City Research Online

City, University of London Institutional Repository

Citation: Nickels, M. R., Blythe, R., White, N., Ali, A., Aitken, L. M., Heyland, D. K. & McPhail, S. M. (2024). Predictors of acute muscle loss in the intensive care unit: A secondary analysis of an in-bed cycling trial for critically ill patients. Australian Critical Care, 36(6), pp. 940-947. doi: 10.1016/j.aucc.2022.12.015

This is the accepted version of the paper.

This version of the publication may differ from the final published version.

Permanent repository link: https://openaccess.city.ac.uk/id/eprint/30207/

Link to published version: https://doi.org/10.1016/j.aucc.2022.12.015

Copyright: City Research Online aims to make research outputs of City, University of London available to a wider audience. Copyright and Moral Rights remain with the author(s) and/or copyright holders. URLs from City Research Online may be freely distributed and linked to.

Reuse: Copies of full items can be used for personal research or study, educational, or not-for-profit purposes without prior permission or charge. Provided that the authors, title and full bibliographic details are credited, a hyperlink and/or URL is given for the original metadata page and the content is not changed in any way.

City Research Online: http://openaccess.city.ac.uk/ publications@city.ac.uk

Predictors of acute muscle loss in the intensive care unit: A secondary analysis of an in-bed cycling trial for critically ill patients.

Marc R Nickels PhD, MPhysSt, BOccTher [a,d,g,*]

Robin Blythe MPH (HlthPol& Mgt), BA(Econ), BCom(IntBusiness) [b]

Nicole White (PhD (Statistics), BAppSc(Hons), BMaths [b]

Azmat Ali BHlthSc(Nutr), GradDipNutr&Diet, AdvAPD [e,g]

Leanne M Aitken PhD, BHSc(Nurs)Hons, GradDipScMed(ClEpi) [f]

Daren K Heyland PhD, BMS, MD(DIST) [h]

Steve M McPhail PhD, BPhysio [b,c,d,i]

A Physiotherapy Department, Ipswich Hospital, West Morton Health, Ipswich, Queensland, Australia

B Australian Centre for Health Services Innovation, Queensland University of Technology, Brisbane, Queensland, Australia

C Centre for Healthcare Transformation, Queensland University of Technology, Brisbane, Queensland, Australia

D School of Public Health & Social Work, Queensland University of Technology, Brisbane, Queensland, Australia

E Nutrition & Dietetics Department, Princess Alexandra Hospital Brisbane, Queensland, Australia

F School of Health Sciences, City, University of London, London, United Kingdom

G Intensive Care Unit, Princess Alexandra Hospital, Metro South Health, Brisbane, Queensland, Australia

H Department of Critical Care Medicine, Queen's University and the Clinical Evaluation Research Unit, Kingston General Hospital, Kingston, Ontario, Canada,

I Clinical Informatics, Metro South Health, Brisbane, Australia

Study Location: Princess Alexandra Hospital, Intensive Care Unit, Brisbane, Australia

* Corresponding Author – Physiotherapy Department, Ipswich Hospital, Ipswich, 4305, Australia,

Email: marc.nickels@health.qld.gov.au (MR Nickels), robin.blythe@qut.edu.au (R Blythe), nm.white@qut.edu.au (N White), nesiali58@gmail.com (A Ali), leanne.aitken.1@city.ac.uk (L.M.Aitken), dkh2@queensu.ca (DK Heyland), steven.mcphail@qut.aedu.au (SM McPhail)

Abstract

Purpose: To assist clinicians to identify critically ill patients at greatest risk of acute muscle loss and to analyse the associations between protein intake, and exercise on acute muscle loss.

Materials and methods: Secondary analysis of a single centre randomised clinical trial of in-bed cycling using a mixed effects model was undertaken to examine the association between key variables and rectus femoris cross-sectional area (RFCSA). Groups were combined and key variables for the cohort were mNUTRIC scored within the first days following ICU admission, longitudinal RFCSA measurements, percent of daily recommended protein intake, and group allocation (usual care, in-bed cycling). RFCSA ultrasound measurements were taken at baseline and days 3,7,10 to quantify acute muscle loss. All patients received usual care nutritional intake while in ICU. Patients allocated to the cycling group commenced in-bed cycling once safety criteria were met.

Results: Analysis included all 72 participants, of which 69% were male, with a mean (SD) age of 56 (17) years. Patients received a mean (SD) of 59% (26%) of the minimum protein dose recommended for critically ill patients. Mixed effects model results indicated that patients with higher mNUTRIC scores experienced greater RFCSA loss (Estimate=-0.41; 95%CI: -0.59 to -0.23). RFCSA did not share a statistically significant association with cycling group allocation (Estimate=-0.59, 95%CI: -1.53 to 0.34), the percentage of protein requirements received (Estimate=-0.48; 95%CI: -1.16 to 0.19), or a combination of cycling group allocation and higher protein intake (Estimate=0.33, 95%CI: -0.76 to 1.43).

Conclusions and relevance: We found that a higher mNUTRIC score was associated with greater muscle loss, but we did not observe a relationship between combined protein delivery and in-bed cycling and muscle loss. The low protein doses achieved may have impacted on the potential for exercise or nutrition strategies to reduce acute muscle loss.

Introduction:

Critically ill patients can lose over 20% of their skeletal muscle during the first 10-days of an intensive care unit (ICU) admission[1]. Protein is an important macronutrient for maintaining lean body mass, supporting immune function, and healing wounds[2]. From a metabolic perspective, skeletal muscle wasting is the result of muscle protein breakdown exceeding protein synthesis[3-5]. Risk factors for skeletal muscle loss in the early stages of critical illness include; inactivity, malnutrition, inflammation, and dysregulation of protein metabolism secondary to critical illness[6-8]. However, it is currently unknown which patients with critical illness are more likely to lose or preserve their skeletal muscle mass. The ability to identify patients at highest risk of skeletal muscle loss could be an important advancement in the care of critically ill patients. If patients at greatest risk of muscle loss can be identified early, then provision of optimal nutrition support or exercise (or a combination of both) may improve patient outcomes.

Critically ill patients often receive less than the minimum recommended dose of 1.2/g/kg of protein[2,9]. The lower than recommended delivery of protein has been associated with acute muscle loss and worse clinical outcomes[10]. However, the challenge remains for clinicians and researchers to identify which critically ill patients are most at risk of acute muscle loss early during a patient's hospitalisation. The modified Nutrition Risk in the Critically Ill (mNUTRIC) is a validated risk score designed to identify critically ill patients who are at risk of adverse consequences related to inadequate nutrition[11,12]. Higher mNUTRIC scores (between 5 and 9) represent greater risk of nutrition-related complications and identifies critically ill patients who are most likely to benefit from optimal nutrition therapy[11,12]. However, no investigations have examined whether the mNUTRIC score is associated with acute muscle loss and whether the mNUTRIC could also be utilised as a risk assessment tool for acute muscle loss.

To date most studies have either not reported nutrition intake or examined the effect of nutrition or exercise in isolation on the maintenance of skeletal muscle during critical illness[13-15]. Theoretically, the combination of sufficient exercise and protein may reduce the amount of skeletal muscle loss in critically ill patients[9]. However, there is limited research that has investigated the combined effects of protein and exercise on skeletal muscle loss in critically ill patients[9,16]. This warrants an analysis of exercise and protein data collected during the recently completed Critical Care In-bed Cycling Study(CYCLIST) randomised controlled trial(RCT). The CYCLIST RCT investigated the effectiveness of a daily in-bed cycling intervention on reducing acute muscle loss[17-19]. During this study participants received nutritional support as standard care. At Day 10 following study enrolment participants lost muscle mass, with the in-bed cycling group losing a mean (SD) 8.4% (19.7%) rectus femoris cross-sectional area (RFCSA) in comparison to the usual-care group who lost 14.7% (21.0%) RFCSA. [17]. The variability of results and hence the overall lack of impact of in-bed cycling to reduce muscle loss (mean difference, coefficient 3.4, 95% confidence interval -6.9% to 13.6%; p=0.52) [17] provided a rationale to further investigate the potential effect of nutrition on acute muscle loss. This planned exploratory analysis will assist to gain insights into the identification of patients at risk of skeletal muscle loss and the associations between in-bed cycling exercise, protein, and muscle loss.

Research questions:

1) Is the mNUTRIC score collected within the first days of ICU admission associated with acute muscle loss during the admission to the ICU?

2) What is the effect of in-bed cycling on muscle loss when compared to usual care, when protein intake is controlled?
3) Does the combination of in-bed cycling, and higher protein intake reduce acute muscle loss compared to usual care?

Methods:

Study setting and population:

We performed a planned secondary analysis of a single centre RCT to examine if characteristics associated with nutrition risk (mNUTRIC score) were evident early during an ICU admission to identify patients at highest risk of acute muscle loss and to explore potential associations between protein intake, in-bed cycling exercise, and acute muscle loss. The study was conducted in a 26-bed tertiary, adult, mixed medical, surgical, and trauma ICU in Brisbane, Australia. Adult patients were eligible for the study if they were expected to be mechanically ventilated for greater than 48-hours and expected to remain in the ICU for more than 2-days after study enrolment. Patients were excluded from the trial if they had pre-existing functional limitations, new neurological conditions, neurological injuries, were unlikely to survive the current to survive the current hospital admission, or conditions that would preclude in-bed cycling.

The methods, implementation, and results of the CYCLIST RCT have previously been described[17-19]. In brief, patients were randomised to usual care physiotherapy or usual care physiotherapy plus additional passive or active in-bed cycling for 30-minutes per day, six days per week. Patients allocated to the cycling group commenced in-bed cycling as soon as safety criteria were met[18]. Usual care physiotherapy typically consisted of respiratory physiotherapy, physical rehabilitation exercise interventions including sitting on the edge of the bed, sit to stand transfers, sitting out of bed and walking. All patients received usual care nutritional intake while in the ICU based on recognised clinical guidelines[2,20]. Usual care at the study site required that nutrition prescription be initiated by the medical team, as per the unit-based protocols. Individualised nutrition prescription included the time of commencement, method of delivery (enteral or parenteral), rate of nutrition delivery and timing of cessation of enteral or parenteral nutrition. This rate was reviewed and modified, if required, by the ICU dietitian within 48-96 hours of admission. Both usual care physiotherapy and nutrition practices were not modified secondary to participants enrolment in the study.

This study received ethics approvals from Metro South Human Research Ethics Committee(EC00167) on 28 April 2016(HREC/16/QPAH/193) and subsequent approval after an administrative review from Queensland University of Technology Human Research Ethics Committee(1600000441). Ethics approval has been granted until 30th April 2023. Site-specific approval(SSA) has been granted by Metro South Centres for Health Research, Research Governance(SSA/16/QPAH/195) on 1 June 2016. CYCLIST Study Protocol Version 2.1 dated 30 March 2017 was approved on 13 April 2017. This trial has been prospectively registered on the Australian and New Zealand Clinical Trial Registry(ACTRN12616000948493).

Data collection:

Our outcome variable, skeletal muscle area, was measured longitudinally by sonographers using ultrasound RFCSA measurement. Baseline RFCSA measurement was completed following study enrolment, and repeated at days 3, 7, and 10 following study enrolment[17,19]. Information regarding patients' protein intake was collected from electronic patient records that commenced from ICU admission until enteral or parenteral nutrition ceased. Participants' protein intake was monitored

from the day that the participants' baseline RFCSA scan was recorded. Protein intake was then calculated based on the protein composition of the nutrition provided. We ceased to record protein intake observations once patients recommenced oral nutrition as they could not be accurately estimated, this typically occurred post-cessation of mechanical ventilation. Other data collected included patients' age, sex, weight, height, severity of illness(APACHE II), mNUTRIC within the first days following an ICU admission, cycling group allocation, length of stay in hospital prior to ICU admission, length of mechanical ventilation, ICU length of stay, delay in provision of nutrition from baseline RFCSA measurement, nutrition feed types, and feed volume received during the patients ICU admission.

The critically ill patients in the study were not well enough to be weighed and measured upon admission and the beds in use do not provide a weighing facility. Patient height and weight was estimated by ICU nurses experienced in completing this task at ICU admission. Body weight was used to determine the daily protein requirements for patients whose BMI was less than 30 and adjusted ideal body weight for patients whose BMI was greater than 30(obese)[20]. The proportion of the daily dose of protein received was determined by dividing the protein received by the minimum daily protein(1.2 g/kg/day). The protein dose recommendations are based on the nutrition guidelines for critically ill patients provided by the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.)[2].

Statistical analysis

We sought to characterise the influences of daily protein intake, in-bed cycling and their interaction on changes in muscle mass over time. We used a mixed effects model to examine the conditional effect of in-bed cycling on RFCSA after adjusting for daily protein intake. Key independent variables included in the model as fixed effects were group allocation (usual care, in-bed cycling), percent of daily recommended protein intake, longitudinal RFCSA measurements(baseline, days 3,7,10) and mNUTRIC score recorded within the first days following an ICU admission. For each follow-up point, percent of daily recommended protein intake was defined as the average intake since the last RFCSA measurement. A two-way interaction term was specified as part of the model to investigate whether the effect of in-bed cycling was moderated by protein intake. Given the longitudinal nature of data collected, we accounted for within-subject variation by assigning a random intercept to each participant. Uncertainty in estimated fixed effects was reported by 95%Confidence intervals(CI) with subsequent hypothesis testing based on Satterthwaite's method[21]. The R statistical software package was used for all statistical analyses(https://www.r-project.org/).

Results:

Patient Characteristics:

A total of 74 patients were randomised in the CYCLIST study. One participant from each group was excluded from analysis. As one participant withdrew consent, and one patient was deemed to be ineligible when it became evident upon waking that they had an ischaemic spinal cord injury (Figure 1). The sample of 72 patients were included in this secondary analysis. The groups were evenly divided with 36 participants allocated to each group. The mean, standard deviation (SD) age was 56(17) years, BMI was 29(6), and 69% were male. Nearly half of the patients(47%) were identified as at higher risk of nutrition-related adverse events with high mNUTRIC scores(between 5 and 9). These figures, along with clinical data, are shown in Table 1. The patients allocated to the in-bed cycling group commenced cycling a median(interquartile range) of 2.3(1.8,3.1) days following admission to the ICU[18].

Table 1. Patient baseline characteristics and clinical outcomes

Patient characteristics at baseline	In-bed cycling group, n = 36	Usual-care group, n = 36	Cohort, n = 72
Age in years	56 (18)	57 (16)	56 (17)
Males, n (%)	23 (64%)	27 (75%)	50 (69%)
APACHE II score, median (IQR)	17 (13, 21)	19 (16, 24)	19 (15, 22)
SOFA (worst score), median (IQR)	9 (8, 12)	9 (7, 11)	9 (7, 12)
SOFA (most organs with dysfunction), median (IQR)	3 (3, 4)	4 (3, 5)	4 (3,4)
Height in centimetres	171 (11)	173 (10)	172 (10)
Weight in kilograms	85 (16)	88 (18)	86 (17)
BMI kg/m^2	29 (5)	30 (8)	29 (6)
Baseline RFCSA cm^2	3.8 (1.6)	4.3 (2.0)	4.0 (1.8)
Modified NUTRIC score, median (IQR)	4 (3, 6)	4 (3, 6)	4 (3, 6)
Modified NUTRIC score 5-9 (high score), n (%)	17 (47%)	17 (47%)	34 (47%)
Days till ICU admission, median (IQR)	0.2 (0.1, 0.6)	0.2 (0.1, 1.3)	0.2 (0.1, 1.0)
Primary Diagnosis on ICU Admission, n (%)			
Trauma	8 (22%)	5 (14%)	13 (18%)
Sepsis	7 (19%)	6 (17%)	13 (18%)
Respiratory presentations	6 (17%)	6 (17%)	12 (17%)
Cardiac or vascular surgery	4 (11%)	7 (19%)	11 (15%)
Other	11 (31%)	12 (33%)	23 (32%)
Clinical Outcomes	In-bed cycling group, n = 36	Usual-care group, n = 36	Cohort, n = 72
Duration of mechanical ventilation (days)	9.2 (8.5)	8.9 (9.6)	9.0 (9.1)
ICU length of stay (days)	10.9 (8.9)	11.0 (9.9)	11.0 (9.4)
Hospital length of stay (days)	22.7 (18.0)	22.5 (11.9)	22.6 (15.2)
Discharge Destination			
Home	31	27	58
Rehabilitation	4	4	8
Died	1	5	6

Values are expressed as mean (standard deviation) unless otherwise specified.
n, number; APACHE II = Acute Physiology and Chronic Health Evaluation II severity of illness score (0-71); SOFA = Sequential Organ Failure Assessment; IQR, interquartile range; MV, mechanical ventilation; ICU, intensive care unit; RFCSA rectus femoris cross sectional area; cm^2, centimetres squared.

Protein Delivery:

Patients received a mean(SD) of 59%(26%) of the minimum protein dose recommended for critically ill patients[2](Table 2). The amount of protein that patients received is displayed in Figure 2.

Table 2. Nutrition received by patients.

Nutrition received	In-bed cycling group, n= 36	Usual-care group, n =36	Cohort, n = 72
Protein intake (g/kg/day)	0.70 (0.32)	0.60 (0.29)	0.66 (0.32)
Total daily protein intake (g/day)	56.2 (22.4)	50.2 (22.1)	53.2 (22.3)
Daily proportion of minimum recommended protein intake (%)	63 (26)	55 (25)	59 (26)

Values are expressed as mean (standard deviation) unless otherwise specified.
n, number; g/kg/day, grams per kilogram per day; g/day, grams per day; %, percentage.

Acute Muscle Loss

Results from the mixed effects model(Table 3) indicated that patients' RFCSA decreased per day spent in ICU following their baseline RFCSA measurement(Estimate:-0.04, 95%CI:-0.08 to-0.01). Each additional point increase in patient mNUTRIC score at baseline corresponded to a reduction in RFCSA of -0.41(95%CI:-0.59 to-0.23). The point estimate of effect for the interaction term representing a combination of cycling group allocation and higher percentage of protein received was consistent with greater retention of RFCSA. However, this interaction between cycling group allocation and protein intake was subject to a high level of uncertainty(Estimate=0.33, 95%CI:-0.76 to 1.43) and was not statistically significant. Cycling group allocation(Estimate=-0.59, 95%CI:-1.53 to 0.34) and higher percentage of protein requirements received(Estimate=-0.48; 95%CI:-1.16 to 0.19) both had non-significant point estimates in this model also. The high levels of uncertainty in these estimates represented by the relatively wide confidence intervals meant there was insufficient evidence to determine statistical significance.

Table 3: Mixed effects model with rectus femoris cross-sectional area as the dependent variable

Term	Estimate (SE)	95% Confidence Interval	T-statistic	p-value
(Intercept)	4.67 (0.31)	4.06 to 5.27	14.90	<0.0001
Cycling group allocation	-0.59 (0.48)	-1.53 to 0.34	-1.23	0.22
Percent of protein requirements met	-0.48 (0.34)	-1.16 to 0.19	-1.40	0.19
Days since RFCSA baseline measurement	-0.04 (0.02)	-0.08 to -0.01	-2.43	0.02
mNUTRIC	-0.41 (0.09)	-0.59 to -0.23	-4.36	<0.0001
Cycling: Protein interaction	0.33 (0.56)	-0.76 to 1.43	0.59	0.56

SE, standard error; RFCSA, rectus femoris cross sectional area; mNUTRIC, modified Nutrition Risk in the Critically Ill.

Discussion:

A secondary analysis of a randomised controlled trial was completed to examine if characteristics associated with nutrition risk (mNUTRIC score) were evident to identify critically ill patients at risk of muscle loss, and to explore potential associations between protein intake, exercise, and acute muscle loss. Patients enrolled in the trial experienced significant muscle loss of approximately half a percent per day during the study period. Further analysis found that participants with a higher mNUTRIC score experienced greater RFCSA muscle loss over time. Hence, the mNUTRIC score may be able to be used to identify patients at higher risk of acute muscle loss. The mixed effects model found that cycling group allocation and high protein was in the direction of improved muscle preservation, but this result was not statistically significant. It was noteworthy, however, that participants in this sample generally did not receive near the recommended daily dose of protein for critically ill patients[2,20]. Thus, the ability of an exercise intervention to maintain skeletal muscle mass in the sample analysed may have been compromised.

A new finding from this analysis was that participants mNUTRIC score was associated with acute muscle loss. The mNUTRIC score is a composite score that includes components likely to be associated with frailty, including advancing age and number of co-morbidities. This finding agrees with other studies that have reported that at ICU admission, patients who present with pre-existing sarcopenia or frailty may be most susceptible to further loss of muscle mass and loss of physical function[7,22].

The mNUTRIC score also incorporates severity of illness(APACHE II), and organ failure burden measured by the Sequential Organ Failure Assessment(SOFA). The association of mNUTRIC with muscle loss is supported by previous research by Puthucheary et.al.(2013), who reported that reduction in RFCSA was associated with organ failure burden[1]. Finally, mNUTRIC includes days from hospital admission to ICU admission. The inclusion of this factor is conceptually supported by a review introducing the concept of acute sarcopenia secondary to hospitalisation[23]. The use of mNUTRIC scores to identify patients potentially susceptible to acute muscle loss early in their ICU admission could be important.

There are a limited number of studies that have investigated the effects of a combined exercise intervention with an increased dose of protein[24-27]. Two RCTs found that a protein intake of 1.5 g/kg/day resulted in better muscle maintenance, when combined with an electrical muscle stimulation exercise interventions[24,25]. A small three-arm RCT with a total of 41 participants found that protein-enriched nutrition plus cycle ergometry was not associated with better outcomes[27]. However, a larger RCT found with 181 participants reported that a protein intake of 1.5g/kg/day in combination with twice daily sessions of in-bed cycling was associated with improved physical quality of life and survival at 3 and 6-months[26]. Several studies are currently being undertaken that are examining whether increased protein intake in combination with exercise, including in-bed cycling, assist to preserve muscle mass and improve patient-centred outcomes[28,29]. Consequently, clinicians can soon expect to gain a better understanding regarding the effect of increased protein intake in combination with exercise interventions.

The finding that patients in this sample experienced acute muscle loss over time is congruent with studies that have examined acute muscle loss with critically ill patients[1,30]. This is an expected finding and is substantiated by previously published findings from the CYCLIST study[17]. However, the addition of nutritional information to the analysis provides clinicians with an improved understanding of protein dose which is a potential confounding variable that warrants consideration when interpreting the effectiveness of an exercise intervention to mitigate muscle loss. Further research regarding impaired protein metabolism in critically ill patients has been published since the completion of the CYCLIST study. A recent study by Chapple et.al.(2022), found that critically ill patients have relatively normal protein digestion and amino acid absorption, however the capacity for critically ill patients to utilise ingested protein for muscle protein synthesis is markedly blunted[31]. Hence overcoming anabolic resistance to protein administration could be a key mechanistic target for interventions that aim to reduce acute muscle loss. Exercise is a mechanism for overcoming anabolic resistance[32,33]. A combination of exercise and protein intake has been shown to be synergistic in healthy populations for the stimulation of muscle protein synthesis compared with either stimulus alone, and this warrants exploration in critically ill adults [34].

Although there was no significant finding related to the effect of nutritional intake in the present study, it is important to note that the nature of observed associations between nutrition and muscle preservation may be related to participants ICU length of stay. Patients with a short ICU length of stay may receive little or no parenteral or enteral nutrition. In comparison, as a usual part of the ICU processes, patients with a longer ICU length of stay are more likely to have a higher severity of illness and receive a greater dose of protein during their ICU admission[35], while simultaneously losing more skeletal muscle over time. If protein intake is insufficient and metabolism is impaired, it is plausible that in-bed cycling, or other interventions, could contribute to increased muscle protein breakdown, potentially leading to increased muscle loss. The positive point-estimate of effect for the interaction term between protein intake and in-bed cycling indicates that higher protein doses and in-bed cycling may be useful for preserving muscle mass, though without reaching statistically significance in the

present study no firm conclusion can be drawn in this regard. The standard errors for protein intake, in-bed cycling, and the interaction term indicated high uncertainty around the impact of these variables, which could be expected as sample size was limited in the CYCLIST trial. Recommendations have been made to increase the of protein delivered during both the initial and chronic ICU phases as well as post ICU discharge[36,37]. Future prospective studies are required to further investigate the association between high protein intake and in-bed cycling [28].

The sub-optimal nutrition received by patients in this study is not uncommon. International observational studies report that the doses of protein that critically ill patients receive are inadequate[38,39]. In healthy people, the maintenance of muscle mass requires an equivalent amount of muscle protein synthesis to maintain the homeostasis of protein metabolism[40]. Muscle protein breakdown is also accelerated during critical illness[1,41], and muscle protein synthesis is blunted[31]. Hence, insufficient doses of protein available for muscle protein synthesis is likely to result in skeletal muscle loss[42]. A recent systematic review and meta-analysis reported that higher doses of protein (with similar energy delivery) reduced muscle loss[29], however this conclusion is based on five small studies and the results require confirmation in a larger prospective trial. For ventilated patients, protein prescription could be modified to be delivered enterally, parentally or intra-venously via amino acids to increase protein delivery[28].

Limitations:

This was a hypothesis-generating secondary analysis of a single centre randomised controlled trial, and causality cannot be inferred from the available data. This was a single centre study with a small sample size, that may limit the generalisability of results. Protein intake via oral nutrition following extubation was not collected. As a focus of future research, incorporating protein intake received orally in ICU, and during acute hospitalisation, and at low versus high doses is likely to provide increased clarity regarding the association between protein intake and functional recovery following a period of critical illness. Patient pre-admission protein intake was likely to have varied between subjects. Some patients may have had a period of prolonged poor nutrition secondary to a slowly deteriorating health state, in comparison to those admitted following an unexpected accident or health event who may have been well nourished prior to their ICU admission. The weight of patients used to calculate the denominator used for nutritional requirements were nurse estimates rather than actual values, however this represents common practice in many ICUs.

Some sonography data were missing, and there was large variability in sonography measurements consistent with the range of RFCSA observed among patients. An optimal method of clinically measuring acute muscle loss in critical care settings remains difficult. RFCSA estimates from sonography measures may have also had some inaccuracy due to the variability in fluid balances experienced by critically ill patients[1]. Prior research has indicated sonography measures may represent an under-estimation of muscle loss in comparison to muscle biopsies[22,29]. However, muscle biopsies are invasive and take considerable specialised expertise to complete. Repeated computerised tomography or magnetic resonance imaging scans may be alternatives but are logistically challenging to complete, especially during the early phases of critical illness[43]. A core outcome set that provides an international consensus regarding the minimum set of outcomes in nutritional and metabolic research with critically ill adults has been established[44] The use of core outcomes are likely to be valuable in understanding the short- and longer-term impacts of nutritional and exercise interventions among patients with critical illness.

Further research

Further research to investigate the effect of different doses of exercise interventions (type, frequency, duration, intensity, single modality, multi-modality) in combination with different doses of protein on patient outcomes remains a priority. Currently, there are at least six studies that are investigating the impact of increased doses of protein and exercise on acute muscle wasting and patient outcomes[29]. The extent to which the studies in progress can deliver the interventions as protocolised, and the results from these studies, will be important for guiding future exercise and nutrition interventions.

In the present study, patients with a higher mNUTRIC score were found to be at greatest risk of acute muscle loss. The mNUTRIC score is calculable within the first two days of admission to an ICU. Further robust large-scale prospective trials are required to determine whether individuals identified as at risk early during their ICU admission would respond to modifications of care, including sustained increased protein dose and early implementation of exercise interventions. Research is required to identify if biomarkers such as prealbumin and creatine kinase can assist to identify critically ill patients at risk of skeletal muscle loss[45-48]. Further advances in this field of research remain an important priority for optimising individualised care and patient centred outcomes for critically ill patients.

Conclusions:

Patients with high mNUTRIC scores are at higher risk of acute muscle loss. Cycling group allocation, amount of protein received, and a combination of cycling group allocation and higher protein intake was not significantly associated with acute muscle wasting in this secondary analysis. The lower than recommended protein intake observed in the present study may have contributed to loss of RFCSA observed. Hence, it remains unclear from this secondary analysis if a combination of optimal protein intake and in-bed cycling reduces acute muscle loss. To improve clinical practice and patient outcomes there is a need to focus future prospective research on patients who are identified at risk of acute muscle loss.

Figure Captions

Figure 1. CONSORT participant flow diagram

Figure 2. Proportion of required minimum recommended dose of protein received at each assessment timepoint by patients in the usual care and in-bed cycling groups.

Legend Figure 2: Sample numbers represent usual care group and in-bed cycling groups respectively. Sample excludes participants ineligible for feeds.

References:

1. Puthucheary, Z.A., et al., *Acute skeletal muscle wasting in critical illness.* JAMA, 2013. **310**(15): p. 1591-600.
2. McClave, S.A., et al., *Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.).* JPEN J Parenter Enteral Nutr, 2016. **40**(2): p. 159-211.
3. Rennie, M.J. and K.D. Tipton, *Protein and amino acid metabolism during and after exercise and the effects of nutrition.* Annu Rev Nutr, 2000. **20**: p. 457-83.
4. van Gassel, R.J.J., M.R. Baggerman, and M.C.G. van de Poll, *Metabolic aspects of muscle wasting during critical illness.* Current Opinion in Clinical Nutrition & Metabolic Care, 2020. **23**(2).
5. Weijs, P.J.M., *Protein nutrition and exercise survival kit for critically ill.* Curr Opin Crit Care, 2017. **23**(4): p. 279-283.
6. Cruz-Jentoft, A.J., et al., *Sarcopenia: revised European consensus on definition and diagnosis.* Age and ageing, 2019. **48**(1): p. 16-31.
7. Kizilarslanoglu, M.C., et al., *Sarcopenia in critically ill patients.* J Anesth, 2016. **30**(5): p. 884-90.
8. Klaude, M., et al., *Protein metabolism and gene expression in skeletal muscle of critically ill patients with sepsis.* Clin Sci (Lond), 2012. **122**(3): p. 133-42.
9. Heyland, D.K., et al., *Combining nutrition and exercise to optimize survival and recovery from critical illness: Conceptual and methodological issues.* Clin Nutr, 2016. **35**(5): p. 1196-206.
10. Yeh, D.D., et al., *Early nutritional inadequacy is associated with psoas muscle deterioration and worse clinical outcomes in critically ill surgical patients.* J Crit Care, 2018. **45**: p. 7-13.
11. Heyland, D.K., et al., *Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool.* Crit Care, 2011. **15**(6): p. R268.
12. Rahman, A., et al., *Identifying critically-ill patients who will benefit most from nutritional therapy: Further validation of the "modified NUTRIC" nutritional risk assessment tool.* Clin Nutr, 2016. **35**(1): p. 158-162.
13. Burtin, C., et al., *Early exercise in critically ill patients enhances short-term functional recovery.* Crit Care Med, 2009. **37**(9): p. 2499-505.
14. Morris, P.E., et al., *Standardized Rehabilitation and Hospital Length of Stay Among Patients With Acute Respiratory Failure: A Randomized Clinical Trial.* JAMA, 2016. **315**(24): p. 2694-702.
15. Wright, S.E., et al., *Intensive versus standard physical rehabilitation therapy in the critically ill (EPICC): a multicentre, parallel-group, randomised controlled trial.* Thorax, 2018. **73**(3): p. 213-221.
16. Arabi, Y.M., et al., *The intensive care medicine research agenda in nutrition and metabolism.* Intensive Care Med, 2017. **43**(9): p. 1239-1256.
17. Nickels, M.R., et al., *Effect of in-bed cycling on acute muscle wasting in critically ill adults: A randomised clinical trial.* J Crit Care, 2020. **59**: p. 86-93.
18. Nickels, M.R., et al., *Acceptability, safety, and feasibility of in-bed cycling with critically ill patients.* Aust Crit Care, 2020. **33**(3): p. 236-243.
19. Nickels, M.R., et al., *Critical Care Cycling Study (CYCLIST) trial protocol: a randomised controlled trial of usual care plus additional in-bed cycling sessions versus usual care in the critically ill.* BMJ Open, 2017. **7**(10): p. e017393.
20. Singer, P., et al., *ESPEN guideline on clinical nutrition in the intensive care unit.* Clin Nutr, 2019. **38**(1): p. 48-79.
21. Kuznetsova, A., P.B. Brockhoff, and R.H.B. Christensen, *lmerTest Package: Tests in Linear Mixed Effects Models.* Journal of Statistical Software, 2017. **82**(13): p. 1-26.

22. Trethewey, S.P., et al., *Interventions for the management and prevention of sarcopenia in the critically ill: A systematic review.* J Crit Care, 2019. **50**: p. 287-295.
23. Welch, C., et al., *Acute Sarcopenia Secondary to Hospitalisation - An Emerging Condition Affecting Older Adults.* Aging and disease, 2018. **9**(1): p. 151-164.
24. Nakamura, K., et al., *High protein versus medium protein delivery under equal total energy delivery in critical care: A randomized controlled trial.* Clin Nutr, 2021. **40**(3): p. 796-803.
25. Badjatia, N., et al., *Neuromuscular Electrical Stimulation and High-Protein Supplementation After Subarachnoid Hemorrhage: A Single-Center Phase 2 Randomized Clinical Trial.* Neurocrit Care, 2021. **35**(1): p. 46-55.
26. de Azevedo, J.R.A., et al., *High-protein intake and early exercise in adult intensive care patients: a prospective, randomized controlled trial to evaluate the impact on functional outcomes.* BMC Anesthesiol, 2021. **21**(1): p. 283.
27. Kagan, I., et al., *Effect of Combined Protein-Enriched Enteral Nutrition and Early Cycle Ergometry in Mechanically Ventilated Critically Ill Patients-A Pilot Study.* Nutrients, 2022. **14**(8).
28. Heyland, D.K., et al., *Nutrition and Exercise in Critical Illness Trial (NEXIS Trial): a protocol of a multicentred, randomised controlled trial of combined cycle ergometry and amino acid supplementation commenced early during critical illness.* BMJ Open, 2019. **9**(7): p. e027893.
29. Lee, Z.-Y., et al., *The effect of higher versus lower protein delivery in critically ill patients: a systematic review and meta-analysis of randomized controlled trials.* Critical Care, 2021. **25**(1): p. 260.
30. Gruther, W., et al., *Muscle wasting in intensive care patients: ultrasound observation of the M. quadriceps femoris muscle layer.* J Rehabil Med, 2008. **40**(3): p. 185-9.
31. Chapple, L.S., et al., *Muscle Protein Synthesis Following Protein Administration in Critical Illness.* Am J Respir Crit Care Med, 2022.
32. Morton, R.W., et al., *Defining anabolic resistance: implications for delivery of clinical care nutrition.* Curr Opin Crit Care, 2018. **24**(2): p. 124-130.
33. Holwerda, A.M., et al., *Dose-Dependent Increases in Whole-Body Net Protein Balance and Dietary Protein-Derived Amino Acid Incorporation into Myofibrillar Protein During Recovery from Resistance Exercise in Older Men.* J Nutr, 2019. **149**(2): p. 221-230.
34. Robinson, M.J., et al., *Dose-dependent responses of myofibrillar protein synthesis with beef ingestion are enhanced with resistance exercise in middle-aged men.* Appl Physiol Nutr Metab, 2013. **38**(2): p. 120-5.
35. Heyland, D.K., N. Cahill, and A.G. Day, *Optimal amount of calories for critically ill patients: depends on how you slice the cake!* Crit Care Med, 2011. **39**(12): p. 2619-26.
36. Wischmeyer, P.E. *Tailoring nutrition therapy to illness and recovery.* Crit Care, 2017. **21**(Suppl 3), 316.
37. van Zanten, A.R.H., et al. *Nutrition therapy and critical illness: practical guidance for the ICU, post-ICU, and long-term convalescence phases.* Crit Care, 2019. **23**(368).
38. Murthy, T.A., et al., *Protein delivery in mechanically ventilated adults in Australia and New Zealand: current practice.* Critical care and resuscitation: journal of the Australasian Academy of Critical Care Medicine, 2021. **23**(4): p. 386-393.
39. Ridley, E.J., et al., *Nutrition Therapy in Australia and New Zealand Intensive Care Units: An International Comparison Study.* JPEN J Parenter Enteral Nutr, 2018. **42**(8): p. 1349-1357.
40. Weijs, P.J., et al., *Proteins and amino acids are fundamental to optimal nutrition support in critically ill patients.* Crit Care, 2014. **18**(6): p. 591.
41. Constantin, D., et al., *Novel events in the molecular regulation of muscle mass in critically ill patients.* J Physiol, 2011. **589**(Pt 15): p. 3883-95.
42. Weijs, P.J., *Fundamental determinants of protein requirements in the ICU.* Curr Opin Clin Nutr Metab Care, 2014. **17**(2): p. 183-9.

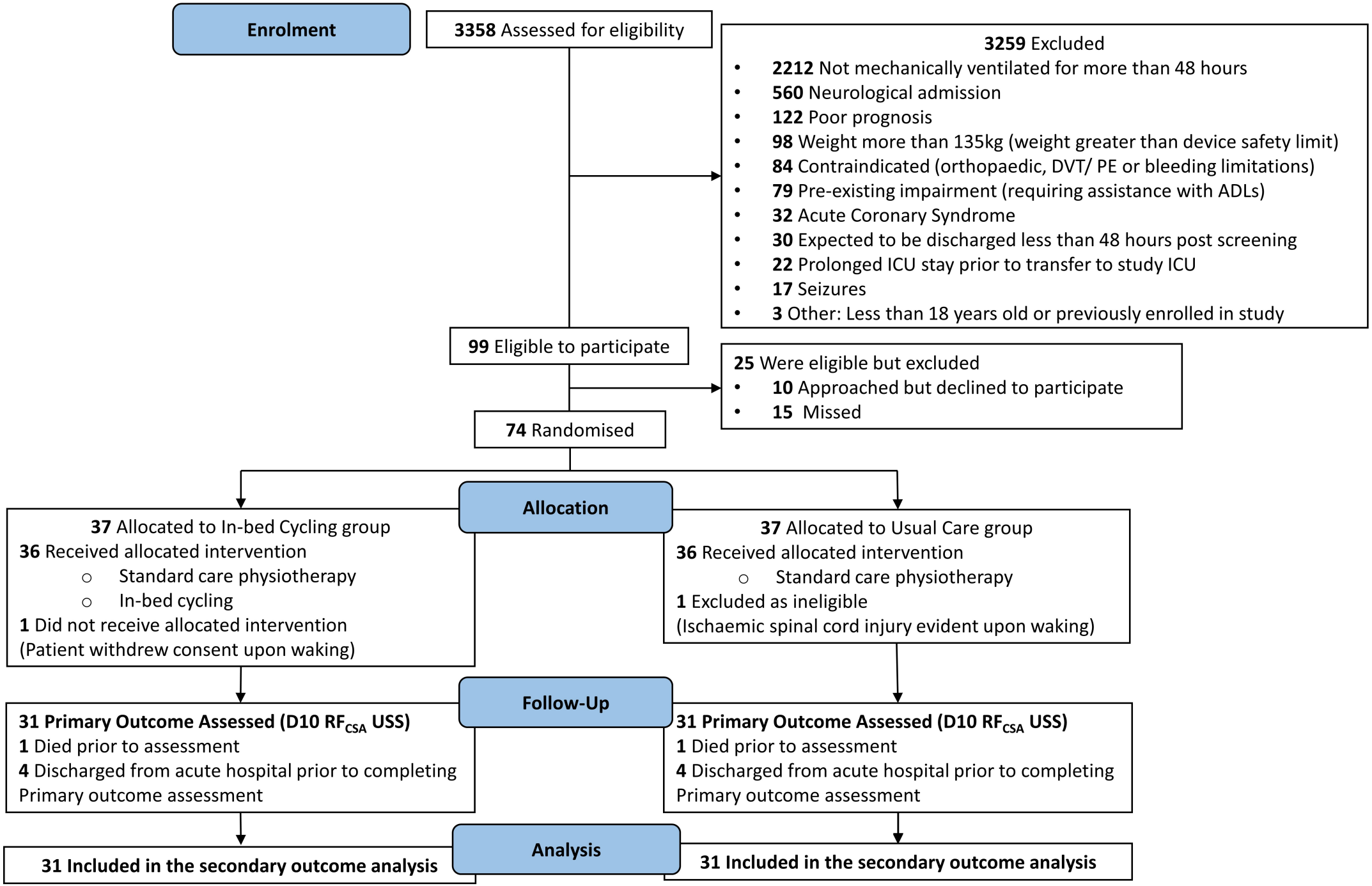
43. Connolly, B., et al., *Ultrasound for the assessment of peripheral skeletal muscle architecture in critical illness: a systematic review.* Crit Care Med, 2015. **43**(4): p. 897-905.
44. Davies, T.W., et al. *Core outcome measures for clinical effectiveness trials of nutritional and metabolic interventions in critical illness: an international modified Delphi consensus study evaluation (CONCISE).* Crit Care, 2022. **26**(240).
45. Luo, L. and M. Wang, *Pre-albumin is a strong prognostic marker in elderly intensive care unit patients.* Journal of Laboratory Medicine, 2021. **45**(4-5): p. 225-228.
46. Moghadam-Kia, S., C.V. Oddis, and R. Aggarwal, *Approach to asymptomatic creatine kinase elevation.* Cleve Clin J Med, 2016. **83**(1): p. 37-42.
47. Nichols, D.C., et al., *Prealbumin Is Associated With In-Hospital Mortality in Critically Ill Patients.* Nutrition in Clinical Practice, 2020. **35**(3): p. 572-577.

Figure Captions

Figure 1. CONSORT participant flow diagram

Figure 2. Proportion of required minimum recommended dose of protein received at each assessment timepoint by patients in the usual care and in-bed cycling groups.

Legend Figure 2: Sample numbers represent usual care group and in-bed cycling groups respectively. Sample excludes participants ineligible for feeds.


Enrolment
3358 Assessed for eligibility
3259 Excluded
• 2212 Not mechanically ventilated for more than 48 hours
• 560 Neurological admission
• 122 Poor prognosis
• 98 Weight more than 135kg (weight greater than device safety limit)
• 84 Contraindicated (orthopaedic, DVT/ PE or bleeding limitations)
• 79 Pre-existing impairment (requiring assistance with ADLs)
• 32 Acute Coronary Syndrome
• 30 Expected to be discharged less than 48 hours post screening
• 22 Prolonged ICU stay prior to transfer to study ICU
• 17 Seizures
• 3 Other: Less than 18 years old or previously enrolled in study
99 Eligible to participate
25 Were eligible but excluded
• 10 Approached but declined to participate
• 15 Missed
74 Randomised
Allocation
37 Allocated to In-bed Cycling group
36 Received allocated intervention
○ Standard care physiotherapy
○ In-bed cycling
1 Did not receive allocated intervention
(Patient withdrew consent upon waking)
37 Allocated to Usual Care group
36 Received allocated intervention
○ Standard care physiotherapy
1 Excluded as ineligible
(Ischaemic spinal cord injury evident upon waking)
Follow-Up
31 Primary Outcome Assessed (D10 RFCSA USS)
1 Died prior to assessment
4 Discharged from acute hospital prior to completing Primary outcome assessment
31 Primary Outcome Assessed (D10 RFCSA USS)
1 Died prior to assessment
4 Discharged from acute hospital prior to completing Primary outcome assessment
Analysis
31 Included in the secondary outcome analysis
31 Included in the secondary outcome analysis

Proportion of recommended protein received (g/kg/day)

1.0

0.5

0.0

Baseline, n=(34,36)

Day 3, n=(23,23)

Day 7, n=(19,12)

Day 10, n=(8,3)

Time point

Group allocation

Usual care

In-bed cycling