full RCT); NCT02377830 (CYCLE Vanguard 46 patient internal pilot)

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Abstract

Background: Survivors of critical illness are at risk of developing physical dysfunction following intensive care unit (ICU) discharge. ICU-based rehabilitation interventions, such as early-in bed cycle ergometry, may improve patients' short-term physical function.

Objective: Before unblinding and trial database lock, we describe a prespecified statistical analysis plan (SAP) for the CYCLE RCT.

Methods: CYCLE (Critical care cycling to improve lower extremity strength) is a 360-patient, international, multi-center, open-label, parallel group randomized control trial (1:1 ratio) with blinded primary outcome assessment at 3 days post-ICU discharge. The CYCLE principal investigator and statisticians prepared this SAP with approval by the steering committee and coinvestigators. The SAP defines the primary and secondary outcomes (including adverse events), and describes the planned, primary, secondary, and subgroup analyses.

The primary outcome for the CYCLE trial is the Physical Function Intensive Care Unit Test-scored (PFIT-s) at 3 days post-ICU discharge. The PFIT-s is a reliable and valid performance-based measure. We plan to use a frequentist statistical framework for all analyses. We will conduct a to analyze the primary outcome, including randomization as an independent variable, adjusting for age (≥ 65 years versus <65 years) and center. We will report the regression results as mean difference in PFIT-s with corresponding 95% confidence intervals (CIs) and p-values. We consider a 1-point difference in PFIT-s score as clinically important. We plan 3 subgroup analyses including age (≥65 years versus <65 years), frailty (Baseline Clinical Frailty Scale ≥5 versus <5) and sex (male versus female).

Results: CYCLE was funded in 2017, and enrollment was completed in May 2023. Data analyses are currently underway, and the first results are expected to be submitted for publication in 2024.

Conclusions: We developed and present an SAP for the CYCLE RCT and will adhere to it for all analyses. This study will add to the growing body of evidence evaluating the efficacy and safety of ICU-based rehabilitation interventions.

Trial registration: NCT03471247 (Full RCT); NCT02377830 (46 patient internal pilot)

Key words: Rehabilitation; mechanical ventilation; cycle ergometry; critical illness; exercise therapy; recovery of function.

Introduction

Background and rationale

Survivors of critical illness are at risk of developing physical dysfunction lasting from 5 to 8 years post- intensive care unit (ICU) discharge.[1, 2] Muscle atrophy can occur quickly during critical illness, in particular for leg muscles which are most vulnerable to developing weakness due to immobility in the ICU.[3] Quadriceps size can decrease approximately 18% during a 10-day stay in the ICU, with a high rate occurring within the first 3 days of ICU admission.[4] *At 1-year follow-up, approximately 35% of ICU survivors had sub-normal 6-minute walk distance, and approximately 50% had not returned to work.[5] Before the pandemic, demand for Canadian ICU services was projected to increase by 40% from 2011 to 2026; based on 75% survival [6] and a conservative estimate of 50% post-ICU disability rate, national healthcare utilization costs by ICU survivors 5 years after hospitalization is estimated at over $1.6 billion.[7]*

Physical rehabilitation started in the ICU can improve patients' functional outcomes at hospital discharge.[8, 9] In a randomized trial, critically ill patients randomized to in-bed cycling starting 2 weeks after ICU admission had farther 6-minute walk distance at hospital discharge compared to those receiving routine physiotherapy alone.[8] In-bed cycling starting earlier in a patient's ICU stay is safe[10-12] and feasible[13], but its efficacy on patients' physical function is unknown. To address this, we planned a randomized trial comparing early in-bed cycling and usual physiotherapy versus usual physiotherapy alone. We report this statistical analysis plan (SAP) according to the guidelines for the content of SAPs in clinical trials.[14]

Objectives

The primary objective of the CYCLE (Critical Care Cycling to Improve Lower Extremity Strength)

RCT is to determine the efficacy of early in-bed cycling (beginning within 4 days of starting invasive mechanical ventilation) and Usual physiotherapy versus Usual physiotherapy alone on patients' physical function at 3 days post- ICU discharge. We hypothesize that patients receiving in-bed cycling and usual physiotherapy will have better physical function at 3 days post-ICU discharge than those receiving usual physiotherapy alone.

Methods

Design

CYCLE is a 360-patient, international, multi-center, open-label, parallel group randomized trial (1:1 ratio) with blinded primary outcome assessment at 3 days post-ICU discharge. Assessors were blinded to treatment group allocation. The study includes patients from a 46-patient internal pilot (NCT02377830).

Sites

The trial involves 17 sites in Canada, Australia, and the United States. Sites were identified through established research networks and chosen to participate based on interest and capacity to conduct the trial. Each site obtained local ethics approval.

Eligibility

Table 1. Trial inclusion and exclusion criteria.[15]

Inclusion and Exclusion Criteria
Inclusion Criteria 1. Adults (>=18 years) 2. Within the first 4 days of mechanical ventilation 3. Expected additional 2 days ICU stay 4. Within the first 7 days of ICU admission 5. Could ambulate independently before hospital admission (with or without a gait aid)

Exclusion Criteria

1. Acute condition impairing patients' ability to cycle (e.g., leg fracture)
2. Acute proven or suspected neuromuscular weakness affecting the legs (e.g., stroke or Guillain-Barré syndrome)
3. Traumatic brain injury
4. Inability to follow commands in local language pre-ICU
5. Severe cognitive impairment pre-ICU
6. Temporary pacemaker (internal or external)
7. Pregnant (or suspected pregnancy)
8. Expected hospital mortality >90%
9. Body habitus unable to fit the bike (e.g., leg amputation, morbid obesity)
10. Specific surgical exclusion as stipulated by surgical or ICU team
11. Palliative goals of care
12. Able to march on the spot at the time of screening
13. Persistent therapy exemptions in the first 4 days of mechanical ventilation:
    i. Increase in vasopressor/ inotrope within the last 2 hours
    ii. Active myocardial ischemia, or unstable/ uncontrolled arrhythmia per ICU team
    iii. Mean arterial pressure <60 mmHg or >110 mmHg or per treating team within the last 2 hours
    iv. Heart rate <40 bpm or >140 bpm within the last 2 hours
    v. Persistent SpO_2 <88% or per treating team within the last 2 hours
    vi. Neuromuscular blocker within the last 4 hours
    vii. Severe agitation (Richmond Agitation and Sedation Scale >2 [or equivalent] [16]) within last 2 hours
    viii. Uncontrolled pain
    ix. Change in goals to palliative care
    x. Team perception that in-bed cycling or physiotherapy is not appropriate for other new reasons (e.g., acute peritonitis, new incision/wound, known/suspected muscle inflammation (e.g., rhabdomyolysis))

Eligible, non-randomized Exclusion Criteria

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

Randomization

Randomization occurred after informed consent was obtained. We concealed allocation and used a central randomization process. We used a web-based, comprehensive, and secure randomization service (http://www.randomize.net/). After obtaining consent, the site research coordinator logged in to the website, registered the patient, and received the randomized assignment, ensuring allocation concealment. We stratified patients by centre and age (≥ 65 years vs. < 65 years old).

Intervention and comparator

Intervention (Cycling + Usual physiotherapy)

Patients randomized to cycling received 30 minutes/ day of in-bed cycling in addition to Usual physiotherapy (PT) interventions, 5 days per week, during their ICU stay. Cycling occurred for a maximum of 28 days or stopped when the patient could march on the spot for 2 consecutive days, whichever occurred first.

Comparison (Usual physiotherapy)

Patients randomized to Usual physiotherapy received interventions per current institutional practice. Based on the patient's alertness and medical stability, Usual physiotherapy included 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.[9, 17-19]

Outcomes

Primary Outcome

The primary outcome for this study was the PFIT-s measured at 3 days post-ICU discharge.[20, 21] The PFIT-s includes 4 items (arm strength, leg strength, ability to stand, and step cadence), each scored from 0 to 3, summed to a maximum of 12 points, and transformed to a total score of 10 (Table 2).[20] Higher scores represent better function. The PFIT-s was developed in an ICU population, includes functional items commonly conducted during physical rehabilitation sessions, and, unlike the 6-minute walk test (6MWT), can be measured serially over time (as few patients can walk at ICU awakening).[22] Psychometric studies of the PFIT-s identified the minimal clinically important difference was 1.0 points.[20, 23] We chose the PFIT-s because we expected all ICU patients would be able to complete part of the assessment even if they could not stand (e.g., arm or leg strength), thereby limiting floor effects.

Table 2: PFIT-s Scoring (adapted from Denehy et al.)[20]

	PFIT-s Component value score			
	0	1	2	3
Shoulder strength	MRC grade 0, 1, or 2	MRC grade 3	MRC grade 4	MRC grade 5
Knee Strength	MRC grade 0, 1, or 2	MRC grade 3	MRC grade 4	MRC grade 5
Sit-to-Stand assistance	Unable	Assist of 2 people	Assist of 1 person	No assistance
Step Cadence	Unable	>0 to 49	50 to <80	>80

MRC = Medical Research Council strength grade (0 to 5)

The PFIT-s is reliable and valid in critically ill patients, with strong psychometric properties (reliability range = 0.996 to 1.00 [21]; convergent validity with the 6MWT and muscle strength [20]). We selected 3 days post-ICU discharge because it is proximal to the intervention and prior studies documented variable delivery of rehabilitation post-ICU[24] that may contaminate later evaluations. Table 3 describes the pre-planned primary outcome, subgroup, and sensitivity analyses.

Table 3: Description of Primary outcome measure, subgroup, and sensitivity analyses

Analysis of Primary Outcome	Description of Outcome	Measurement Timing	Analysis
Physical Function ICU Test-scored[1,2]	Based on 4 patient activities: arm strength, leg strength, ability to stand, and step cadences. Total scores range from 0 to 10 with higher scores meaning better function.	3 days after ICU discharge	Linear regression, adjusted for age and clinical site
Subgroup Analyses			
Objective	**Hypothesis**	**Analysis**	
i. To determine if age modifies the effect of cycling plus usual physiotherapy versus usual phjysiotherapy alone on the primary outcome.	Cycling will be more effective in older patients than in younger patients.	Linear regression adjusted for age and clinical site, which also includes a term for the interaction between age (≥65 years versus <65 years) and randomized allocation	
ii. To determine if baseline clinical frailty modifies the effect of cycling plus usual physiotherapy versus usual physiotherapy alone on the primary outcome.	Cycling will be more effective in patients with baseline frailty than in patients without baseline frailty.	Linear regression adjusted for age and clinical site, which also includes the main effect of frailty (≥5 versus <5) and a term for the interaction between frailty and randomized allocation	
iii. To determine if sex modifies the effect of cycling plus usual physiotherapy versus usual physiotherapy alone on the primary outcome.	Cycling will be more effective in male than in female patients.	Linear regression adjusted for age and clinical site, which also includes the main effect of sex and a term for the interaction between sex and randomized allocation	
Sensitivity Analyses			
i. To account for ICU mortality on the primary outcome.	Accounting for mortality will not change the effect of cycling on the primary outcome.	Linear regression, adjusted for age and clinical site. All patients will be included. Those who died prior to 3 days post-ICU discharge will be assigned a PFIT-s score of 0.	
ii. To determine the effect of cycling plus usual physiotherapy versus usual	Including only patients with blinded assessment of the primary outcome will not	Linear regression, adjusted for age and clinical site. Only patients with blinded	

physiotherapy alone including only blinded assessment of primary outcome.	change the effect of cycling on the primary outcome.	PFIT-s assessments will be included.
iii. To determine the effect of cycling plus usual physiotherapy versus usual physiotherapy alone under maximal protocol conditions.	Cycling will more greatly be associated with increased function in patients with higher protocol adherence.	Linear regression, adjusted for age and clinical site. Only patients who received the randomized intervention or had a temporary exemption on ≥80% of planned intervention days will be included.
iv. To determine the effect of cycling plus usual physiotherapy versus usual physiotherapy alone in those patients with completed assessment of the primary outcome.	Including only patients with complete assessment of the primary outcome will not change the effect of cycling on the primary outcome.	Linear regression adjusted for age and clinical site. Only patients with a total score for the PFIT-s at 3 days post-ICU discharge will be included.
v. To determine if the cycling effect is affected by centre, we will conduct analysis adjusting for age only.	Excluding adjustment for clinical site will not change the estimated effect of cycling on the primary outcome.	Repeat the primary linear regression adjusted for age only (i.e., exclude clinical site)

Secondary Outcomes

Secondary outcomes include performance-based, patient-reported, and those collected by chart review. Performance-based measures included muscle strength (Medical Research Council Sum Score)[25, 26] and function (30-second sit to stand,[27, 28] 2-minute walk test).[29] The 30-second sit-to-stand and 2-minute walk test are reliable in critically ill or frail elderly populations; these tests also have age- and sex-matched norms.[28, 29] Patient-reported measures included the Patient-Reported Functional Scale for the ICU (PRFS-ICU),[30, 31] critical care-related psychological distress using the Intensive Care Psychological Assessment Tool (IPAT),[32, 33] health-related quality-of-life using the EuroQuol (EQ-5D-5L™),[34-36] and the Hospital Anxiety and Depression Scale (HADS).[37] We also collected frailty (Clinical Frailty Scale),[38] Katz activities of daily living (ADL) scale,[39] duration of mechanical ventilation, length of stay (ICU and hospital),

mortality at multiple time points(ICU, hospital, 90-day post-randomization), and change in living location at hospital discharge from baseline. Due to funding limitations, we restricted 90-day post-randomization outcomes to those enrolled after March 7, 2018. Table 4 describes our pre-planned secondary outcome analyses and their timing.

Table 4: Description of Secondary outcome measures and analyses

Outcome	Description of Outcome	Measurement Timing	Analysis
Physical Function ICU Test [20, 21]	Patients complete 4 activities: arm strength, leg strength, ability to stand, and step cadences. Total scores range from 0 to 10 with higher scores representing better function. The PFIT-s has strong psychometric properties (reliability range=0.996 to 1.00; convergent validity with the 6 min walk distance and muscle strength).[20, 21]	ICU awakening, ICU discharge, hospital discharge	Includes survivors at each time point. Separate linear regressions for each timepoint, adjusted for age
Medical Research Council Sum Score [40, 41]	Standardized physical exam of 6 muscle groups (3 upper, 3 lower), using a 6-point scale (0=no contraction; 5= contraction sustained against maximal resistance), summed to a total score. Total scores range from 0 to 60 with higher scores representing more strength. The MRC Sum Score has excellent inter-rater reliability (ICC, 95% CI: 0.98, 0.95 to 1.00).[25]	ICU awakening, ICU discharge, 3 days after ICU discharge, hospital discharge	Includes survivors at each time point. Separate linear regressions for each timepoint, adjusted for age
ICU-Acquired Weakness - Medical Research Council Sum Score, categorized as <48 versus ≥48 [40, 41]	Standardized physical exam of 6 muscle groups (3 upper, 3 lower), using a 6-point scale (0=no contraction; 5= contraction sustained against maximal resistance), summed to a total score. Total scores range from 0 to 60 with higher scores representing more strength	ICU awakening, ICU discharge, 3 days after ICU discharge, hospital discharge	Includes survivors at each time point. Separate logistic regressions for each timepoint, adjusted for age
30 second sit to	Patient completes as many full	ICU awakening, ICU	Includes survivors

Outcome	Description of Outcome	Measurement Timing	Analysis
stand test [27, 42]	sit to stand repetitions as possible within 30 seconds. Higher scores represent better strength. The 30 second sit to stand test has good inter-rater reliability with critically ill patients (ICC, 95% CI: 0.85, 0.76 to 0.90).[43]	discharge, 3 days after ICU discharge, hospital discharge	at each time point. Separate linear regressions for each timepoint, adjusted for age
2-minute walk test [29, 44]	Patient walks as far as possible over 2 minutes. Higher scores represent better endurance. The 2-minute walk test has good inter-rater reliability with critically ill patients (ICC, 95% CI: 0.78, 0.66 to 0.87).[43]	ICU discharge, 3 days after ICU discharge, hospital discharge	Includes survivors at each time point. Separate linear regressions for each timepoint, adjusted for age
Intensive Care Psychological Assessment [32]	Patients answer 10 questions related to psychological distress in the ICU using a 3-point scale (0=no; 1=yes, a bit; 2=yes, a lot), summed to a total score. Total scores range from 0 to 20, with higher scores representing more distress. The Intensive Care Psychological Assessment has good test-retest reliability (r=0.8) and concurrent validity with other measures of anxiety and depression.[32]	Following ICU awakening assessment	Includes survivors. Linear regression, adjusted for age
Patient-reported functional score for ICU [45]	Patients answer 6 questions about their current perception of function, using an 11-point scale (0=unable to perform activity; 10=able to perform activity at same level as before ICU admission), summed to a total score. Total scores range from 0 to 60, with higher scores representing better function. The patient-reported functional score for ICU has excellent inter-rater reliability (ICC, 95% CI: 0.91, 0.76 to 0.97).[45]	ICU discharge, hospital discharge, 90-days post-randomization	Includes survivors at each time point. Separate linear regressions for each timepoint, adjusted for age
Euro-QOL 5D 5L Index [36]	Patients answer 5 questions about their current perception of mobility, self-care, usual activities, pain/discomfort, and	ICU discharge, hospital discharge, 90 days post-	Includes survivors at each time point. Separate linear

Outcome	Description of Outcome	Measurement Timing	Analysis
	anxiety/depression, scored according to a prescribed algorithm. Higher scores represent better perceptions of health.	randomization	regressions for each timepoint, adjusted for age
Euro-QOL Visual Analogue Scale [36]	Patients rate their overall health on a 100-point visual analogue scale (0= worst health; 100= best health).	ICU discharge, hospital discharge, 90 days post-randomization	Includes survivors at each time point. Separate linear regressions for each timepoint, adjusted for age
Katz Activities of Daily Living scale [39]	The patient's ability to complete 6 tasks: bathing, dressing, toileting, feeding, continence, and bed mobility. A rater assesses whether the patient is dependent or independent according to pre-specified criteria. Total scores range from 0 to 6, with higher scores representing better function.	ICU discharge, hospital discharge	Includes survivors at each time point. Separate linear regressions for each timepoint, adjusted for age
Clinical Frailty Scale [38]	Frailty includes a reduction in physical reserve and loss of function across multiple body systems. The clinical frailty scale is a 9-point scale, with higher scores representing more frailty. The Clinical Frailty Scale is reliable by chart review conducted by ICU research coordinators, occupational therapists, and geriatric residents.[46]	Hospital discharge, 90 days post-randomization	Includes survivors at each time point. Separate linear regressions for each timepoint, adjusted for age
Hospital Anxiety and Depression Scale (HADS).[37]	Patients answer 14 questions on a 4-point scale (7 related to anxiety, 7 related to depression); higher scores (maximum 21 points) represent worse anxiety or depression.	90 days post-randomization	Includes survivors. Linear regression, adjusted for age.
Duration of mechanical ventilation	Days of invasive mechanical ventilation via endotracheal tube or tracheostomy	ICU discharge	Linear regression, adjusted for age
ICU Length of Stay	Days in ICU	ICU discharge	Linear regression, adjusted for age
Hospital Length of Stay	Days in hospital	Hospital discharge	Linear regression, adjusted for age
Mortality	Death	ICU discharge, hospital discharge, 90 days post-	Separate Cox proportional hazards models for

Outcome	Description of Outcome	Measurement Timing	Analysis
		randomization	each timepoint, adjusted for age
Hospital Discharge Location	Same or better living location at hospital discharge from baseline	Hospital discharge	Includes survivors. Logistic regression, adjusted for age

Adverse Events

We collected the following adverse events if they occurred during or immediately after in-bed cycling or usual physiotherapy interventions, if they were attributable by the clinical team to the randomized intervention, and if they resulted in a clinical deterioration of the patient's status [8, 12, 47-49]: concern for myocardial ischemia or suspected new unstable/ uncontrolled arrhythmia; sustained symptomatic bradycardia (<40 bpm) or tachycardia (>140 bpm); sustained hypertension (mean arterial pressure >120 mmHg); sustained O_2 desaturation below baseline (typically <90% or 88%); marked ventilator dysynchrony; bleeding at femoral catheter site; new bruising at femoral catheter site. Serious adverse events were unplanned extubation, cardiac arrest, or fall to knees during usual physiotherapy activities.

Sample Size

Our sample size of 360 patients was based on identifying a 1.0 point mean difference[50] between the Cycling + Usual physiotherapy and Usual physiotherapy groups for the Physical Function Test for ICU-scored (PFIT-s) measured at 3 days after ICU discharge.[20, 21] Previous psychometric studies of the PFIT-s identified the minimal clinically important difference was 1.0 points.[20, 23] Logistic regression analysis of patients enrolled in TryCYCLE [12] and the CYCLE pilot randomized study [13] 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 requiring paid assistance for activities of daily living at hospital

discharge.[50] Based on a standard deviation of 2.5 points at ICU discharge,[12, 51] a 1.0 point difference between groups,[20, 23, 50] and 90% power (0.05 alpha), we needed to randomize and analyze 266 patients (133 per group). Based on 66 patients enrolled in the CYCLE Pilot RCT, we anticipated approximately 35% total 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). Therefore, we recruited 360 patients overall.

Framework

This trial was based on a superiority trial hypothesis that patients receiving in-bed cycling and usual physiotherapy early in their ICU stay will have better physical function at 3 days post-ICU discharge than those receiving usual physiotherapy alone.

Statistical Analysis

Interim Analysis

We conducted one blinded interim analysis that included the first 180 patients enrolled (half of the sample size) to assess for benefit and harm (serious adverse events). We used conservative statistical guidelines for data monitoring based on the modified Haybittle-Peto rule.[52] The Data Monitoring Committee (DMC) recommended continuation of the trial on September 29, 2020 based on this single interim analysis. To maintain the overall type-I error rate (i.e., α), we evaluated the primary endpoint using a fixed simple conservative $\alpha=0.001$ for the interim analyses and plan to use $\alpha=0.05$ for the final analysis.

Timing of final analysis

The first publication of the trial results will be prepared for the Cycling + Usual physiotherapy vs. Usual physiotherapy groups when every patient has reached 90 days post-randomization, and data for vital status at hospital discharge have been received. Longer-term endpoints for the economic evaluation will be reported in a separate publication. In this document, we will outline only the analyses included in the primary CYCLE manuscript.

Timing of outcome assessments

Supplement Table 1 outlines the schedule of study procedures with five timepoints for outcome assessments. The ICU Awakening timepoint was based on the physiotherapist's assessment of the patient's ability to consistently follow 5 verbal commands[41]. A patient's discharge may be delayed for reasons unrelated to their readiness for discharge (e.g., hospital beds not available at transfer ward). Thus, the ICU discharge measures occurred when the patient was discharged from the ICU or when a discharge order was written for the patient, whichever occurred first. The 3-day post-ICU timepoint occurred at 3 days following the patient's physical discharge from the ICU. The hospital discharge timepoint occurred when a discharge from acute care order was written for the patient for the index admission (including transfer to alternative level of care). The 90-day timepoint occurred at 90 days following randomization.

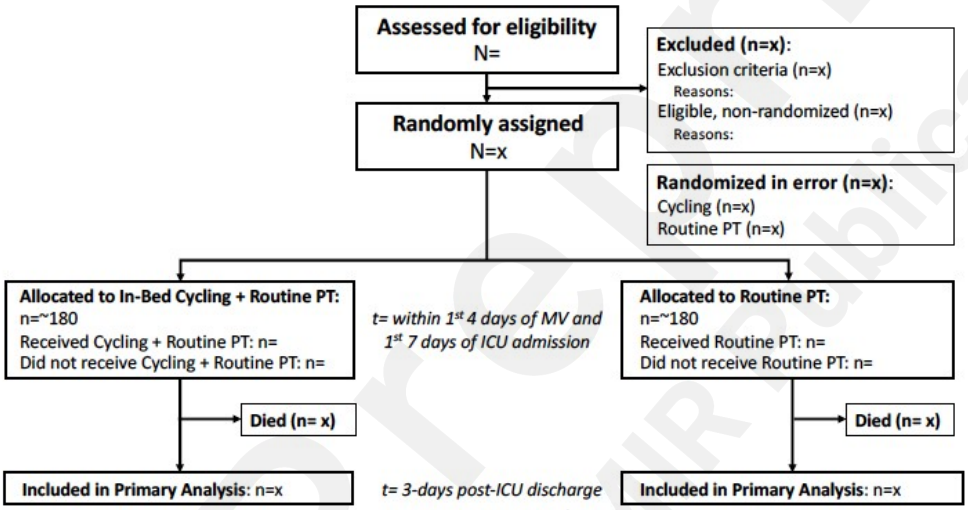
Other Principles

All statistical tests will be 2-sided and will be performed using a 5% significance level. We will report the two-sided 95% confidence intervals and perform all analyses using the most current version of SAS 9.4 (Cary, NC). We will report our final RCT in accordance with 1) the CONSORT 2010 Statement for reporting parallel group randomised trials [53]; 2) the Extension_for Reporting

Trials of Nonpharmacologic Treatments [54]; 3) the Guidelines for Reporting Outcomes in Trial Reports, The CONSORT-Outcomes 2022 Extension [55]; and 4) the CONSORT 2024 statement.[56]

Trial Profile – Figure 1 CONSORT Diagram

We will report the total number of patients screened (i.e., meeting all inclusion criteria), and those with exclusion criteria based on screening logs from participating sites. For eligible patients, we will report reasons for non-enrollment. We will document patient withdrawals and losses to follow-up in our CONSORT diagram.



Protocol Adherence

Definitions:

"*Study days*" included all days in the ICU from the day of randomization up to 28 days post-randomization.

We did not plan for the randomized intervention to occur in the following circumstances:

- On days when a patient was randomized after normal physiotherapist working hours
- On days when a patient was transferred out of ICU before 12:00 pm
- On weekend days or statutory holidays
- For those randomized to in-bed cycling, patients who had marched on the spot for 2 consecutive days (and continued marching or had higher mobility for the remainder of their ICU stay)
- On days when a patient did not meet criteria to receive usual physiotherapy, based on institutional policies for delivery of usual care

The remaining days were "*Planned intervention days*". On weekdays (i.e., non-holiday Monday through Friday), physiotherapists reviewed study patients for one or more of the following "Temporary exemptions" before offering the randomized intervention:

1. Increase in vasopressor/ inotrope within the last 2 hours
2. Active myocardial ischemia, or unstable/ uncontrolled arrhythmia per ICU team
3. Mean arterial pressure <60 mmHg or >110 mmHg or per treating team within the last 2 hours
4. Heart rate <40 bpm or >140 bpm within the last 2 hours
5. Persistent SpO_2 <88% or per treating team within the last 2 hours
6. Neuromuscular blocker within the last 4 hours
7. Severe agitation (Richmond Agitation and Sedation Scale >2 [or equivalent][16]) within the last 2 hours
8. Uncontrolled pain
9. Change in goals to palliative care
10. Team perception that in-bed cycling or therapy was not appropriate for other new reasons (e.g., acute peritonitis, new incision/wound, known/suspected rhabdomyolysis)

If the patient had no "*Temporary exemptions*", we offered the randomized intervention.

Each "Planned intervention day" without a "Temporary exemption" was an "*Eligible day*". An eligible day where a patient did not receive the randomized intervention, was a "*Missed opportunity*". Missed opportunities may have occurred due to:

1. Patient factors (e.g., patient not available due to a test, or declined)
2. Therapist factors (e.g., therapist not available due to vacation or sickness)
3. Equipment factors for patients in the Cycling arm (e.g., cycle ergometer malfunction)

Definition of protocol adherence

We define percent adherence whereby the numerator includes days in which patients received the randomized intervention or had a Temporary exemption and the denominator includes all planned intervention days (patients received the randomized intervention, Temporary exemptions, and Missed opportunities). We will report descriptive statistics on the percent protocol fidelity for the cohort by randomization group.

Major Protocol Deviation

If a patient who was randomized to Usual physiotherapy alone received cycling, this was considered a major protocol deviation.

Analysis populations

We will include all eligible randomized patients (i.e., excluding post-randomization exclusions representing non-eligible patients), according to the treatment they were randomized to receive. The analyses of our primary outcome will only include patients who survived to 3 days post-ICU discharge, as specified in our original protocol and sample size calculation.[15] The analysis of the

PFIT-s at other timepoints (ICU awakening, ICU discharge, and hospital discharge) and all performance-based (strength and function) and patient-reported (e.g., quality-of-life) outcomes will only include patients who survive to the given timepoint. We will only include those discharged from the hospital alive in the analysis of hospital discharge location. The analysis of the duration of mechanical ventilation, ICU and hospital length of stay and mortality will include all enrolled patients.

Analysis of the Primary Outcome

To determine if there is a difference in PFIT-s score at 3 days after ICU discharge between the Cycling + Usual physiotherapy and Usual physiotherapy groups, we will conduct a linear regression, including randomization (Cycling + Usual physiotherapy vs. Usual physiotherapy) as an independent variable. [57] We will adjust for age (≥ 65 years versus <65 years) and clinical site as these were used as randomization stratification variables. We will report the results of the regression as mean difference in PFIT-s with corresponding 95% confidence intervals (CIs) and p-values. Although the goal was to have all outcome assessors remain blinded to treatment allocation, this was not always feasible. To maximize use of available data, we will include all PFIT-s measures at 3 days post-randomization, regardless of blinding status of the outcomes assessor and report the proportion of assessments performed by blinded assessors.

To account for incomplete component data in the PFIT-s at 3 days post-ICU, we will concurrently consider data from the PFIT-s, 30-second sit-to-stand, and 2-minute walk tests. We will evaluate all PFIT-s data components at 3 days post-ICU discharge. We will identify all patients with any incomplete physical function data and review the scored values for all 4 components of the PFIT-s (i.e., shoulder flexion, knee extension, level of assistance required for the sit-to-stand, and step cadence). In the PFIT-s, a score of “0” represents a lack of physical ability to complete the outcome measure. Thus, if a patient attempted the item and was unsuccessful, the item receives a

score of “0”, which is a true 0 (Table 2). See the supplementary appendix for further details. Table 3 describes the primary outcome analysis.

Subgroup analyses

We will perform three exploratory *a priori* subgroup analyses to investigate potential treatment effect modification for the primary outcome. All subgroup analyses will be adjusted for age and center.

i. Age ≥65 years versus <65 years.
ii. Baseline Clinical Frailty ≥5 versus <5.
iii. Male versus female.

In separate linear regression models for each of the three subgroup analyses, we will include randomized treatment allocation, the subgroup variable, and the interaction between the subgroup variable and randomized treatment allocation as independent variables. These analyses will be adjusted for age and center. We hypothesize that the treatment effect will be greater for older compared to younger patients [58], greater in patients with frailty compared to those without [58], and greater in males compared to females [59, 60]. For statistical significance in the subgroup analyses, we will use an alpha of 0.10 for the interaction term. We will assess the credibility of any statistically significant subgroup effect using the method of Schandelmaier *et al*.[61] We will report these data in a forest plot.

Sensitivity analyses

To assess the robustness of findings, we will conduct five sensitivity analyses for the primary outcome. All sensitivity analyses will be adjusted for age and center, unless specified.

i. To account for ICU mortality on the primary outcome, we will conduct an analysis where we include all patients who died prior to 3 days post-ICU discharge and will assign a PFIT-s score of 0 for those patients.

ii. We will conduct a linear regression analysis that includes only PFIT-s assessments performed by assessors blinded to treatment allocation.

iii. We will conduct an analysis where we only include patients with adherence to the protocol on ≥80% of planned ICU days. Adherence is defined as either received the randomized intervention or had a temporary exemption.

iv. We will investigate the effect of missing data by conducting a complete case analysis, including only those patients with a total PFIT-s score at 3 days post ICU discharge.

v. To determine if the cycling effect is affected by the center, we will conduct an analysis adjusting for age only.

See Table 3 for further details.

Analyses of Secondary Outcomes

For each continuous secondary outcome, we will conduct a linear regression analysis.[57] We will conduct secondary outcome analyses adjusting for age (≥ 65 years versus <65 years) only. To avoid the risk of overfitting, we will not adjust for center when analysing our secondary outcomes. We will report the results of the linear regressions as mean differences with corresponding 95% CIs. If needed to normalize the data, we will perform the linear regression on the log-transformed outcome. [57] If the data are still skewed, we will perform nonparametric analyses. Given secondary analyses are underpowered and therefore hypothesis-generating, we will not present p-values. In the Supplementary appendix, we describe the scoring algorithm to account for incomplete data in the 30-second sit-to-stand and 2-minute walk tests based on a patient's observed function.

We will analyze time to ICU-, hospital-, and 90-day mortality using Cox proportional hazards regression analysis.[62] We will report hazard ratios (HRs) and corresponding 95% CIs.[62] All other binary outcomes will be analyzed using logistic regression analysis, reporting odds ratios

(ORs) with corresponding 95% CIs.[57] We will check the assumptions of the different regression analyses by examining residuals and using other relevant methods. Table 4 describes secondary outcomes analyses.

Adverse Events

For the safety analysis, we will only include the days on which the patients received the randomized intervention (i.e., days at risk of a safety event associated with rehabilitation activities). We will report the frequency and percentage of patients with severe and serious adverse events, by group. We will also report the frequency and percentage of randomized intervention days with severe and serious adverse events, by group.

Missing Data

We will use multiple imputation to account for missing data in performance-based and patient-reported outcomes.[63-65] In the Cox proportional hazards analyses for ICU and hospital mortality outcomes, we will censor patients with incomplete follow-up at the time of last contact.

Tables and Figures

We will summarize categorical data as counts and percentages. We will summarize continuous data as means, standard deviations, or median and interquartile range, if data are non-normally distributed. We will not conduct tests of statistical significance between randomized groups; rather, we will note the clinical importance of any imbalance between groups. We will report subgroup analyses in a forest plot.

Funding, Registration, and Ethics Approval

This work is supported by grants from the Canadian Institutes of Health Research (Project Grant #155919; CYCLE Vanguard Catalyst Grant #151715), Canada Foundation for Innovation, Ontario Ministry of Research and Innovation. Michelle Kho, Deborah Cook, and Margaret Herridge are each funded by a Canada Research Chair. Patrick Archambault is funded by a Fonds de recherche du Québec – Santé (FRQS) Clinical Scholar Award. Ian Ball is funded by an Academic Medical Organization of Southwestern Ontario (AMOSO) Innovation Grant. Frederick D'Aragon holds a research career award from the Fond de recherche du Québec-Santé. Shane English is supported by a Heart and Stroke Foundation National New Investigator Award. Restorative Therapies (Baltimore, MD) provided 4 RT-300 supine cycle ergometers at Ottawa Civic Hospital, London Health Sciences (Victoria site), Duke University Medical Center, and University of Maryland, Baltimore for this research. The funding sources and equipment manufacturer had no role in the design of this randomized trial and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results. Trial registration: NCT03471247 (Full RCT); NCT02377830 (46 patient internal pilot). CYCLE is approved by the Research Ethics Boards of all participating centres and Clinical Trials Ontario (Project 1345).

Document History

Version 1.0 of the SAP was finalized January 9, 2024. It was uploaded to clinicaltrials.gov on January 24, 2024.

Results

CYCLE was funded in 2017, and enrollment was completed in May 2023. Data analyses are currently underway, and the first results are expected to be submitted for publication in 2024.

Discussion

The CYCLE RCT is the largest trial of in-bed cycling for critically ill, mechanically ventilated adults, to date. This SAP complements the protocol paper [15] and was publicly available before data analysis (NCT03471247). We will adhere to it for all analyses, enhancing the rigour of our trial. The CYCLE RCT will add to the growing body of evidence evaluating the efficacy and safety of ICU-based rehabilitation interventions.

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Data Availability

The data sets generated during and/or analyzed during this study are not publicly available because we did not receive participant consent for data sharing. Data will be available from the corresponding author on reasonable request 1-year after publication of the main manuscript.

Authors' Contributions

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Conflicts of interest

Restorative Therapies (Baltimore, MD) provided 4 RT-300 supine cycle ergometers at Ottawa Civic Hospital, London Health Sciences (Victoria site), Duke University Medical Center, and University of Maryland, Baltimore for this research. The funding sources and equipment manufacturer had no role in the design of this randomized trial and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Abbreviations

6MWT – 6-minute walk test

ADL – Activities of Daily Living

CFS – Clinical Frailty Scale

CI – Confidence interval

CONSORT – Consolidated Standards for Reporting Trials

CYCLE - Critical care cycling to improve lower extremity strength

DMC – Data Monitoring Committee

HADS - Hospital Anxiety and Depression Scale

ICU – Intensive care unit

IPAT - Intensive Care Psychological Assessment Tool

MRC – Medical Research Council

PFIT-s - Physical Function Intensive Care Unit Test-scored

PRFS-ICU - Patient-Reported Functional Scale for the ICU

PT – Physiotherapy

RCT – Randomized control trial

SAP – Statistical analysis plan

SDM – Substitute decision maker

References

1. Herridge MS, Tansey CM, Matte A, Tomlinson G, Diaz-Granados N, Cooper A, et al. Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med. 2011 Apr 7;364(14):1293-304. PMID: 21470008.
2. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. JAMA. 2010 Oct 27;304(16):1787-94. PMID: 20978258. doi: 10.1001/jama.2010.1553.
3. Brower RG. Consequences of bed rest. Crit Care Med. 2009 Oct;37(10 Suppl):S422-8. PMID: 20046130. doi: 10.1097/CCM.0b013e3181b6e30a00003246-200910001-00019 [pii].
4. Puthucheary ZA, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, et al. Acute skeletal muscle wasting in critical illness. JAMA. 2013 Oct 16;310(15):1591-600. PMID: 24108501. doi: 10.1001/jama.2013.278481.
5. Herridge MS, Cheung AM, Tansey CM, Matte-Martyn A, Diaz-Granados N, Al-Saidi F, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. N Engl J Med. 2003 Feb 20;348(8):683-93. PMID: 12594312.
6. Needham DM, Bronskill SE, Calinawan JR, Sibbald WJ, Pronovost PJ, Laupacis A. Projected incidence of mechanical ventilation in Ontario to 2026: Preparing for the aging baby boomers. Crit Care Med. 2005 Mar;33(3):574-9. PMID: 15753749. doi: 00003246-200503000-00015 [pii].
7. Cheung AM, Tansey CM, Tomlinson G, Diaz-Granados N, Matte A, Barr A, et al. Two-year outcomes, health care use, and costs of survivors of acute respiratory distress syndrome. Am J Respir Crit Care Med. 2006 Sep 1;174(5):538-44. PMID: 16763220. doi: 10.1164/rccm.200505-693OC.
8. Burtin C, Clerckx B, Robbeets C, Ferdinande P, Langer D, Troosters T, et al. Early exercise in critically ill patients enhances short-term functional recovery. Crit Care Med. 2009 Sep;37(9):2499-505. PMID: 19623052.
9. Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet. 2009 May 30;373(9678):1874-82. PMID: 19446324. doi: 10.1016/S0140-6736(09)60658-9.
10. Camargo Pires-Neto R, Fogaca Kawaguchi YM, Sayuri Hirota A, Fu C, Tanaka C, Caruso P, et al. Very early passive cycling exercise in mechanically ventilated critically ill patients: physiological and safety aspects--a case series. PLoS One. 2013;8(9):e74182. PMID: 24040200. doi: 10.1371/journal.pone.0074182.
11. Kho ME, Martin RA, Toonstra AL, Zanni JM, Mantheiy EC, Nelliot A, et al. Feasibility and safety of in-bed cycling for physical rehabilitation in the intensive care unit (ICU). J Crit Care. 2015 2015;30(6):e1-5. doi: 10.1016/j.jcrc.2015.07.025.
12. Kho ME, Molloy AJ, Clarke FJ, Ajami D, McCaughan M, Obrovac K, et al. TryCYCLE: A Prospective Study of the Safety and Feasibility of Early In-Bed Cycling in Mechanically Ventilated Patients. PLoS One. 2016;11(12):e0167561. PMID: 28030555. doi: 10.1371/journal.pone.0167561.
13. Kho ME, Molloy AJ, Clarke FJ, Reid JC, Herridge MS, Karachi T, et al. Multicentre pilot randomised clinical trial of early in-bed cycle ergometry with ventilated patients. BMJ Open Respir Res. 2019;6(1):e000383. PMID: 30956804. doi: 10.1136/bmjresp-2018-000383.
14. Gamble C, Krishan A, Stocken D, Lewis S, Juszczak E, Dore C, et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. JAMA. 2017 Dec 19;318(23):2337-43. PMID: 29260229. doi: 10.1001/jama.2017.18556.
15. Kho ME, Reid J, Molloy AJ, Herridge MS, Seely AJ, Rudkowski JC, et al. 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. BMJ Open.

2023 Jun 23;13(6):e075685. PMID: 37355270. doi: 10.1136/bmjopen-2023-075685.
16. Ely EW, Truman B, Shintani A, Thomason JW, Wheeler AP, Gordon S, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). JAMA. 2003 Jun 11;289(22):2983-91. PMID: 12799407. doi: 10.1001/jama.289.22.2983 [doi] 289/22/2983 [pii].
17. Morris PE, Goad A, Thompson C, Taylor K, Harry B, Passmore L, et al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. Crit Care Med. 2008 Aug;36(8):2238-43. PMID: 18596631.
18. Koo K. Survey of Acute Rehabilitation in Canadian Intensive Care Units. Hamilton, ON: McMaster University; 2012.
19. Denehy L, Skinner EH, Edbrooke L, Haines K, Warrillow S, Hawthorne G, et al. Exercise rehabilitation for patients with critical illness: a randomized controlled trial with 12 months of follow-up. Crit Care. 2013 Jul 24;17(4):R156. PMID: 23883525. doi: 10.1186/cc12835.
20. Denehy L, de Morton NA, Skinner EH, Edbrooke L, Haines K, Warrillow S, et al. A physical function test for use in the intensive care unit: validity, responsiveness, and predictive utility of the physical function ICU test (scored). Phys Ther. 2013 Dec;93(12):1636-45. PMID: 23886842. doi: 10.2522/ptj.20120310.
21. Skinner EH, Berney S, Warrillow S, Denehy L. Development of a physical function outcome measure (PFIT) and a pilot exercise training protocol for use in intensive care. Crit Care Resusc. 2009 Jun;11(2):110-5. PMID: 19485874.
22. Zanni JM, Korupolu R, Fan E, Pradhan P, Janjua K, Palmer JB, et al. Rehabilitation therapy and outcomes in acute respiratory failure: an observational pilot project. J Crit Care. 2010 Jun;25(2):254-62. PMID: 19942399. doi: S0883-9441(09)00275-5 [pii] 10.1016/j.jcrc.2009.10.010.
23. Parry SM, Denehy L, Beach LJ, Berney S, Williamson HC, Granger CL. Functional outcomes in ICU - what should we be using? - an observational study. Crit Care. 2015 Mar 29;19(1):127. PMID: 25888469. doi: 10.1186/s13054-015-0829-5.
24. Hopkins RO, Miller RR, 3rd, Rodriguez L, Spuhler V, Thomsen GE. Physical therapy on the wards after early physical activity and mobility in the intensive care unit. Phys Ther. 2012 Dec;92(12):1518-23. PMID: 22491481. doi: 10.2522/ptj.20110446.
25. Fan E, Ciesla ND, Truong AD, Bhoopathi V, Zeger SL, Needham DM. Inter-rater reliability of manual muscle strength testing in ICU survivors and simulated patients. Intensive Care Med. 2010 Jun;36(6):1038-43. PMID: 20213068. doi: 10.1007/s00134-010-1796-6 [doi].
26. Hermans G, Clerckx B, Vanhullebusch T, Segers J, Vanpee G, Robbeets C, et al. Interobserver agreement of Medical Research Council sum-score and handgrip strength in the intensive care unit. Muscle Nerve. 2012 Jan;45(1):18-25. PMID: 22190301. doi: 10.1002/mus.22219 [doi].
27. Jones CJ, Rikli RE, Beam WC. A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. Res Q Exerc Sport. 1999 Jun;70(2):113-9. PMID: 10380242. doi: 10.1080/02701367.1999.10608028.
28. Tveter AT, Dagfinrud H, Moseng T, Holm I. Health-related physical fitness measures: reference values and reference equations for use in clinical practice. Arch Phys Med Rehabil. 2014 Jul;95(7):1366-73. PMID: 24607837. doi: 10.1016/j.apmr.2014.02.016.
29. Pin TW. Psychometric properties of 2-minute walk test: a systematic review. Arch Phys Med Rehabil. 2014 Sep;95(9):1759-75. PMID: 24814460. doi: 10.1016/j.apmr.2014.03.034.
30. Reid JC, Clarke F, Cook DJ, Molloy AJ, Rudkowski J, Kho ME. Interrater reliability and responsiveness of the icu patient-reported functional scale. Crit Care Med. 2016;44(12):284.
31. Reid JC, Clarke F, Cook DJ, Molloy AJ, Rudkowski JC, Stratford PW, et al. Reliability, responsiveness, and validity of the Patient-Reported Functional Scale for the Intensive Care Unit (PRFS-ICU): A pilot study. Annals of Intensive Care. 2017.

32. Wade DM, Hankins M, Smyth DA, Rhone EE, Mythen MG, Howell D, et al. Detecting acute distress and risk of future psychological morbidity in critically ill patients: Validation of the Intensive care psychological assessment tool. Crit Care. 2014 Sep 24;18(5):519. PMID: 25248614. doi: 10.1186/s13054-014-0519-8.
33. Wade DM, Howell DC, Weinman JA, Hardy RJ, Mythen MG, Brewin CR, et al. Investigating risk factors for psychological morbidity three months after intensive care: a prospective cohort study. Crit Care. 2012;16(5):R192. PMID: 23068129. doi: 10.1186/cc11677.
34. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011 Dec;20(10):1727-36. PMID: 21479777. doi: 10.1007/s11136-011-9903-x.
35. van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012 Jul-Aug;15(5):708-15. PMID: 22867780. doi: 10.1016/j.jval.2012.02.008.
36. Xie F, Pullenayegum E, Gaebel K, Bansback N, Bryan S, Ohinmaa A, et al. A Time Trade-off-derived Value Set of the EQ-5D-5L for Canada. Med Care. 2016 Jan;54(1):98-105. PMID: 26492214. doi: 10.1097/MLR.0000000000000447.
37. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983 Jun;67(6):361-70. PMID: 6880820.
38. Bagshaw SM, Stelfox HT, McDermid RC, Rolfson DB, Tsuyuki RT, Baig N, et al. Association between frailty and short- and long-term outcomes among critically ill patients: a multicentre prospective cohort study. CMAJ. 2014 Feb 4;186(2):E95-102. PMID: 24277703. doi: 10.1503/cmaj.130639.
39. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of Illness in the Aged. The Index of Adl: A Standardized Measure of Biological and Psychosocial Function. JAMA. 1963 Sep 21;185:914-9. PMID: 14044222. doi: 10.1001/jama.1963.03060120024016.
40. Kleyweg RP, van der Meche FG, Schmitz PI. Interobserver agreement in the assessment of muscle strength and functional abilities in Guillain-Barre syndrome. Muscle Nerve. 1991 Nov;14(11):1103-9. PMID: 1745285.
41. De Jonghe B, Sharshar T, Lefaucheur JP, Authier FJ, Durand-Zaleski I, Boussarsar M, et al. Paresis acquired in the intensive care unit: a prospective multicenter study. JAMA. 2002 Dec 11;288(22):2859-67. PMID: 12472328.
42. O'Grady HK, Edbrooke L, Farley C, Berney S, Denehy L, Puthucheary Z, et al. The sit-to-stand test as a patient-centered functional outcome for critical care research: a pooled analysis of five international rehabilitation studies. Crit Care. 2022 Jun 13;26(1):175. PMID: 35698237. doi: 10.1186/s13054-022-04048-3.
43. Costigan FA, Rochwerg B, Molloy AJ, McCaughan M, Millen T, Reid JC, et al. I SURVIVE: inter-rater reliability of three physical functional outcome measures in intensive care unit survivors. Can J Anaesth. 2019 May 30. PMID: 31147985. doi: 10.1007/s12630-019-01411-x.
44. Bohannon RW, Wang YC, Gershon RC. Two-Minute Walk Test Performance by Adults 18 to 85 Years: Normative Values, Reliability, and Responsiveness. Arch Phys Med Rehabil. 2015 Mar;96(3):472-7. PMID: 25450135. doi: 10.1016/j.apmr.2014.10.006.
45. Reid JC, Clarke F, Cook DJ, Molloy A, Rudkowski JC, Stratford P, et al. Feasibility, Reliability, Responsiveness, and Validity of the Patient-Reported Functional Scale for the Intensive Care Unit: A Pilot Study. J Intensive Care Med. 2020 Dec;35(12):1396-404. PMID: 30669936. doi: 10.1177/0885066618824534.
46. Shears M, Takaoka A, Rochwerg B, Bagshaw SM, Johnstone J, Holding A, et al. Assessing frailty in the intensive care unit: A reliability and validity study. J Crit Care. 2018 Jun;45:197-203. PMID: 29574340. doi: 10.1016/j.jcrc.2018.02.004.
47. Nydahl P, Sricharoenchai T, Chandra S, Kundt FS, Huang M, Fischill M, et al. Safety of Patient Mobilization and Rehabilitation in the Intensive Care Unit. Systematic Review with Meta-

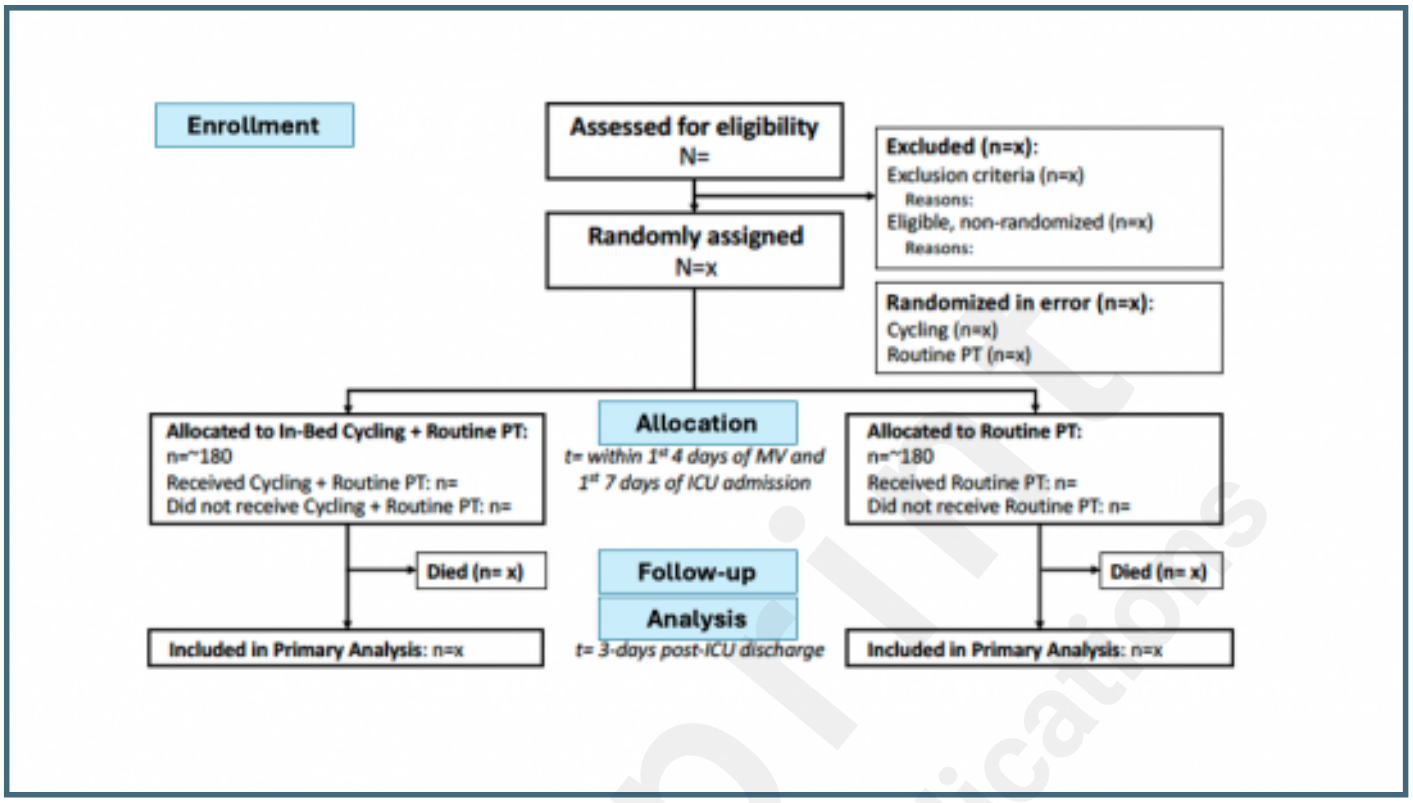
Analysis. Annals of the American Thoracic Society. 2017 May;14(5):766-77. PMID: 28231030. doi: 10.1513/AnnalsATS.201611-843SR.
48. Adler J, Malone D. Early mobilization in the intensive care unit: a systematic review. Cardiopulm Phys Ther J. 2012 Mar;23(1):5-13. PMID: 22807649.
49. Sricharoenchai T, Parker AM, Zanni JM, Nelliot A, Dinglas VD, Needham DM. Safety of physical therapy interventions in critically ill patients: A single-center prospective evaluation of 1110 intensive care unit admissions. J Crit Care. 2014 Dec 30;29:395-400. PMID: 24508202. doi: 10.1016/j.jcrc.2013.12.012.
50. Kho ME, Heels-Ansdell D, Thabane L, Cook DJ, and the TryCYCLE and CYCLE Pilot RCT investigators, editors. ICU Discharge Function Predicts Poor Hospital Discharge Outcomes: Lessons from the CYCLE Research Program. Critical Care Canada Forum; 2017; Toronto, ON Canada.
51. Nordon-Craft A, Schenkman M, Edbrooke L, Malone DJ, Moss M, Denehy L. The physical function intensive care test: implementation in survivors of critical illness. Phys Ther. 2014 Oct;94(10):1499-507. PMID: 24810863. doi: 10.2522/ptj.20130451.
52. Pocock SJ. When (not) to stop a clinical trial for benefit. JAMA. 2005 Nov 02;294(17):2228-30. PMID: 16264167. doi: 10.1001/jama.294.17.2228.
53. Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:c869. PMID: 20332511.
54. Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P, Group CN. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. Ann Intern Med. 2017 Jul 04;167(1):40-7. PMID: 28630973. doi: 10.7326/M17-0046.
55. Butcher NJ, Monsour A, Mew EJ, Chan AW, Moher D, Mayo-Wilson E, et al. Guidelines for Reporting Outcomes in Trial Reports: The CONSORT-Outcomes 2022 Extension. JAMA. 2022 Dec 13;328(22):2252-64. PMID: 36511921. doi: 10.1001/jama.2022.21022.
56. Tunn R, Boutron I, Chan AW, Collins GS, Hróbjartsson A, Moher D, et al. Methods used to develop the SPIRIT 2024 and CONSORT 2024 Statements. J Clin Epidemiol. 2024 May;169:111309. PMID: 38428538. doi: 10.1016/j.jclinepi.2024.111309.
57. Pagano M, Gavreau K. Principles of Biostatistics. Second ed: Brooks/Cole CENGAGE Learning; 2000. ISBN: 9780534229023.
58. Jones JRA, Karahalios A, Puthucheary ZA, Berry MJ, Files DC, Griffith DM, et al. Responsiveness of Critically Ill Adults With Multimorbidity to Rehabilitation Interventions: A Patient-Level Meta-Analysis Using Individual Pooled Data From Four Randomized Trials. Crit Care Med. 2023 Oct 1;51(10):1373-85. PMID: 37246922. doi: 10.1097/CCM.0000000000005936.
59. Chi NF, Huang YC, Chiu HY, Chang HJ, Huang HC. Systematic Review and Meta-Analysis of Home-Based Rehabilitation on Improving Physical Function Among Home-Dwelling Patients With a Stroke. Arch Phys Med Rehabil. 2020 Feb;101(2):359-73. PMID: 31689417. doi: 10.1016/j.apmr.2019.10.181.
60. Oikawa SY, Callahan DM, McGlory C, Toth MJ, Phillips SM. Maintenance of skeletal muscle function following reduced daily physical activity in healthy older adults: a pilot trial. Appl Physiol Nutr Metab. 2019 Oct;44(10):1052-6. PMID: 30794431. doi: 10.1139/apnm-2018-0631.
61. Schandelmaier S, Briel M, Varadhan R, Schmid CH, Devasenapathy N, Hayward RA, et al. Development of the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) in randomized controlled trials and meta-analyses. CMAJ. 2020 Aug 10;192(32):E901-E6. PMID: 32778601. doi: 10.1503/cmaj.200077.
62. Collett D. Modelling Survival Data in Medical Research: Chapman & Hall; 1994. ISBN: 0412448904.
63. Zhang Y, Alyass A, Vanniyasingam T, Sadeghirad B, Florez ID, Pichika SC, et al. A systematic survey of the methods literature on the reporting quality and optimal methods of handling

participants with missing outcome data for continuous outcomes in randomized controlled trials. J Clin Epidemiol. 2017 Aug;88:67-80. PMID: 28579378. doi: 10.1016/j.jclinepi.2017.05.016.
64. Little RJA, Rubin DB. Statistical Analysis with Missing Data. Newy York, UNITED STATES: John Wiley & Sons, Incorporated; 2002. ISBN: 9781118625866.
65. Rubin DB. Multiple imputation for nonresponse in surveys: John Wiley & Sons; 2004. ISBN: 0471655740.

Supplementary Files

Figures

CONSORT patient flow diagram.



Multimedia Appendixes

Peer Review Report - Canadian Institutes of Health Research.
URL: http://asset.jmir.pub/assets/4081980c5cb75191e83be88537c037ee.pdf

Supplementary appendix.
URL: http://asset.jmir.pub/assets/a3b0d202d30258c0e7b2b2eb912e8205.pdf

CONSORT (CONsolidated Standards Of Reporting Trials) Checklist.
URL: http://asset.jmir.pub/assets/c677a8fad40b5e81dd19a5423e22f84e.docx