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Multicentre pilot randomised clinical trial of early in-bed cycle ergometry with ventilated patients

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ABSTRACT

Introduction Acute rehabilitation in critically ill patients can improve post-intensive care unit (post-ICU) physical function. In-bed cycling early in a patient's ICU stay is a promising intervention. The objective of this study was to determine the feasibility of recruitment, intervention delivery and retention in a multi centre randomised clinical trial (RCT) of early in-bed cycling with mechanically ventilated (MV) patients.

Methods We conducted a pilot RCT conducted in seven Canadian medical-surgical ICUs. We enrolled adults who could ambulate independently before ICU admission, within the first 4 days of invasive MV and first 7 days of ICU admission. Following informed consent, patients underwent concealed randomisation to either 30 min/day of in-bed cycling and routine physiotherapy (Cycling) or routine physiotherapy alone (Routine) for 5 days/week, until ICU discharge. Our feasibility outcome targets included: accrual of 1–2 patients/month/site; >80% cycling protocol delivery; >80% outcomes measured and >80% blinded outcome measures at hospital discharge. We report ascertainment rates for our primary outcome for the main trial (Physical Function ICU Test-scored (PFIT-s) at hospital discharge).

Results Between 3/2015 and 6/2016, we randomised 66 patients (36 Cycling, 30 Routine). Our consent rate was 84.6 % (66/78). Patient accrual was (mean (SD)) 1.1 (0.3) patients/month/site. Cycling occurred in 79.3% (146/184) of eligible sessions, with a median (IQR) session duration of 30.5 (30.0, 30.7) min. We recorded 43 (97.7%) PFIT-s scores at hospital discharge and 37 (86.0%) of these assessments were blinded.

Discussion Our pilot RCT suggests that a future multicentre RCT of early in-bed cycling for MV patients in the ICU is feasible.

Trial registration number NCT02377830.

Key messages

- Is it feasible and safe to conduct a multicentre pilot randomised clinical trial (RCT) of early in-bed cycling with mechanically ventilated (MV) patients with frontline physiotherapists?
- Our pilot RCT suggests that a multicentre RCT is feasible, but strategies to optimise enrolment and cycling intervention delivery will be needed.
- We outline practical considerations for conducting a large RCT of early in-bed cycling with MV patients.

INTRODUCTION

Patients surviving critical illness are at risk of significant physical disability up to 8 years after discharge from the intensive care unit (ICU).[1 2] Patients admitted to ICU have increased morbidity and case complexity, and more are surviving after critical illness.[3] In a prospective cohort study of 391 medical surgical ICU survivors, function at 7 days post-ICU predicted function 1 year later, suggesting that rehabilitation interventions initiated during or immediately after ICU discharge could improve long term outcomes.[4]

However, important barriers to conducting early rehabilitation early in a patient's ICU stay exist, including the presence of an endotracheal tube and the use of vasoactive medications and continuous sedation.[5] In-bed cycling started in the ICU can improve physical function at hospital discharge and is a promising early intervention for mechanically ventilated (MV) patients. During cycling, patients can transition from passive to active cycling, while intubated and receiving vasoactive medications or sedative infusions.[6]

While several studies document the feasibility or safety[6–9] of in-bed cycling, surprisingly few randomised clinical trials (RCTs) exist. In a 90-patient RCT, those who started cycling 14 days after ICU admission had farther 6 min walk test scores at hospital discharge.[10] In an RCT of 21 patients with sepsis, those

who received short-term early cycling demonstrated preserved muscle fibre cross-sectional area at 7 days.[11] In a 49-patient RCT, those who started passive cycling 3 days after ICU admission had larger improvements in strength scores at ICU discharge.[12] However, in a recent RCT of 314 patients that added both in-bed cycling and neuromuscular electrical stimulation to early mobilisation in critically ill patients did not improve muscle strength at ICU discharge.[13] The functional impact of early cycling alone on MV patients within the first week of ICU admission has not been evaluated.

Before embarking on a large RCT, a pilot RCT is needed for several reasons.[14] Despite widespread awareness of in-bed cycling, this technology is not commonly available in ICUs.[15] Previous studies documented important methodological challenges conducting rehabilitation RCTs with critically ill patients including suboptimal recruitment,[16 17] impaired intervention delivery[18] and losses to follow-up.[19] Our objective was to conduct a pilot RCT to assess the feasibility of recruitment, intervention delivery and retention to inform a larger RCT.[14 20]

METHODS

Our full pilot trial protocol is published elsewhere.[21] Briefly, we included patients who could ambulate independently at baseline (with or without a gait aid), within the first 4 days of MV and the first 7 days of ICU admission. The research coordinator started screening patients on ICU admission and ascertained patients' ambulation status based on chart review and/or history from the patient or substitute decision maker. We excluded patients who could not follow simple commands in English at baseline, could not receive cycling (eg, did not fit equipment, acute leg fracture), had confirmed or suspected neuromuscular weakness per the critical care team, had a temporary pacemaker, were not likely to survive their hospital stay or had palliative goals of care or were pregnant. To ensure that the intervention started early, we also excluded those who had temporary exemptions unresolved within the first 4 days of MV (eg, haemodynamic (eg, increasing vasoactive medications, myocardial infarction, uncontrolled arrhythmia, hypotension or hypertension, bradycardia or tachycardia) or respiratory instability (eg, SpO_2<88%, neuromuscular blockers)).[21]

Research coordinators obtained written informed consent from patients or more commonly, their substitute decision makers, if patients were unable to consent. After informed consent was obtained, research coordinators randomised patients using a web-based, computer-generated block randomisation system (http://www.randomize.net). We initiated the allocated intervention as soon as possible after randomisation. Patients were allocated to either 30 min of cycling/day and routine physical therapy interventions (Cycling) or routine physical therapy interventions (Routine) alone until ICU discharge or 28 days, whichever occurred first, and regardless of sedation status. When patients randomised to cycling could successfully march on the spot for two consecutive days, we discontinued cycling and focused on more challenging progressive mobility activities.

Our primary feasibility objective was to evaluate our ability to conduct blinded assessments of the Physical Function ICU test-scored (PFIT-s)[22 23] at hospital discharge, anticipating that this would be the primary outcome for a full RCT. Trained physiotherapists (PTs) conducted all performance-based measures. Electronic online supplementary file 1 describes the two study arms, baseline and outcome measures.[24] Four further feasibility objectives were: (1) accrual of 1–2 patients/month/site; (2) >80% cycling protocol delivery; (3)>80% outcomes measured and (4) >80% blinded outcome measures at hospital discharge.

Analysis

We calculated the 60-patient sample size based on identifying a 0.25 standardised effect size between the two arms for the PFIT-s at hospital discharge.[21] For binary variables, we calculated counts and percentages. For continuous variables, we calculated the mean and SD or median and IQR, as appropriate. For between-group comparisons, we conducted Student's t-test with 95% CI or Wilcoxon Rank Sum test as appropriate. We planned a subgroup analysis to assess whether or not there were differences in achieving our feasibility objectives for patients ≥65 and for those <65 years old, hypothesising that no difference would exist. We considered results to be statistically significant when p≤0.05 and conducted all analyses using SAS V.9.4 for Windows (SAS Institute, Cary, North Carolina, USA). Local ethics committees approved our research.

RESULTS

Between 25/3/2015 and 22/6/2016, we enrolled patients in seven Canadian ICUs. Before trial initiation, we provided standardised education and onsite training on the cycle ergometer to 36 ICU PTs. We enrolled an additional 6 patients for a total of 66 patients (36 Cycling and 30 routine) to compensate for 2 patients randomised to cycling who did not receive any cycling and 2 patients who had missing hospital discharge assessments. We enrolled two extra patients to maintain trial momentum across the sites and ensure we had no additional missing hospital discharge assessments.

Accrual

Our consent rate (95% CI) was 84.6% (74.7, 91.8). Our mean (SD) enrolment was 1.1 (0.3) patients/month/site and 4.1 patients/month overall. Of 256 eligible patients, 190 (74.2%) were not randomised, primarily due to PT capacity (123 (64.7%)). Figure 1 outlines the participant flow diagram. Table 1 outlines patient characteristics. Table 2 summarises the ICU interventions received by both groups.

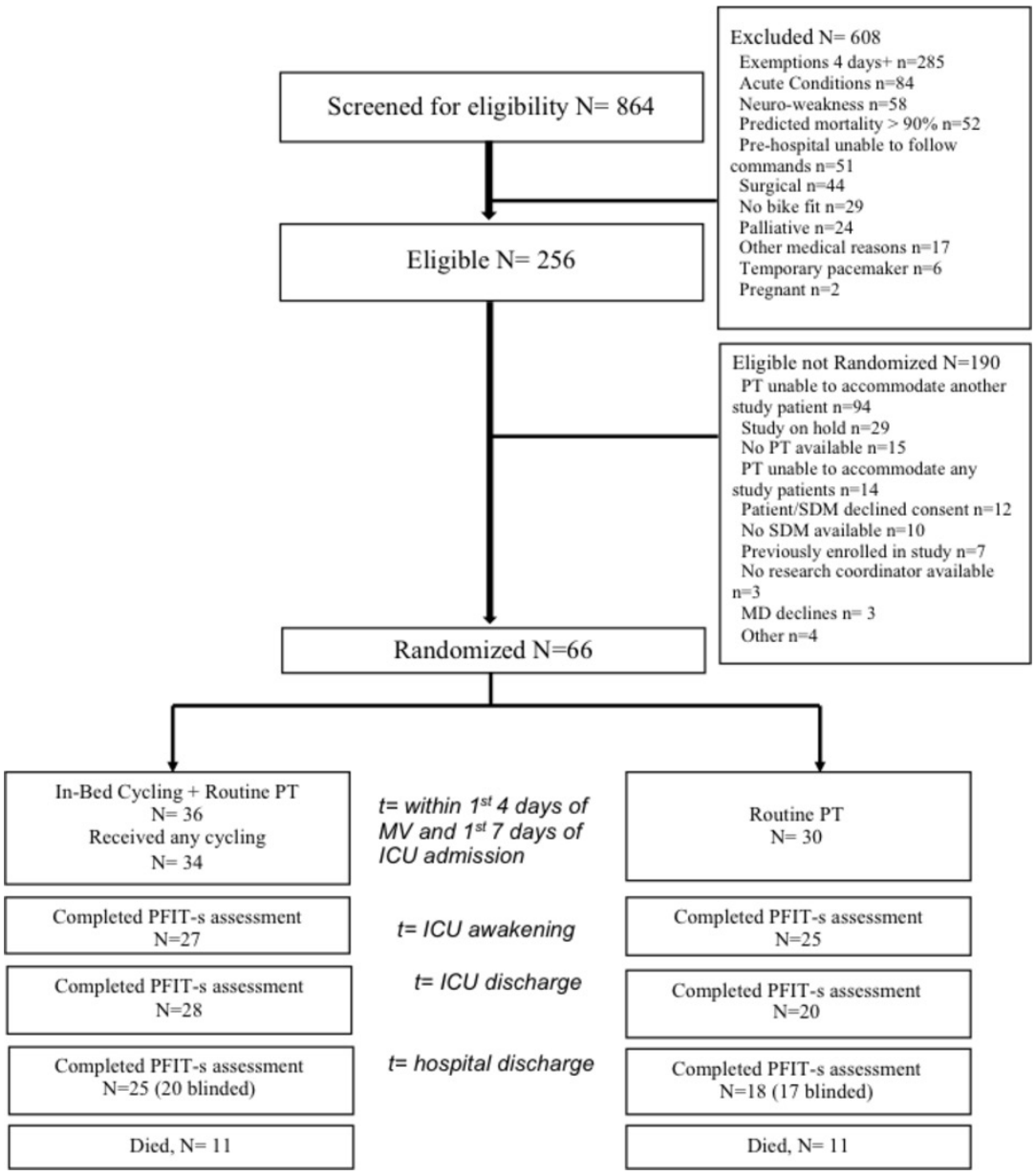

Figure 1 Patient flow diagram. Multiple reasons may account for patient exclusions or patients eligible but not randomised. ICU, intensive care unit; MV, mechanically ventilated; PFIT-s, Physical Function ICU Test-scored; PT, physiotherapist.

Cycling intervention protocol delivery

No patients in the routine group received cycling. Out of 36 patients randomised, 34 (94.4%) received cycling. The median (IQR) time from ICU admission to initiation of cycling was 3 (2, 5) days. Patients cycled on 146 (79.3%) of all eligible days, with a median (IQR) delivery of 88% (67, 100) per patient. The total median (IQR) duration of cycling over the ICU stay/patient was 84 (49, 182) min. Each patient received a median (IQR) of 3 (2, 6) cycling sessions, for a median duration of 30 (30, 31) min per session. Including the bike set-up and take down, this required 45 (39, 50) min per session of PT time. Two patients did not receive any cycling because one marched on the spot for two consecutive days immediately following randomisation, and one had persistent exemptions.

Overall, 78.8% (115) of all cycling sessions reached 30 min. Cycling and routine PT occurred within the same session on 94 (64.4%) occasions. Out of 146 sessions, 16 patients did not reach 30 min in 31 (21.2%) sessions due to fatigue (14, 9.6%), patient request (8, 5.5%) or miscellaneous reasons (eg, tachycardia, tachypnoea, agitation and so on (9, 6.1%)). Table 3 outlines the temporary exemptions and reasons why patients did not cycle on eligible days.

Routine care

Electronic online supplementary file 2 summarises the duration and types of routine physiotherapy interventions received by both groups. The median (IQR) time from ICU admission to initiation of routine physiotherapy was

Table 1 Patient demographics and baseline characteristics

	Total N=66	Cycling N=36	Routine N=30
Age, mean (SD)	61.6 (16.9)	60.0 (16.8)	63.6 (17.1)
Female, n (%)	26 (39.4)	9 (25.0)	17 (56.7)
Race, n (%)			
White	61 (92.4)	33 (91.7)	28 (93.3)
Other	5 (7.6)	3 (8.3)	2 (6.7)
Prehospital living status, n (%)			
Home (independent)	47 (71.2)	29 (80.6)	18 (60.0)
Home (unpaid caregiver assistance)	8 (12.1)	2 (5.6)	6 (20.0)
Assisted living facility	5 (7.6)	2 (5.6)	3 (10.0)
Home (home care)	3 (4.5)	1 (2.8)	2 (6.7)
Retirement home	1 (1.5)	0	1 (3.3)
Other	3 (4.5)	1 (2.8)	2 (6.7)
APACHE II score, mean (SD)	23.5 (8.6)	24.6 (10.0)	22.1 (6.4)
Medical admission, n (%)	52 (78.8)	29 (80.6)	23 (76.7)
Admission diagnosis, n (%)			
Respiratory	36 (54.5)	18 (50.0)	18 (60.0)
Sepsis	11 (16.7)	5 (13.9)	6 (20.0)
Gastrointestinal	8 (12.1)	6 (16.7)	2 (6.7)
Metabolic	4 (6.1)	4 (11.1)	0
Cardiovascular/vascular	3 (4.5)	1 (2.8)	2 (6.7)
Renal	2 (3.0)	1 (2.8)	1 (3.3)
Neurological	2 (3.0)	1 (2.8)	1 (3.3)
Charlson Comorbidity Index, mean (SD)	1.92 (1.60)	1.94 (1.72)	1.90 (1.47)
Functional Comorbidity Index, mean (SD)	2.32 (2.25)	2.22 (2.46)	2.43 (2.01)
Pre-ICU Katz ADL score, mean (SD)	5.65 (0.98)	5.67 (1.01)	5.63 (0.96)
Pre-ICU Functional Status Score for ICU, mean (SD)	33.2 (4.6)	32.8 (5.1)	33.7 (3.9)
Frailty score before ICU admission, mean (SD)	3.47 (1.68)	3.36 (1.68)	3.60 (1.69)
Location before ICU admission, n (%)			
Emergency room in study hospital	22 (33.3)	12 (33.3)	10 (33.3)
Hospital ward	19 (28.8)	10 (27.8)	9 (30.0)
Operating room/ post-operative recovery room	13 (19.7)	6 (16.7)	7 (23.3)
ICU in other hospital	5 (7.6)	3 (8.3)	2 (6.7)
Emergency in other hospital	4 (6.1)	4 (11.1)	0
Other	3 (4.5)	1 (2.8)	2 (6.7)

This table summarises patient demographics, baseline characteristics and patient outcomes. APACHE II is a 13-item instrument with scores from 0 to 71, higher scores representing higher severity of illness;[37] Charlson Comorbidity Index includes 19 categories of comorbidity, with higher scores representing more comorbidity;[38] Functional Comorbidity Index includes 18 items associated with physical function, with higher scores representing higher comorbid illness;[39] Katz score is a 6-item instrument assessing independence in bathing, dressing toileting, transferring, continence and feeding, with higher scores representing more independence.[40]
ADL, activities of daily living; APACHE II, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; SD, standard deviation.

3 (2, 4) days. We identified no differences in the duration of routine physiotherapy between groups. The total median (IQR) duration of routine physiotherapy over the ICU stay per patient was 118 (58, 215) min (Cycling=119 (39, 233); Routine=114 (66, 213)). Each patient received a median (IQR) of 5 (3, 9) routine physiotherapy sessions, for a median duration of 21 (15, 30) min per session (Cycling=20 (7, 31); Routine=23 (17, 30)). Patients received routine physiotherapy with a femoral catheter in situ on 10 (4.0%) and 26 (13.1%) days in the Cycling and Routine groups, respectively. Post-ICU, there was no difference in the median (IQR) days of physiotherapy on

Table 2 ICU interventions by group

	Total	Cycling	Routine
	N=66	N=36	N=30
Mechanical ventilation			
Days of invasive mechanical ventilation, median (IQR), days	8 (5–19)	8.5 (5–17)	8 (5–19)
Days of ETT airway access, median (IQR), days	7 (5–13)	7 (5–13)	8 (5–13)
Non-invasive mechanical ventilation, n (%)	9 (13.6)	6 (16.7)	3 (10.0)
Other advanced ventilation, n (%)*	4 (6.1)	2 (5.6)	2 (6.7)
Other advanced life support			
Vasopressor or inotrope infusion, n (%)	39 (59.1)	24 (66.7)	15 (50.0)
Renal replacement therapy, n (%)	8 (12.1)	4 (11.1)	4 (13.3)
Infusions			
Opiates, n (%)	44 (66.7)	26 (72.2)	18 (60.0)
Benzodiazepines, n (%)	24 (36.4)	14 (38.9)	10 (33.3)
Propofol, n (%)	49 (74.2)	26 (72.2)	23 (76.7)
Neuromuscular blockers, n (%)	7 (10.6)	2 (5.6)	5 (16.7)

This table summarises ICU exposures received by the Cycling and Routine physical therapy groups.
*Other advanced ventilation includes extracorporeal membrane oxygenation and nitric oxide.
ETT, endotracheal tube; ICU, intensive care unit; IQR, interquartile range.

the wards between group (Cycling=6 (3, 11); Routine=6 (3, 15)).

Adverse events

In the cycling group, one patient experienced a supraventricular tachycardia in one session requiring early cycling termination. Patients biked with a femoral catheter in situ on 4 (2.7%) days, with no accidental removals. During 445 days of routine physiotherapy, 4 patients experienced 4 (0.80%) adverse events (1 Cycling, 3 Routine): uncontrolled arrhythmia (n=2), 1 desaturation to 80% and 1 elevated heart rate during ambulation (both returned to baseline following rest). No further medical follow-up was required after these events. In both the Cycling and Routine groups, patients did not sustain any myocardial ischaemia, unplanned extubations or bleeding at femoral catheter sites.

Outcome measure assessment

We recorded 43 (97.7%) PFIT-s scores at hospital discharge and assessors blinded to treatment allocation measured 37 (86.0%). Electronic online supplementary file 3 outlines the outcome measures. There was no difference in PFIT-s score between Cycling and Routine groups at any time point. Table 4 summarises patient mortality and discharge disposition.

Subgroup analysis

We identified no difference in most of our feasibility outcomes between those <65 and those ≥65 years: PFIT-s outcomes ascertainment at hospital discharge or blinded PFIT-s outcomes (data not shown). Cycling delivery was 13.6% lower in those <65 years (72.1% vs 85.7%).

DISCUSSION

Our data suggest it is feasible and safe to conduct a multicentre RCT of early in-bed cycling with critically ill MV patients; however, frontline PT capacity is an important consideration for the full RCT.

Considerations for the full RCT

We conducted this trial with frontline ICU PTs that included study participants as part of their clinical caseload. PT capacity was a barrier for enrolment due to unexpected staffing shortages and limited ability to enrol concurrent study patients. Therapist workload accounted for missed cycling on 10% of eligible days (table 3). These issues highlight important considerations for timely enrolment and study completion and for optimising exposure to the cycling intervention in the full RCT. Other acute care rehabilitation investigators experienced similar challenges.[25] For example, a multicentre study of early stroke rehabilitation reported that staff absences due to parental leave led to delayed recruitment to achieve the target sample size.[25] Potential strategies to improve enrolment include increased frontline ICU PT staffing or dedicated research ICU PTs for in-bed cycling. Further research to understand barriers and facilitators of early in-bed cycling from quantitative and qualitative perspectives is needed.

Our study highlights the importance of optimising rehabilitation on eligible days due to competing priorities in the ICU environment. We offered ICU physiotherapy

Table 3 Patients randomised to cycling: temporary exemptions, reasons for not cycling on eligible days and advanced life support received during cycling

Days with temporary exemptions (n=95)	N (%)*
ICU team perception that patient is medically unstable for other reasons (eg, uncontrolled bleeding, impending intubation)	48 (50.5)
Cardiac	25 (26.3)
MAP <60 or >110 or out of range	10 (10.5)
Active myocardial ischaemia or unstable/uncontrolled arrhythmia	6 (6.3)
Increase in inotropes/vasopressors within last 2 hours	5 (5.3)
HR <40 or >140 bpm	4 (4.2)
Respiratory	12 (12.6)
Neuromuscular blocker within last 4 hours	7 (7.4)
SpO_2<88% or out of range	5 (5.3)
Other reasons	29 (30.5)
Change in goals to palliative care	14 (14.7)
Severe agitation (RASS>2)	8 (8.4)
Uncontrolled pain	7 (7.4)
Eligible days where cycling did not occur (n=38)	**N (%)†**
Therapist not available—workload	16 (8.7)
Patient declined	14 (7.6)
No CYCLE-trained PT available	2 (1.1)
Other patient activity prioritised	2 (1.1)
Family declined	1 (0.5)
Patient not available—out of ICU or in ICU (procedures, tests)	1 (0.5)
Bike not available	1 (0.5)
Missing data	1 (0.5)
Advanced life support received during cycling sessions (n=146)	N (%)
Mechanical ventilation	114 (78.1)
Oral endotracheal tube	98 (67.1)
Tracheostomy	13 (8.9)
Non-invasive	3 (2.1)
Days with temporary exemptions (n=95)	**N(%)***
Renal replacement therapy	6 (4.1)
Vasopressor or inotrope infusion	12 (8.2)

*Totals sum greater than 95 because each day could have more than one temporary exemption. Data are reasons as a proportion of 95 days.
†Total sum greater than 38 because each day could have more than one reason for not cycling. Data are reasons as a proportion of 184 eligible days. Of 38 days, 20 (52.6%) patients missed 1 or more eligible days of cycling; Therapist factors: 6 (30.0%) patients did not receive cycling due to physical therapist workload; 4 (20.0%) patients did not receive cycling because the physical therapist prioritised other therapeutic activities; patient factors: 11 (55.0%) patients declined 1 or more cycling sessions and 2 (10.0%) patients did not receive cycling due to other reasons.
bpm, beats per minute; HR, heart rate; ICU, intensive care unit; MAP, mean arterial pressure; PT, physiotherapist; RASS, Richmond Agitation and Sedation Scale.

5 days per week, consistent with the current ICU therapist staffing models in the majority of our participating centres. Cycling and routine rehabilitation occurred on 79% and 75% of all eligible days, respectively. While the rehabilitation and cycling exposure was modest compared with patients' median 11 day ICU length of stay, the optimal timing and dose of rehabilitation interventions in the ICU is not known.[26] Thus, it is critical we provide rehabilitation at every possible opportunity. Our median duration of 21 min of routine physiotherapy per session exceeded reported values in recent RCTs, which varied from 7 to 13 min per session.[18 27] Potentially modifiable targets to increase cycling exposure or rehabilitation interventions include augmenting therapist capacity, different staffing models, improved care coordination and strategies to encourage patient engagement.

Relationship to previous studies

Recent RCTs of rehabilitation interventions in the ICU reported discordant results. These discrepancies may be due to challenges with the types of enrolled patients (eg, case-mix, or pre-morbid functional status) or trial conduct (eg, accrual, intervention delivery, and outcome measurement).[17–19 28] For example, a single-centre, 150-patient RCT of intensive exercise started in the ICU with medical-surgical patients versus usual care demonstrated no difference in 6 min walk test at 1 year.[17] However, this study was stopped before achieving the target sample of 200 patients due to lack of funding.[17] A 4-centre, 308-patient RCT of 90 vs 30 min of daily ICU rehabilitation demonstrated no difference in quality of life at 6 months.[18] However, on average, patients did not receive the protocol as intended, and the intervention and control group only received 23 and 13 min of daily rehabilitation, respectively.[18] A 5-centre, 120-patient RCT of intensive physical therapy versus usual care in patients with acute respiratory failure demonstrated no difference in physical function at 1 month; however, 63% had missing primary outcome measures.[19] Learning from these important studies, our pilot RCT suggests that enrolment, intervention delivery and outcome measurement are feasible in our future large RCT.

A landmark early rehabilitation study randomised 106 patients to early occupational and physiotherapy interventions within 1.5 days of MV compared with routine care, which started at 7.4 days post-ICU admission.[29] More patients randomised to early rehabilitation were functionally independent at hospital discharge, compared with those who were not (59% vs 35%, p=0.02). In contrast, a recent study of early intensive versus standard rehabilitation found no difference in physical components score at 6 months; however, investigators did not successfully implement the intervention as described above.[18] Other studies of early rehabilitation interventions demonstrated no differences in hospital length of stay[30] or function.[31 32] Similar to previous RCTs,[27–32] few adverse events occurred during either of our early rehabilitation interventions, despite very different approaches to early rehabilitation.

Two international, multicentre RCTs studied early goal directed mobilisation (EGDM) in surgical[28] and medical-surgical ICU patients.[27] EGDM involves targeting a daily specific mobility goal, led by PTs in consultation

Table 4 Patient outcomes

Outcome	ICU discharge		Hospital discharge	
	Cycling	Routine	Cycling	Routine
Mortality, n (%)	9 (25.0)	9 (30.0)	11 (30.6)	11 (36.7)
Length of stay, median (IQR) days	13.5 (7.5–25.5)	10 (9–24)	27 (13.5–47)	25 (19–45)
Clinical Frailty Score, mean (SD)			5.0 (1.7)	5.3 (1.7)
Hospital disposition for survivors, N (%) (N=44)			N=25	N=19
Home—independent			11 (44.0)	6 (31.6)
Home—home care			3 (12.0)	4 (21.1)
Home—unpaid caregiver			2 (8.0)	4 (21.1)
Inpatient rehabilitation			5 (20.0)	2 (10.5)
Other hospital			3 (12.0)	2 (10.5)
Other			1 (4.0)	1 (5.3)

This table summarised patients' outcomes post-ICU.
ICU, intensive care unit; IQR, interquartile range; SD, standard deviation.

with the ICU multidisciplinary team. In a 5-centre RCT, 200 postsurgical ICU patients were randomised to EGDM facilitated by a dedicated critical care staff member versus standard care. Those receiving EGDM (n=104) achieved higher ICU mobility levels and had better functional mobility at hospital discharge than those who did not.[28] In the 5-centre, 50-patient unblinded TEAM pilot RCT, those randomised to EGDM (n=29) achieved higher ICU mobility score levels at ICU discharge[33] and longer duration of therapy (median (IQR) 20 (0–40) vs 7 (0–15) min per day)) than those randomised to usual care. The full TEAM RCT to study the effects of early mobilisation on the primary outcome of the number of days alive and out of hospital is currently underway (NCT03133377)

As anticipated in this pilot trial focused on feasibility metrics,[14] we did not identify any between group differences. From ICU awakening to hospital discharge, patients' strength, function and quality of life improved. However, patients still demonstrated important disability at hospital discharge. For example, patients completed a median of 5 sit to stand repetitions at hospital discharge. This value falls well below that of the lowest average normative value of 14 repetitions in 80–90-year-old community dwelling women.[34] Similarly, the median 2 min walk test distances varied from 76 m (cycling) to 61 m (routine), which are much lower than the lowest normative value of 134.3 m in 80–85-year-old women.[35] Our patients may require ongoing outpatient rehabilitation interventions to improve their function. Over 60% of all of our survivors required some assistance posthospital discharge (table 4).

Limitations and strengths

This study was not designed to evaluate the effect of cycling on patient-important outcomes due to the pilot trial design and attendant sample size. We did not protocolise routine physical therapy or sedation because at the time of trial design, there was no consensus on optimal implementation of either intervention.[36] We originally planned to use this trial as an internal pilot with blinded PFIT-s measures at hospital discharge;[21] however as we concluded our trial, the Towards RECOVER study identified the prognostic importance of physical function measures at 7 days post-ICU and function 1 year later.[4] Thus, for the future RCT, we will conduct the primary

Table 5 Three primary modifications for the main CYCLE RCT

Item	Modification
1. Enrolment	► Increase frontline ICU PT staffing or identify dedicated research ICU PTs for in-bed cycling.
2. Intervention delivery	► To increase cycling exposure or rehabilitation interventions, consider augmenting therapist capacity, different staffing models, improved care coordination, and strategies to encourage patient engagement. ► Conduct further research to understand barriers and facilitators of early in-bed cycling from quantitative and qualitative perspectives.
3. Primary outcome	► Conduct the PFIT-s post ICU discharge rather than at hospital discharge to evaluate the effect of cycling on more survivors closely following their ICU discharge.

This table summarises key modifications for the main CYCLE RCT based on lessons learned from the pilot RCT.
ICU, intensive care unit; PFIT-S, Physical Function ICU Test-scored; PT, physiotherapist; RCT, randomised clinical trial.

outcome measure 3 days post ICU discharge rather than at hospital discharge to evaluate the effect of cycling on more survivors closely following their ICU discharge.

Strengths of this study include evaluation of a PT-led intervention in seven ICUs, underscoring the importance of an interprofessional approach to rehabilitation. We engaged the largest number of centres and conducted the largest multiprofessional trial of early in-bed cycling in the field to-date. Randomisation was concealed. This was an unblinded trial in conduct, but blinded outcome ascertainment was performed for 86% of patients. There was no contamination of control patients receiving cycling. Table 5 highlights three key revisions for the main RCT.

CONCLUSION

In-bed cycling is a promising early intervention for MV patients to improve physical function. Our pilot RCT suggests that a multicentre RCT is feasible but strategies to optimise enrolment and cycling intervention delivery will be needed. Lessons learnt through this pilot trial have informed the vanguard phase of a large multicentre CYCLE trial of early rehabilitation in critically ill patients using in-bed cycling, now underway (NCT02377830).

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