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Earlier and enhanced rehabilitation of mechanically ventilated patients in critical care: A feasibility randomised controlled trial

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ABSTRACT

Background: Systematic reviews of early rehabilitation within intensive care units have highlighted the need for robust multi-centre randomised controlled trials with longer term follow up. This trial aims to explore the feasibility of earlier and enhanced rehabilitation for patients mechanically ventilated for ≥5 days and to assess the impact on possible long term outcome measures for use in a definitive trial.
Methods: Patients admitted to a large UK based intensive care unit and invasively ventilated for ≥5 days were randomised to the rehabilitation intervention or standard care on a 1:1 basis, stratified by age and SOFA score. The rehabilitation intervention involved a structured programme, with progression along a functionally based mobility protocol according to set safety criteria.
Results: 103 out of 128 eligible patients were recruited into the trial, achieving an initial recruitment rate of 80%. Patients in the intervention arm mobilized significantly earlier (8 days vs 10 days, $p = 0.035$), at a more acute phase of illness (SOFA 6 vs 4, $p < 0.05$) and reached a higher level of mobility at the point of critical care discharge (MMS 7 vs 5, $p < 0.01$).
Conclusion: We have demonstrated the feasibility of introducing a structured programme of rehabilitation for patients admitted to critical care.

1. Introduction

Approximately 270,000 patients are admitted annually to general critical care units in England, with around a third of this requiring mechanical ventilation [1]. A strong correlation between muscular weakness and prolonged mechanical ventilation has been observed, with survivors experiencing significant physical, cognitive and mental health impairments. The muscle weakness experienced by ICU patients is multifactorial, with sarcopenia from pre-morbid conditions, disuse atrophy from bed rest [2] and ICU acquired weakness (ICUAW) all contributing factors [3]. Muscle wasting occurs early and rapidly during the first week of critical illness, correlates with the degree of organ failure [4], and is associated with failure to wean from the ventilator and increased in-hospital mortality [5,6]. Preventing the physical consequences of critical illness and supporting recovery from intensive care has therefore been identified as a high priority area for critical care research [7].

Early and progressive mobilisation has been demonstrated to be both safe and feasible for patients admitted to critical care [8]. When implemented, programmes of early mobility have demonstrated improvements in physical function and mobility levels, alongside significant reductions in both ICU and hospital length of stay, ventilation days and a reduction in both the incidence and duration of delirium [9-12]. Despite this, point prevalence surveys have shown rehabilitation levels within critical care to remain low, particularly for patients still requiring mechanical ventilation and with ongoing organ dysfunction [13,14]. Recently published randomised controlled trials of early rehabilitation within the ICU have failed to show long term significant benefits, but they have been limited by recruiting patients with short lengths of stay in the ICU and therefore lower levels of ICUAW, or mismatches in the baseline characteristics [15-18].

An important consideration when interpreting the results of such trials remains the use of the term “early”, which in itself has yet to be defined and onset of interventions varying by as much as 1 week [19]. The patients most at risk of prolonged sequelae are often still too acutely unwell for active mobilisation to be commenced safely in the first few days of critical illness. For these patients the important factor may instead be

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the implementation of "earlier" interventions, whereby mobilisation can be initiated at a more acute stage of the patient's illness than would otherwise occur rather than simply focussing on a one size fits all approach. After 10 days in the ICU, the admission diagnosis and physiological derangement become less important than simple antecedent patient characteristics such as age, sex and chronic health status in determining outcome and although only representing 5% of all ICU admissions, these patients with "persistent critical illness" consume significant resource and require dedicated future research [20]. Older ICU survivors in particular suffer prolonged and persistent decline in cognitive and physical function with those with a length of stay >2 weeks at highest risk for 1-year mortality and disability [21].

Our group has previously published the results of a quality improvement project, where a new supportive rehabilitation team was created with a focus on promoting early and enhanced rehabilitation for patients at high risk of prolonged ICU and hospital stays [11]. The introduction of the team led to a significant improvement in mobility at ICU discharge, and this was associated with a significant reduction in ICU length of stay (LOS), ventilator days and in-hospital mortality. However, only a minority of the eligible ICU patients was treated by the team and unmeasured confounding factors may have impacted on results seen. In a before and after design, it was difficult to define on an individual patient level the constituent parts of standard and enhanced care. The rehabilitation intervention therefore required further evaluation prior to a multicentre trial.

The aim of this trial was to explore the feasibility of delivery of earlier and enhanced rehabilitation for patients mechanically ventilated for ≥5 days and to assess the impact on possible long term outcome measures for use in a future definitive trial. Specifically, the objectives were to:

- Estimate rates of recruitment and consent from eligible patients and to describe the baseline characteristics of the participants in terms of co-morbidities, physical function and illness severity.
- Test the rehabilitation intervention in terms of compliance, differentiation from standard care and ability to increase mobility levels at ICU discharge.
- Estimate retention of participants and response rates to follow-up questionnaires.
- Evaluate a range of clinical and patient-reported outcome measures to aid selection of the most appropriate primary outcome measure for a definitive trial, with estimates of variance for sample size calculation.

2. Material and methods

The protocol for this trial has been previously published in full [22]. Ethical approval was obtained from the Research Ethics Committee East Midlands – Nottingham 1 (reference15/EM/0114) on the 8th April 2015 and trial was registered with ISRCTN registry (ISRCTN90103222). Written informed consent was obtained from all participants, a personal consultee or a Registered Medical Practitioner. The conduct and reporting of the trial conforms to CONSORT extension guidelines [23]. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

3. Design

We conducted a single centre, 1:1 randomised controlled feasibility trial of earlier and enhanced rehabilitation for patients admitted to critical care. There was no a priori calculation of sample size, with a target recruitment of 100 patients specified to allow adequate assessment of outcome measures.

4. Participants

Patients admitted to the critical care unit of a large tertiary referral university teaching hospital were recruited between June 2016 and September 2017. Inclusion criteria were adults (≥16 years of age) who had been invasively ventilated for at least 4 days and expected to continue for at least 24 h. Patients were not eligible for the trial if they had a profound neurological deficit (defined as unlikely to return to a Glasgow Coma Score of at least 14), an orthopaedic injury with contraindications to mobilise (e.g. pelvic fracture), were unable to mobilise at least 10 m prior to admission (with or without an aid), had pre-existing neuromuscular disease, had been invasively ventilated at another facility for >48 h prior to admission or in hospital for >7 days prior to the onset of mechanical ventilation. Patients were also excluded if withdrawal of treatment was expected within 24 h of potential recruitment.

5. Randomisation and blinding

Participants were randomised on a 1:1 basis to enhanced rehabilitation or standard care using a computer based stratified blocked randomisation, stratified for age (<50 years vs ≥50 years) and SOFA score on the day of recruitment (<9 versus ≥9). Recruitment and completion of assessments was undertaken by the research nursing team who were independent from the therapy team delivering rehabilitation. Given the nature of the intervention, it was not possible to blind physiotherapists or participants to group allocation.

6. Study interventions

6.1. Standard care

All patients within our institution are assessed by the physiotherapy team within 24 h of admission to critical care to obtain background information on reason for admission, as well as any pre-existing conditions that may be relevant. They then continue to be seen on a daily basis on weekdays, with rehabilitation commencing based on the individual physiotherapists own clinical reasoning. Physiotherapy provision is funded at a ratio of 1 physiotherapist to 10 patients, with an average treatment time of 30–45 min per patient per day Monday to Friday with one physiotherapist. When discharged to the ward environment, a telephone handover is provided to the receiving therapist who then continues the rehabilitation until the patient is deemed safe for discharge, with no further input provided by the critical care team.

6.2. Enhanced rehabilitation (intervention group)

Physiotherapy sessions for subjects assigned to the intervention group were delivered by members of a specialist critical care rehabilitation team who were separate to the normal physiotherapy team, aiming to minimise contamination between groups. Following recruitment and randomisation subjects in the intervention group were assigned a physiotherapy key worker who completed a standardized comprehensive assessment. This was used to gain additional background information regarding pre-existing physical function, any psychological history and pre admission exercise capacity. Following this assessment an individually tailored rehabilitation programme was devised, with the rehabilitation plan displayed in the subjects' bed space to aid communication and track daily achievements. Weekly goal setting meetings were held to review progress and update treatment plans as required. To facilitate ongoing rehabilitation following critical care discharge both verbal and written handovers were provided to ward therapy staff. For patients achieving a Manchester Mobility Score (MMS) of ≤4 at critical care discharge (unable to stand independently), ongoing rehabilitation was provided by the key worker in conjunction with the ward therapists for the first week following discharge from critical care. This aimed to ensure a seamless handover of care and maximise ongoing

rehabilitation. More detailed information regarding the rehabilitation pathway is available from our previously published protocol [22].

6.3. Both groups

All medical care provided was at the discretion of the responsible intensivist. Rehabilitation interventions by all members of the clinical team at each stage of the patient pathway were carefully recorded by the research team, with reasons for any missed rehabilitation sessions documented. In accordance with current unit practice, all patients with a length of stay over 14 days were discussed at weekly multidisciplinary team meetings attended by consultant medical staff, physiotherapists, senior nursing staff, speech and language therapists and occupational therapists, with collaborative treatment goals set, reviewed and updated.

7. Outcome measures

The objective of this study was to evaluate the feasibility of the enhanced rehabilitation intervention in terms of recruitment process, compliance and differentiation from standard care, and to provide pilot data as to outcome measures and variance for a phase III trial. For the recruitment process, this was assessed as the proportion of eligible patients who were recruited and completed all study assessments. Compliance and differentiation of groups was assessed by the time to first mobilisation defined as Manchester Mobility Score (MMS) of ≥2 (sitting on the edge of the bed or higher), dose of physiotherapy in terms of therapy time, recording of reasons for missed sessions, the daily maximum MMS achieved, and mobility level at ICU discharge.

As this was a feasibility trial numerous additional outcomes were collected to assess any potential impact of the intervention on other key areas. These included hospital based outcomes such as ICU and hospital length of stay and mortality, as well as measures of physical function (Barthel Index) strength (MRC sum score and grip dynamometry) and health related quality of life (SF36 v2). Completion of Barthel and SF-36 scores at 3 and 12 month assessments were via telephone interview, with a follow up sent by post if no response was received.

8. Statistical analysis

Ordinal and continuous variables were compared between arms using Mann-Whitney tests. Data were summarised as either medians with interquartile ranges (IQRs), or as the proportions of patients within various intervals for ordinal variables with small ranges. Nominal variables were compared between arms using Fisher's exact tests. All analyses were performed using IBM SPSS 22 (IBM Corp. Armonk, NY). Cases with missing data were excluded on a per-analysis basis, and $p < 0.05$ was deemed to be indicative of statistical significance throughout.

9. Results

A total of 103 out of 128 eligible patients were recruited into the trial, achieving an initial recruitment rate of 80%. One patient withdrew from the study, and did not allow their data to be used, and so was excluded from the analysis. This left 50 patients in the standard treatment arm, and 52 patients in the enhanced treatment arm (see Fig. 1). For the cohort as a whole, the median age was 62 years (IQR: 47–70), and the majority of patients were male (61%). Table 1 compares a range of baseline and demographic factors between the two study arms, with no significant differences detected between the groups. Approximately half of patients allocated to each group had at least one comorbidity measured using the Charlson co morbidity index.

Median time to first mobilisation was significantly shorter in the intervention group (8 days vs 10 days, $p = 0.035$), with a higher SOFA score at 1st mobilisation (6 vs 4, $p = 0.0278$) and a higher level of mobility achieved at ITU discharge (MMS 7 vs 5, $p = 0.016$). No significant difference was observed regarding average daily duration of therapy, although subjects in the intervention arm received a higher proportion of 'active' rehabilitation sessions (defined as achieving an MMS ≥ 2 during the session) and were more likely to walk >30 m at the point of critical care discharge (73% vs 47%, $p = 0.006$). There were also significantly more 'missed' therapy sessions in the control group (16% vs 10%, $p < 0.001$), the reasons for which are given in Table 2. Patients in the intervention group were more likely to have an individualised treatment plan formulated including goals for rehabilitation set within critical care (100% vs 62%, $p < 0.0001$) and updated weekly throughout the ICU stay (100% vs 16%, $p < 0.0001$). As with previous studies in this area, early activity was safe and feasible within critical care. There were 27 recorded SAE's during the study period, although none of these were attributable to the intervention.

There was no evidence of significant differences between the groups for any of the in-hospital outcomes, components of length of stay, or mortality (see Tables 3 and 4). The median mental component summary score (MCS) of the SF36 was found to be similar in the two arms when measured at baseline (enhanced vs. standard: 40 vs. 44, $p = 0.582$), ITU discharge (33 vs. 39, $p = 0.499$) and at hospital discharge (36 vs. 41, $p = 0.346$). However, by three months post-discharge, the score was found to be significantly higher in the enhanced arm, with a median of 57, compared to 51 in the standard treatment arm ($p = 0.042$).

9.1. Missing data

Some of the factors considered had a large quantity of missing data, with data unavailable in over 50% of the cohort in some cases (e.g. anxiety/depression scores). For the factors relating to ICU/Hospital discharge, this was largely due to nurses not having the opportunity to collect the necessary data before the patient was discharged, hence it is reasonable to assume that these data are missing at random. However, for data collected on admission, some instances of missing data reflect cases where the patient was too unwell to complete the assessment, hence excluding these cases may have introduced bias.

The rates of missing data for each factor were compared between the two arms, with the results reported in Supplementary Table 1. This found no significant differences in the rates of missing data between arms for any of the factors included in the analysis. Hence, if any selection bias were present, the prevalence appears to be similar in the two arms, which should have largely negated the effect of this on the comparisons between arms.

10. Discussion

More patients are surviving critical illness, and strategies to address the long term physical and psychological sequelae of critical illness are urgently needed. In this single centre trial, we assessed the feasibility of introducing a programme of earlier and enhanced rehabilitation for patients admitted to critical care and mechanically ventilated for ≥5 days. This population was specifically chosen to target patients most at risk of ICU acquired weakness, aiming to find the balance between excluding those with short stays and expected faster trajectories of recovery, whilst still ensuring rehabilitation could be commenced early enough to be effective.

Our results demonstrate that recruiting to a trial was feasible, with 103/128 (80%) of eligible patients randomised. Patients in the intervention arm were actively mobilized earlier (8 vs 10 days; $p = 0.035$) and the higher SOFA scores at first mobilisation suggest this was taking place at a more acute phase of the patients illness. The intervention group also achieved a higher level of mobility within critical care (MMS 7 vs 5, $p = 0.016$), with 73% able to walk at the point of ITU discharge. Of note, this trial was performed in a critical care unit that had already successfully implemented a quality improvement initiative in earlier mobilisation [11]. The mobility levels achieved at ICU discharge

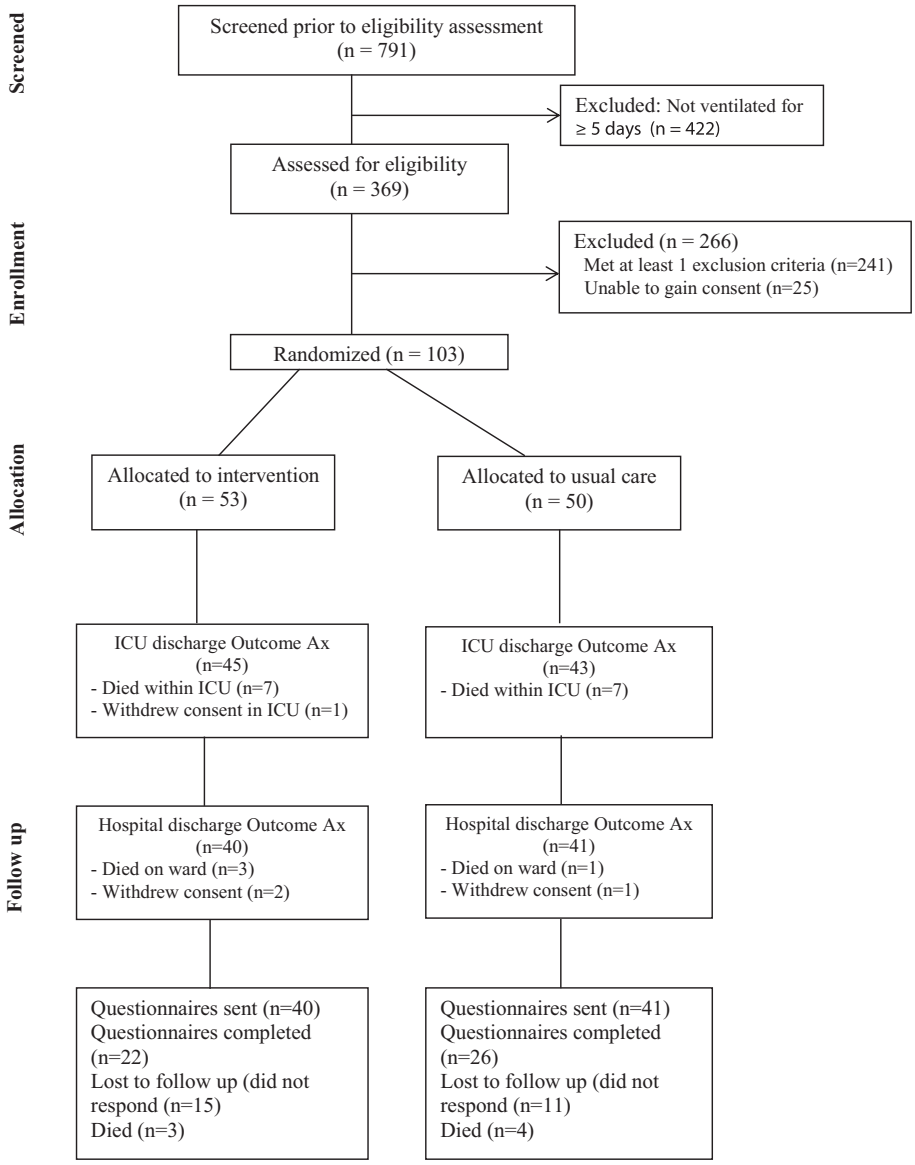

Fig. 1. CONSORT participant flow diagram for primary endpoints.

in the standard arm of this trial are equivalent to the levels achieved post implementation of the QI project (MMS 5 = the ability to step transfer with assistance). Thus, the improvements seen are in addition to previous benefits, and not attributable to a "return to baseline" following the end of the QI initiative.

It is useful to compare our findings with those of the other published trials. As stated previously, a QI project had been completed for earlier rehabilitation within our ICU and as such may have represented a population receiving a higher level of rehabilitation than other similar units. Average daily duration of physiotherapy was 35.4 min in the standard care group, with active rehabilitation occurring in 51% of these sessions and all but one patient mobilising within the ICU. This demonstrates a greater intensity of physical rehabilitation than that provided as standard care in other previous trials [15-18]. The recently published EPICC trial [15], which aimed to compare a higher intensity of physiotherapy for patients admitted to critical care, failed to demonstrate improvements in either short term outcomes or overall recovery at 3 months. This is a similar finding to other recent trials which have attempted to increase the dose or frequency of physiotherapy in those with already established services, which have failed to recreate the positive outcomes seen in other early rehabilitation trials [17,18].

Significant differences were seen between groups in the structure of therapy treatment, with higher levels of goals set and reviewed within the intervention arm. This was achieved with no significant difference in either the total number of sessions or the average duration of therapy delivered between groups, although compliance and delivery of active rehabilitation sessions was higher in the intervention group. Our data supports the hypothesis that the implementation of early and structured rehabilitation is about more than just increasing the dose of physiotherapy. The key to implementation is promoting a cultural change which supports rehabilitation and having a robust structure in place to ensure ongoing consistency with service delivery [24].

Designed as a feasibility trial, our study was not powered to look at any specific long term outcome. A slight reduction was seen between groups in ventilator days and ICU length of stay which would warrant further investigation, although no difference was observed for either total hospital length of stay or mortality. MRC sum scores and grip strength did not differ between groups at ICU discharge, highlighting the limitations in relating functional recovery to measures of muscle strength. Patient reported outcome measures of Barthel, Hospital Anxiety and Depression and SF-36 also showed no difference between groups, except in the mental component score of the SF-36 at 3 months.

Table 1
Patient demographics.

	Standard		Enhanced		p-Value
	N	Statistic	N	Statistic	
Age	50	61 (47–70)	52	62 (46–68)	0.656
Gender (% male)	50	31 (62%)	52	31 (60%)	0.841
SOFA	50	10 (6–13)	52	10 (7–14)	0.845
Apache 11	38	17 (14–21)	41	18 (15–22)	0.336
Charlson comorbidity index	50		52		0.965*
0		25 (50%)		25 (48%)	
1		12 (24%)		15 (29%)	
2+		13 (26%)		12 (23%)	
Admission speciality	50		52		0.752
Cardiothoracics		11 (22%)		9 (17%)	
Medicine		10 (20%)		16 (31%)	
Neurosurgery		7 (14%)		7 (13%)	
Surgery		19 (38%)		16 (31%)	
Trauma/burns		3 (6%)		4 (8%)	
Chronic respiratory disease	50	8 (16%)	52	11 (21%)	0.613
Heart disease	50	11 (22%)	52	9 (17%)	0.622
ES renal failure	50	4 (8%)	52	4 (8%)	1.000
Chronic liver disease	50	7 (14%)	52	5 (10%)	0.551

Data are reported as median (IQR), with p-values from Mann-Whitney tests, or as N (Column %), with p-values from Fisher's exact tests, unless stated otherwise.
* p-Value from a Mann-Whitney test on the untransformed factor.

The biggest limitation to our study is the lack of blinding and potential for contamination across groups. Due to the size of our critical care unit it was possible to ensure patients in the intervention and control groups were assessed and treated by different physiotherapists. This was not the case however with medical staff, nurses or other members of the MDT which may have impacted on the care provided for each group. Another significant limitation is the degree of missing data and the high loss to follow up rate. This occurred despite the presence of dedicated research nurses for data collection and was related to a number of factors. An example of this was the completion of questionnaires in critical care or on return to the ward, where a number of patients lacked the cognitive ability at this time point. The missing data limits the precision of the results and could be a source of bias, although the rate of non-completion was similar for outcomes between groups. The loss to follow up for the SF36 questionnaires was also similar to those seen in other trials assessing critical care survivors following hospital discharge [15,18].

Table 2
Physiotherapy activity.

	Control (n = 43)	Enhanced (n = 44)	p
Number of completed sessions	560	616	
Missed sessions	108	65	<**0.001**
Patient declined	16	16	
Clinical deterioration	17	15	
Weekend	36	27	
Procedure	7	6	
Lack of staff	13	1	
Not documented	19	0	
Average daily duration (mins)	35.4	38.3	0.1577
Active rehabilitation	284 (51%)	394 (64%)	**0.0001**
Time to 1st mobilisation (days)	10 (7–12)	8 (7–11)	**0.035**
SOFA at 1st mobilisation	4 (3–6)	6 (4–8.25)	**0.0278**
MMS at ICU discharge	5 (4–7)	7 (5–7)	**0.016**
1–2	5 (12%	3 (7%)	
3–5	18 (42%)	9 (20%)	
6–7	20 (47%)	32 (73%)	**0.006**
Goals set at least once in ICU	62%	100%	<**0.0001**
Goals updated weekly	16%	100%	<**0.0001**
Documented treatment plan updated weekly	16%	100%	<**0.0001**

Data are reported as median (IQR), with p-values from Mann-Whitney tests, or as N (Column %), with p-values from Fisher's exact tests, unless stated otherwise. Active rehabilitation is defined as achieving an MMS of ≥ 2 during the session.
Bold p-values are significant at $p < 0.05$.

Table 3
In-hospital outcomes.

	Standard		Enhanced		p-Value
	N	Statistic	N	Statistic	
Days on ITU	43	18 (12–28)	45	16 (13−21)	0.339
ICU dependency days	43	17 (10–26)	45	14 (12−21)	0.613
Days vented	43	12 (6–17)	44	10 (7–15)	0.210
Sedation days	43	7 (5–11)	44	8 (5–9)	0.870
Days on ward	42	10 (7–18)	42	12 (6–20)	0.899
Total length of stay (days)	42	29 (20–46)	43	29 (22–41)	0.984
ITU readmission	42	2 (5%)	44	2 (5%)	1.000
Mortality*					
ICU	50	7 (14%)	52	7 (13%)	1.000
Ward	43	1 (2%)	45	3 (7%)	0.617
Post-discharge (3 months)	42	5 (12%)	42	4 (10%)	1.000
Cumulative mortality	50	13 (26%)	52	14 (27%)	1.000

Data are reported as median (IQR), with p-values from Mann-Whitney tests, or as N (Column %), with p-values from Fisher's exact tests, unless stated otherwise.
* With the exception of the cumulative mortality rates, the quoted statistics are non-cumulative, i.e. the ward mortality rate excludes any patients that died in ICU. Cumulative mortality represents the overall mortality rate between admission and three months post-discharge.

11. Conclusion

We have demonstrated that it is feasible to recruit patients to a trial of earlier and enhanced rehabilitation and that by improving the structure of therapy intervention it is possible to reduce the time to first mobilisation and improve the mobility level at ICU discharge. These effects were seen in a critical unit with an already high level of active rehabilitation compared to national and international studies. The long term effect of this improvement in mobility within the ICU warrants

Table 4
Patient outcomes.

	Standard		Enhanced		p-Value
	N	Statistic	N	Statistic	
Bartel					
Pre-admission	38	100 (95–100)	35	100 (85–100)	0.293
ITU discharge	22	55 (35–75)	26	45 (35–80)	0.955
Hospital discharge	21	90 (85–95)	17	85 (80–95)	0.334
MRC					
ITU discharge	34	53 (48–58)	35	53 (44–58)	0.767
Hospital discharge	34	58 (53–60)	35	58 (54–60)	0.833
Anxiety					
ITU discharge	15	8 (6–13)	25	7 (5–14)	0.703
Hospital discharge	18	7 (5–9)	17	5 (3−12)	0.466
Depression					
ITU discharge	15	6 (4–14)	25	9 (5–13)	0.466
Hospital discharge	19	7 (4–10)	17	8 (4–11)	0.795
Grip					
ITU discharge	33	15.4 (7.4–18.9)	35	13.1 (9.1–17.8)	0.614
Hospital discharge	34	16.7 (12.6–20.7)	35	17.1 (11.8–22.4)	0.818
PCS					
Baseline	34	38.5 (27.6–55.0)	36	39.3 (30.3–51.8)	0.829
ITU discharge	18	29.9 (26.3–33.4)	19	29.1 (25.5–36.0)	0.822
Hospital discharge	19	30.5 (26.5–36.3)	17	32.2 (27.3–36.8)	0.552
3 Months	23	37.6 (35.8–47.6)	22	46.1 (35.5–52.3)	0.307
MCS					
Baseline	34	44.0 (32.0–54.7)	36	40.2 (28.5–57.8)	0.587
ITU discharge	18	38.7 (27.0–47.4)	19	33.2 (25.9–43.0)	0.499
Hospital discharge	19	41.3 (29.6–51.6)	17	35.8 (25.1–46.2)	0.346
3 Months	23	51.2 (26.4–57.4)	22	57.4 (38.4–60.4)	**0.042**

Data are reported as median (IQR), with p-values from Mann-Whitney tests, or as N (Column %), with p-values from Fisher's exact tests, unless stated otherwise.
Bold p-values are significant at $p < 0.05$.

further investigation in a phase III trial, which will need to ensure that the mobility programme is robustly structured and delivered.

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The authors have no conflicts of interests to declare.

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