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A bi-national, multi-center, pilot, feasibility RCT of early goal-directed mobilization in ICU

The TEAM Study Investigators

The Trial of Early Activity and Mobilization (TEAM) Study is a collaboration between the ANZICS Clinical Trials Group and the Australian and New Zealand Intensive Care Research Centre. The members of the Writing Committee for the TEAM Study (Carol Hodgson Ph.D. (Chair), Rinaldo Bellomo M.D., Michael Bailey Ph.D., Susan Berney Ph.D., Linda Denehy Ph.D., Belinda Gabbe Ph.D., Megan Harrold Ph.D., Alisa Higgins PT, Theodore Iwashyna M.D., Rebecca Papworth P.T., Rachael Parke Ph.D., Shane Patman Ph.D., Jeff Presneill M.D., Manoj Saxena M.D., Elizabeth Skinner Ph.D., Claire Tipping P.T., Paul Young M.D. and Steven Webb M.D.) take responsibility for the content of this article.

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Abstract

Objectives: The primary objective was to determine if the early goal-directed mobilization (EGDM) intervention could be delivered to patients receiving mechanical ventilation with increased maximal levels of activity compared to standard care.

Design: A pilot, randomized controlled trial

Setting: Five intensive care units (ICUs) in Australia and New Zealand

Participants: Fifty critically ill adults, mechanically ventilated for greater than 24 hours.

Intervention: Patients were randomly assigned to either EGDM (intervention) or to standard care (control). EGDM comprised functional rehabilitation treatment conducted at the highest level of activity possible for that patient assessed by the ICU mobility scale (IMS) while receiving mechanical ventilation.

Measurements and Main Results: The IMS, strength, ventilation duration, ICU and hospital length of stay and total inpatient (acute and rehabilitation) stay as well as six month post-ICU discharge health related quality of life, activities of daily living, and anxiety and depression were recorded.

The mean age was 61 years and 60% were male. Time from ICU admission to randomisation was 3 days. The intervention group (N=29) received a greater level of mobilization. The highest level of activity (IMS) recorded during the ICU stay between the intervention and control groups was mean (95%CI) 7.3 (6.3 – 8.3) versus 5.9 (4.9 – 6.9), $p=0.05$. The proportion of patients who walked in ICU was almost doubled with EGDM (intervention N=19 (66%) versus control N= 8 (38%), $p=0.05$). There was no difference in total inpatient stay (days) between the intervention versus control groups (20 [15-35] versus 34 [18-43], $p=0.37$). There were no adverse events. There was no difference in six-month outcomes.

Conclusion / Key Practice Points: Delivery of EGDM within an RCT was feasible and safe. EGDM resulted in increased duration of active exercises and an increase in the mobility milestones achieved during the ICU stay.

Muscle weakness that develops during the ICU stay, called ICU acquired weakness (ICU-AW), [1, 2] manifests as generalised muscle weakness that is often severe and prolonged. [3] It develops early and rapidly in many ICU patients who receive mechanical ventilation for 24 hours or more and is associated independently with prolongation of the subsequent duration of mechanical ventilation, ICU, and hospital stay. [4-7] An association between ICU-AW and mortality in the first year following ICU discharge has been demonstrated. [8, 9]

Early mobilization of critically ill patients is a candidate intervention to reduce the incidence and severity of ICU-AW and improve outcomes, including one or more of reduced duration of mechanical ventilation, shorter ICU length of stay, improved long-term functional independence, and reduced mortality. [10, 11] There are no published large multi-center trials to determine the effects of early mobilization in ICU and little evidence to support the feasibility of individual patient randomization across multiple sites using early mobilization which is a complex 'process-of-care' intervention. [12, 13] In ICUs in Australia and New Zealand regular physiotherapy is a part of standard care. In a prospective inception-cohort study conducted in 12 ICUs in 2013, only 315 out of 1395 physiotherapy sessions observed in 192 patients receiving mechanical ventilation involved active mobilization. [8] The focus of interest for this current pilot study was to determine if an intervention could be developed and delivered that resulted in a greater 'dose' of early mobilization in patients who are receiving mechanical ventilation.

Early goal-directed mobilization (EGDM) was developed as a candidate intervention to prevent ICU-AW and improve function. The definition of EGDM was a program of physiotherapist-directed active physical exercises intended to maximise physical activity at the highest functional level the patient could achieve. (Figure 1) The aim of this study was to investigate whether individual patient randomisation to EGDM was feasible in a multi-center study and to inform the design of a definitive trial of EGDM compared to standard care.

Methods

Trial design and setting: From 4th September 2013 to 3rd October 2014, a prospective feasibility, parallel group, assessor-blinded randomized clinical trial was conducted in five ICUs in Australia and New Zealand, including tertiary teaching hospitals with a combination of mixed medical, surgical, and trauma beds. The trial protocol was approved by the ethics committee at Monash University (the coordinating center for the trial) and at each participating institution. Informed consent was obtained from all patients or their legal surrogates. This study was registered at ClinicalTrials.gov (NCT01927510) prior to enrolment of any patient.

Study population:

Invasively ventilated patients 18 years and over were assessed for enrolment into the study. Patients were eligible for inclusion to the study if they were expected to be ventilated the day after tomorrow, and less than 48 hours had passed since eligibility criteria were met. Patients were excluded if this was a second or subsequent ICU admission during a single hospital admission; if they were unable to follow simple verbal commands in English; their death was deemed inevitable and imminent by the ICU consultant; if they were unable to walk without assistance of another person prior to onset of acute illness necessitating ICU admission; if they were diagnosed with dementia prior to current acute illness as assessed by hospital records; if they were agitated to a degree which in the opinion of the treating clinician precluded safe implementation of early mobility; if they had written rest in bed orders due to documented injury or process that precluded mobilization such as suspected or proven instability of spine or pelvis; severe acute brain injury; or if in the opinion of the treating clinician it was unsafe to commence mobility therapy.

Patients were assessed daily and were excluded from eligibility for a given session on that day if they were physiologically unstable as defined as any of the following, based on international consensus recommendations.[14]

- i. Cardiovascular instability: unresolved rhythm disturbance with any bradycardia requiring pharmacological support; any tachycardia with ventricular rate > 150 beats / min; Lactate > 4.0 (m/mol) due to inadequate tissue perfusion; or norepinephrine > 0.2mcg/kg/min (or unit equivalent) or any dose of norepinephrine between 0.1 and 0.2 mcg/kg/min with more than a 25% increase in last 6 hours; cardiac index < 2.0 L/min/ m².

- ii. Respiratory instability: $FiO_2 > 0.6$; $PEEP > 15$; $RR > 45$; or current use of nitric oxide, prone positioning, prostacycline, or high frequency oscillatory ventilation.

Randomisation

Randomisation was undertaken using concealed envelopes, stratified by site to a maximum of 20 patients, with a block size of 10. Patients were randomly assigned in a 1:1 ratio, to EGDM beginning on the day of enrolment (intervention) or to standard care with physiotherapy delivered as ordered by the primary care team (control). Because of the nature of the intervention, all clinicians involved in their care were aware of study-group assignments, however ICU discharge assessment (strength and function) was blinded and six month outcome assessors were blinded.

Intervention – Early Goal-Directed Mobility (EGDM)

The EGDM protocol included active functional activities, comprising rolling, sitting, standing and walking. The patient could receive assistance from staff or equipment but the patient actively participated in the exercise at the highest functional level.[15] The goal of EGDM was to maximise safe physical activity (Figure 1).[15] A physical therapy mobility team led EGDM. The mobility team was defined as ICU clinical staff sufficient to provide the intervention (e.g., the ICU physiotherapist, and an allied health assistant together with the bedside nurse). Sedation was adjusted to facilitate exercise at the highest level of activity possible using the ICU mobility scale (IMS), but specific sedation management practices were not protocolized by the trial and were per usual unit practice.

The goal for patients allocated to EGDM was to undertake active exercises for one hour per day that could be completed in one session of treatment or divided into several sessions throughout the day at the discretion of the treating physiotherapist. The active exercises did not have to be done at the highest level for the entire duration of the treatment (e.g., If the IMS was scored at 10 the patient was able to walk, but they may have completed some of the 60 minutes of active exercise time walking, standing, sitting or in supine lying depending on their endurance and physiological response to exercise).

Patients were not mobilized if they were physiologically unstable at the time of the mobilization episode defined according to the consensus criteria above or, in the opinion of the treating clinician, it was not safe to perform the intervention. A detailed exercise protocol was provided separately to the site investigator for the early mobilization treatment group. Funding was allocated for an extra hour of physical therapy per day to intervention group patients. All usual unit practice was continued in the control groups, with no restrictions on physical therapy or sedation practice.

Primary Outcome – Feasibility of intervention delivery

The pre-specified primary objectives of the pilot study were to determine if EGDM resulted in (1) a higher maximal level of activity measured using the IMS (e.g. where in bed activities = 1; sitting over the edge of the bed = 3; standing = 4; and walking independently = 10)[15] and (2) increased duration of activity measured in minutes per day during the ICU stay compared to standard care.

Secondary Outcomes

The secondary outcomes were:

- the time from admission to randomization (feasibility of the delivery of *early mobilization*) and from admission to first mobilization
- duration of mechanical ventilation, ICU and hospital length of stay and total inpatient stay (i.e. the total number of days in the acute hospital and the rehabilitation hospital in-patient stay)
- serious adverse events including: falling to the floor, cardiac arrest, rapid atrial fibrillation, ventricular tachycardia or other dangerous arrhythmia during exercise, oxygen saturation less than 80% for greater than 3 minutes, unplanned extubation or loss of any invasively inserted line
- ventilator-free days and ICU-free days at day 28
- physical function with the Physical Function in ICU Test (PFIT), the Functional Status Score in ICU test (FSS-ICU)[16] and the Medical Research Council Manual Muscle Test (MRC-SS)
- ICU acquired weakness (ICUAW), defined as being present if the patient had MRC-SS < 48 at ICU discharge [3, 9, 17]

In order to assess suitability for use in future clinical trials, telephone follow-up was tested in survivors at 6 months by a blinded central assessor. The independent activities of daily living (IADL)[18], return to work, health related quality of life (EQ5D)[19], health care utilisation and Hospital Anxiety and Depression (HADS)[20] were measured using a central, blinded outcome assessor.

Sample size

As a pilot feasibility trial, the dual purposes of this study were to establish feasibility and to inform future sample size. In accordance with our previous feasibility studies[21, 22], a minimum of 20 patients per group was deemed necessary to facilitate meaningful assessment of feasibility and safety.

Data analysis

Data were analysed using the intention-to-treat approach. The primary outcome was the separation between the intervention and the control group of the highest level of activity, measured using the IMS that was achieved during the ICU stay and this was analysed by assessment for normality of distribution and analysed using independent t-tests. Differences between study sites for the primary outcome were analysed using Kruskal-Wallis tests. The period of time that the patient was actively exercising per day was measured in minutes and between-group analyses were conducted using Wilcoxon Rank Sum Test. Proportions were compared using chi-square tests for equal proportion or Fishers exact tests where numbers were small. Comparison of RASS proportions (proportion of patients who were deeply sedated) over the first seven days were determined using binomial repeated measures modelling. Results were reported as means with standard deviation for normally distributed variables, medians with interquartile ranges for non-normally distributed continuous variables, and frequencies and percentages for categorical variables.

Patients who died during the hospital stay were assigned scores of 0 for ventilator-free days, ICU-free days and functional scores. Time to event data were compared using log-rank tests and reported using Kaplan Meier survival curves. Additional

sensitivity analysis was performed using logistic regression models adjusting for baseline *a priori* defined covariates (age, APACHE II including chronic health evaluation, functional co-morbidities). Analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and a two- sided p-value of 0.05 was considered to be statistically significant.

Results

There were 50 patients enrolled in the study, 21 patients in the control group and 29 patients in the intervention group (Figure 2 CONSORT diagram), with both groups having in excess of 200 cumulative ICU days of mobilization data. The median (IQR) time from ICU admission to randomization was 3 (2-4) days, and the median (IQR) time from ICU admission to first EGDM session in the intervention arm was 3 (2-4) days. Demographic and baseline results are reported in Table 1. There may have been imbalance at baseline with respect to age, comorbidities and severity of illness with intervention patients being older and sicker with more functional comorbidities than control patients (Table 1). The five sites were recruiting patients for different time periods (based on ethical approval of the study) and the sites recruited a mean of 9.5 patients per site (range 4-19), with an average recruitment rate of 2 patients per site month.

Primary Outcome

Higher levels of activity (IMS) were achieved for patients randomized to the EGDM intervention versus control groups, with mean IMS (95%CI) being 7.3 (6.3 – 8.3) versus 5.9 (4.9 – 6.9), unadjusted $p=0.05$, respectively. After adjustment for baseline variables the mean IMS (95%CI) for intervention patients was 7.5 (6.5 – 8.5) and for control patients 5.6 (4.6 – 6.6), $P=0.01$. There was no evidence of heterogeneity between study sites for the IMS scores ($P=0.58$).

Patients receiving EGDM also received a greater duration of active exercises each day whilst admitted to the ICU in the seven days after randomization (median 20 minutes per day [IQR 0 – 40] for EGDM compared with 7 minutes per day [IQR 0 – 15] for control, $P=0.002$). At day 3 following enrolment there was separation between the intervention and control group for both highest level of activity (Figure 3) and

duration of active exercise (median [IQR] intervention 20 minutes [0 – 40] versus control group 8 [0 to 10], $P=0.002$).

During the first seven days, 161 of 350 (46%) of all Richmond Agitation Sedation Scale assessments were in the light sedation range (RASS, -2 to 1). There was no difference between the groups in the amount of “light sedation” in the first seven days (intervention group 89 (45%) of 196 assessments versus control group 72 (47%) of 154, $P=0.87$). There was no significant difference between the groups during the first seven days for the presence of femoral lines (intervention group 13 (45%) versus control group 12 (57%), $P=0.39$).

During the ICU stay there were 26 EGDM patients (90%) who stood compared with 13 control patients (62%) ($P= 0.02$). The proportion of patients who walked during their ICU admission was also higher in the EGDM group (intervention 19 (66%) versus control 8 (38%), $P=0.05$), However, among patients who did stand or walk, there were no differences in the time from enrolment to first achievement of these milestones (time to stand median [IQR] intervention 3.0 days [2.0 – 6.0] versus control group 3.0 days [2.4 to 4.5], $P=0.88$ and time to walk median [IQR] intervention 6.0 days [3.0 – 12.0] versus control group 6.0 days [3.0 to 8.0], $P=0.97$).

Outcomes at hospital discharge are reported in Table 2. Within the cohort, ICU and hospital survival were both 94% with one death occurring in the control group and two in the intervention group ($P = 0.75$).

There were no serious adverse events reported that occurred in conjunction with an episode of EGDM. Adverse events requiring a mobilization episode to stop were reported in four of the control group patients (agitation was reported in two patients and transient hypotension in two patients) and one adverse event was reported in the intervention group (agitation) that required the exercise session to be ceased

Follow-up

At 6 months after randomisation, 6 of the 47 patients discharged alive from hospital were lost to follow-up and 4 (9%) declined the interview. The remaining 37 (79%) patients were interviewed (intervention group $N=22$; control group $N=15$). There were no differences between the groups for health related quality of life, anxiety and

depression (HADS score showed moderate depression for both the intervention group and the control groups), activities of daily living or return to work (Table 3).

Discussion

Key findings

A pilot RCT was conducted to evaluate the feasibility of implementing EGDM to achieve active exercises early during the ICU stay using a mobility team. It was found that EGDM could be safely delivered early after intubation and mechanical ventilation (within 3 days). In addition, this pilot study demonstrated that between the control and EGDM groups with respect to both the highest level of activity achieved during the ICU stay and the time spent exercising. There were more patients in the EGDM group who stood and walked in the ICU. There was adequate recruitment, retention and compliance with the intervention and 6 month follow-up across two countries.

Relationship to previous studies

There are few previous randomized studies of early mobilization in intensive care.[11, 23-25] These studies are mostly single center and have commenced mobilisation or rehabilitation at varied times during the ICU stay. Burtin et al reported the time to start rehabilitation with additional cycle ergometry was 10 days in the control group and 14 days in the intervention group.[23] These authors described this time difference between groups as an important confounder to their primary outcome of physical function and corrected for this discrepancy in their analysis. Similarly, Denehy et al randomized patients who had been admitted to ICU for five days or more and therefore the rehabilitation intervention was not early.[24] Schweickert et al randomized patients across two sites in the intervention group at a median of 1.5 days after intubation, however this included passive movements if the patient was unconscious with a sedation protocol in place. The EGDM protocol implemented in this pilot study included active mobilization, as passive movement were conducted in both groups as passive movements are standard care across Australia and New Zealand.[8] This may account for the 1.5 day difference in time from ICU admission to mobilization between this study and the publication from Schweickert et al in 2009.

The question of international practice differences has been raised in studies of ICU mobilization when the control group (standard care) is significantly different. A previously conducted multi-center bi-national cohort study showed that early mobilization is not common in ICU despite Australia and New Zealand having physiotherapists as part of the multi-disciplinary team across all sites.[8] Australia and New Zealand standard care is similar to previous international studies, likely because Australia and New Zealand ICUs do not have a separate respiratory therapist role, and so physiotherapists often play a large role in pulmonary care.[11]

Implications of study findings

Patients with potentially reversible critical illness are treated in ICUs and often receive mechanical ventilation, a lifesaving intervention, but this is routinely managed with sedation and immobility, which results in prolonged periods of bed rest.[26, 27] While many patients survive, substantial proportions of patients fail to recover completely and do not return to their pre-morbid level of health[28]. Use of EGDM is a candidate intervention to reduce immobility and bed rest in ICU. This pilot study confirmed that EGDM can be successfully implemented across multiple sites, delivered separation between the intervention and the control groups and confirmed the feasibility of conducting an adequately powered RCT with a patient-centred primary outcome. The ICU population included in this study were representative of a mixed medical / surgical adult ICU population with high severity of illness. Follow-up in previous Phase III studies from our group has been highly successful (>90%)[29] and it is anticipated that the number of patients lost to follow-up would be reduced with improved study methods and funding in a larger trial.

Strengths and limitations

This study was designed to test feasibility and separation in a complex intervention delivered early during the ICU stay. The strengths include the multi-center study design, including sites in both Australia and New Zealand, the short time from randomization to EGDM, the randomization of patients with assessor blinding of primary outcome measures and the central co-ordination of long-term outcome assessment. The limitations include the inability to blind the clinicians delivering the intervention. The sample size was insufficient to have statistical power to detect

clinically relevant differences in patient-centered outcomes. The study design allowed substantial testing of process and outcomes and will inform a larger study.

Conclusions

Early-goal directed mobilization, comprising early active exercises during mechanical ventilation, was feasible and safe. The EGDM resulted in increased duration of active exercises and an increase in the mobility milestones achieved during the ICU stay. This pilot study confirms the feasibility of EGDM and suggests that further studies investigating EGDM are warranted to test patient-centered outcomes.

Authorship:

All authors contributed to conception and design and acquisition of data and drafting the article or revising it critically for important intellectual content; CH and MB contributed to analysis and interpretation of data; and all authors had final approval of the version to be published.

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Authors Contribution:

CH chaired the group, conceived and participated in the design of the study, analysed the data and drafted the manuscript. MB analysed the data and reviewed the manuscript. RB and SW conceived the study and gave oversight to all aspects of the study. AH, JP, LD, HB, MH, SB, ES, PY, MS participated in the design of the study. HB, MH, SB, ES, PY, MS were responsible for data at their own site and drafted the manuscript. All authors read and approved the final manuscript.

References:

1. Cuthbertson BH, Roughton S, Jenkinson D, Maclennan G, Vale L: **Quality of life in the five years after intensive care: a cohort study.** *Critical care (London, England)* 2010, **14**(1):R6.
2. Herridge MS, Tansey CM, Matte A, Tomlinson G, Diaz-Granados N, Cooper A, Guest CB, Mazer CD, Mehta S, Stewart TE *et al*: **Functional disability 5 years after acute respiratory distress syndrome.** *The New England journal of medicine* 2011, **364**(14):1293-1304.
3. Saxena MK, Hodgson CL: **Intensive care unit acquired weakness.** *Anaesth Intensive Care Med* 2012, **13**(4):145-147.
4. Ali NA, O'Brien JM, Jr., Hoffmann SP, Phillips G, Garland A, Finley JC, Almoosa K, Hejal R, Wolf KM, Lemeshow S *et al*: **Acquired weakness, handgrip strength, and mortality in critically ill patients.** *Am J Respir Crit Care Med* 2008, **178**(3):261-268.
5. Connolly BA, Jones GD, Curtis AA, Murphy PB, Douiri A, Hopkinson NS, Polkey MI, Moxham J, Hart N: **Clinical predictive value of manual muscle strength testing during critical illness: an observational cohort study.** *Critical care (London, England)* 2013, **17**(5):R229.
6. Garnacho-Montero J, Amaya-Villar R, Garcia-Garmendia JL, Madrazo-Osuna J, Ortiz-Leyba C: **Effect of critical illness polyneuropathy on the withdrawal from mechanical ventilation and the length of stay in septic patients.** *Critical care medicine* 2005, **33**(2):349-354.
7. Puthuchery ZA, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, Hopkinson NS, Padhke R, Dew T, Sidhu PS *et al*: **Acute skeletal muscle wasting in critical illness.** *JAMA : the journal of the American Medical Association* 2013, **310**(15):1591-1600.
8. TEAM, Study, Investigators: **Early mobilization and recovery in mechanically ventilated patients in ICU: A bi-national, multi-centre, prospective cohort study.** In: *Critical care (London, England)*. vol. In press; 2015.
9. Hermans G, Van Mechelen H, Clerckx B, Vanhullebusch T, Mesotten D, Wilmer A, Casaer MP, Meersseman P, Debaveye Y, Van Cromphaut S *et al*: **Acute outcomes and 1-year mortality of intensive care unit-acquired weakness. A cohort study and propensity-matched analysis.** *Am J Respir Crit Care Med* 2014, **190**(4):410-420.
10. Needham DM: **Mobilizing patients in the intensive care unit: improving neuromuscular weakness and physical function.** *JAMA : the journal of the American Medical Association* 2008, **300**(14):1685-1690.
11. Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, Spears L, Miller M, Franczyk M, Deprizio D *et al*: **Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial.** *Lancet* 2009, **373**(9678):1874-1882.
12. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, Moore L, O'Cathain A, Tinati T, Wight D *et al*: **Process evaluation of complex interventions: Medical Research Council guidance.** *BMJ* 2015, **350**:h1258.
13. Delaney A, Angus DC, Bellomo R, Cameron P, Cooper DJ, Finfer S, Harrison DA, Huang DT, Myburgh JA, Peake SL *et al*: **Bench-to bedside review: the evaluation of complex interventions in critical care.** *Critical care (London, England)* 2008, **12**(2):210.
14. Hodgson CL, Stiller K, Needham DM, Tipping CJ, Harrold M, Baldwin CE, Bradley S, Berney S, Caruana LR, Elliott D *et al*: **Expert consensus and recommendations on safety criteria for active mobilization of mechanically ventilated critically ill adults.** *Critical care (London, England)* 2014, **18**(6):658.
15. Hodgson CL, Needham D, Haines K, Bailey M, Ward A, Harrold M, Young PJ, Zanni J, Buhr H, Higgins AM *et al*: **Feasibility and inter-rater reliability of the ICU Mobility Scale.** *Heart and Lung* 2014, **43**(1):19-24.
16. Zanni JM, Korupolu R, Fan E, Pradhan P, Janjua K, Palmer JB, Brower RG, Needham DM: **Rehabilitation therapy and outcomes in acute respiratory failure: an observational pilot project.** *J Crit Care* 2010, **25**(2):254-262.

17. Stevens RD, Marshall SA, Cornblath DR, Hoke A, Needham DM, de Jonghe B, Ali NA, Sharshar T: **A framework for diagnosing and classifying intensive care unit-acquired weakness.** *Critical care medicine* 2009, **37**(10 Suppl):S299-308.
18. Graf C: **The Lawton Instrumental Activities of Daily Living (IADL) Scale.** *Medsurg Nurs* 2009, **18**(5):315-316.
19. Oeyen SG, Vandijck DM, Benoit DD, Annemans L, Decruyenaere JM: **Quality of life after intensive care: a systematic review of the literature.** *Critical care medicine* 2010, **38**(12):2386-2400.
20. Sukantarat KT, Williamson RC, Brett SJ: **Psychological assessment of ICU survivors: a comparison between the Hospital Anxiety and Depression scale and the Depression, Anxiety and Stress scale.** *Anaesthesia* 2007, **62**(3):239-243.
21. Hodgson CL, Tuxen DV, Davies AR, Bailey MJ, Higgins AM, Holland AE, Keating JL, Pilcher DV, Westbrook AJ, Cooper DJ *et al*: **A randomised controlled trial of an open lung strategy with staircase recruitment, titrated PEEP and targeted low airway pressures in patients with acute respiratory distress syndrome.** *Critical care* 2011, **15**(3):R133.
22. Shehabi Y, Bellomo R, Reade MC, Bailey M, Bass F, Howe B, McArthur C, Murray L, Seppelt IM, Webb S *et al*: **Early goal-directed sedation versus standard sedation in mechanically ventilated critically ill patients: a pilot study.** *Critical care medicine* 2013, **41**(8):1983-1991.
23. Burtin C, Clerckx B, Robbeets C, Ferdinande P, Langer D, Troosters T, Hermans G, Decramer M, Gosselink R: **Early exercise in critically ill patients enhances short-term functional recovery.** *Critical care medicine* 2009, **37**(9):2499-2505.
24. Denehy L, Skinner EH, Edbrooke L, Haines K, Warrillow S, Hawthorne G, Gough K, Hoorn SV, Morris ME, Berney S: **Exercise rehabilitation for patients with critical illness: a randomized controlled trial with 12 months of follow-up.** *Critical care (London, England)* 2013, **17**(4):R156.
25. Kayambu G, Boots R, Paratz J: **Early physical rehabilitation in intensive care patients with sepsis syndromes: a pilot randomised controlled trial.** *Intensive Care Med* 2015, **41**(5):865-874.
26. Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H, Zawistowski C, Bemis-Dougherty A, Berney SC, Bienvenu OJ *et al*: **Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference.** *Crit Care Med* 2012, **40**(2):502-509.
27. Vasilevskis EE, Ely EW, Speroff T, Pun BT, Boehm L, Dittus RS: **Reducing iatrogenic risks: ICU-acquired delirium and weakness--crossing the quality chasm.** *Chest* 2010, **138**(5):1224-1233.
28. Skinner EH, Haines KJ, Howe B, Hodgson CL, Denehy L, McArthur CJ, Sellar D, Di Marco E, Mulvany K, Ryan DT *et al*: **Health-Related Quality of Life in Australasian Survivors of H1N1 Influenza Undergoing Mechanical Ventilation. A Multicenter Cohort Study.** *Annals of the American Thoracic Society* 2015, **12**(6):895-903.
29. Peake SL, Delaney A, Bailey M, Bellomo R, Cameron PA, Cooper DJ, Higgins AM, Holdgate A, Howe BD, Webb SA *et al*: **Goal-directed resuscitation for patients with early septic shock.** *The New England journal of medicine* 2014, **371**(16):1496-1506.

Table 1. Demographic Data

	EGDM	Control
Age, years, mean \pm SD	64 \pm 12	53 \pm 15
Gender, female, N (%)	8 (38)	12 (41)
APACHE II, mean \pm SD	19.8 \pm 9.8	15.9 \pm 6.9
Functional Comorbidity Index, median [IQR]	2 [10-3]	1 [0-2]
Pre-admission IMS, mean \pm SD	9.9 \pm 0.3	9.9 \pm 0.2
Sepsis, N (%)	19 (65)	14 (66)
Any vasopressor (day 1-7), N (%)	12 (41)	10 (48)
Any femoral catheter (day 1-7), N (%)	13 (45)	12 (57)
Time from ICU admission to randomization, days, median [IQR]	3 [2-6]	3 [2-4]

EGDM = early goal-directed mobilization; ICU= intensive care unit; IMS= ICU mobility scale; IQR= interquartile range; N= number; SD = standard deviation

Table 2. Hospital Outcomes

	EGDM (N=29)	Control (N=21)	P
Duration of ventilation, median [IQR]	5.4 [3.5-10.0]	7.0 [5.0-12.0]	0.18
Ventilator free days (mean \pm SD)	19.2 \pm 7.4	17.1 \pm 8.7	0.40
Extubated within 5 days from randomisation, N (%)	14 (48)	5 (24)	0.08
MRC-SS (mean \pm SD)	50.4 \pm 7.5	45.2 \pm 13.2	0.10
ICU Acquired Weakness, N (%)	7/25 (28)	10/20 (50)	0.13
PFIT (mean \pm SD)	7.4 \pm 3.6	7.4 \pm 3.6	0.83
FSS-ICU (mean \pm SD)	23.6 \pm 8.2	21.4 \pm 10.2	0.38
IMS mean, [IQR]	7.3 [6.3–8.3]	5.8 [4.9–6.9]	0.05
Mobility milestones during ICU			
Sit out of bed, N (%)	26 (90)	17 (81)	0.38
Stand, N (%)	26 (90)	13 (62)	0.02
Walk, N (%)	19 (66)	8 (38)	0.05
Death in ICU, N (%)	2 (7)	1 (5)	0.75
Death in Hospital, N (%)	2 (7)	1 (5)	0.75
ICU length of stay, days, median [IQR]	9 [6-17]	11 [8-19]	0.28
Hospital length of stay, median [IQR]			
Total length of stay (hospital and inpatient rehabilitation), days, median [IQR]	19 [14-30]	29 [16-34]	0.33
Patients discharged to home, N (%)	20 [15-35]	34 [17.5-42.5]	0.37
	19 (66)	13 (62)	0.69

EGDM = early goal-directed mobilization; ICU = intensive care unit; IMS = ICU mobility scale maximum score during the ICU stay; IQR = interquartile range; FSS-ICU = functional status score for the ICU; MRC-SS = medical research council manual muscle test sum score; N = number; PFIT = physical function in ICU score; SD = standard deviation; P = probability value

Table 3. Six month outcomes

	EGDM (N=22)	Control (N=15)	P
EQ5D VAS	61±20	70±13	0.13
EQ5D Utility	0.60±0.28	0.67±0.7	0.90
EQ5D mobility score of moderate to severe, N(%)	8 (38%)	5 (24%)	0.85
IADL	6.5±1.9	7±1.3	0.81
HADS	11.6±9.1	11.3±7.1	0.91
Return to work, N(%)	4 of 8 (50)	4 of 8 (50)	0.99

EGDM = early goal-directed mobilization; HADS = hospital anxiety and depression scale; IADL = independent activities of daily living; VAS = visual analogue score; P = probability value

Early Goal Directed Mobilization

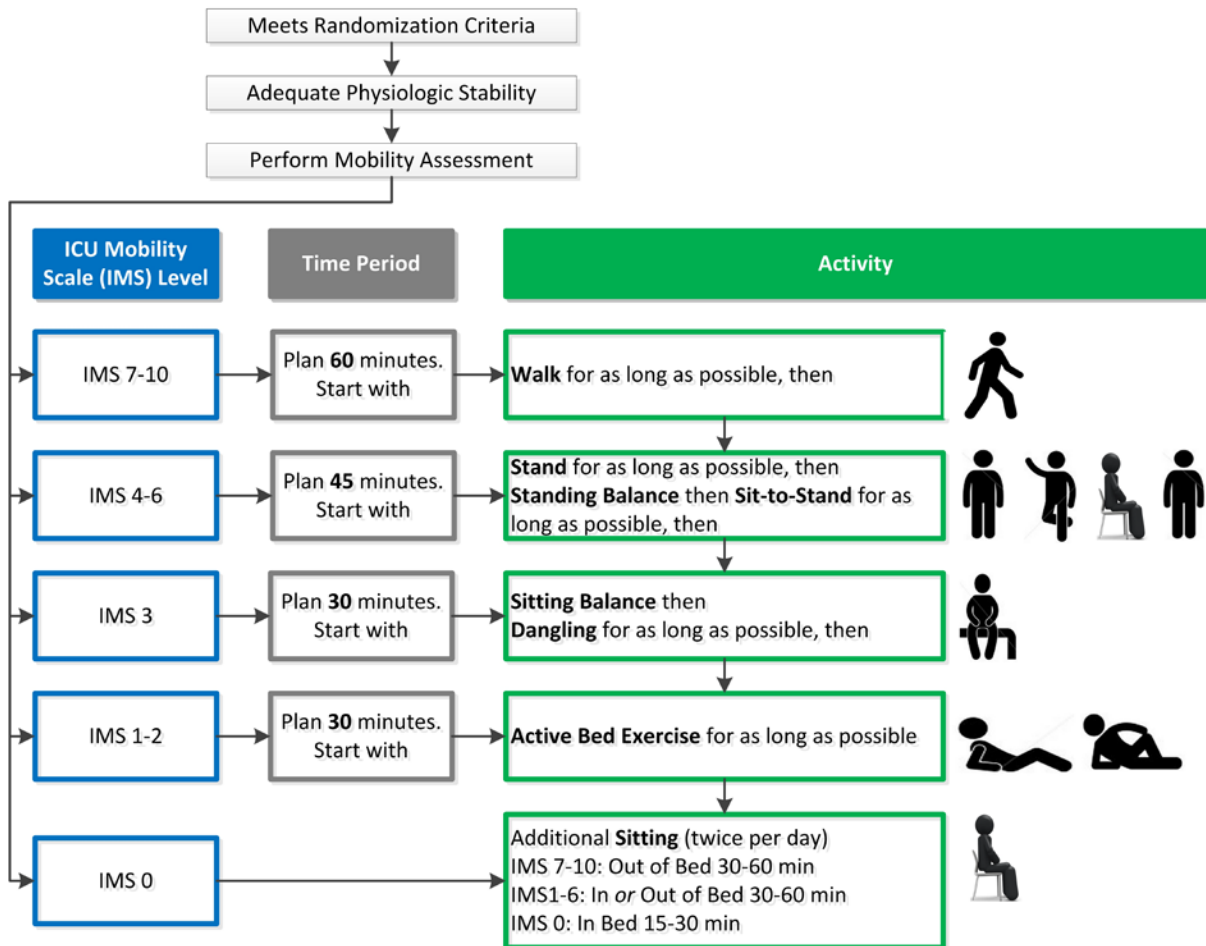


Figure 1. Early goal-directed mobilization algorithm.

Once randomized and physiological stability is achieved, the mobility team assessed the ICU mobility scale (IMS) and targeted exercise at the highest possible level of the IMS for as long as possible.

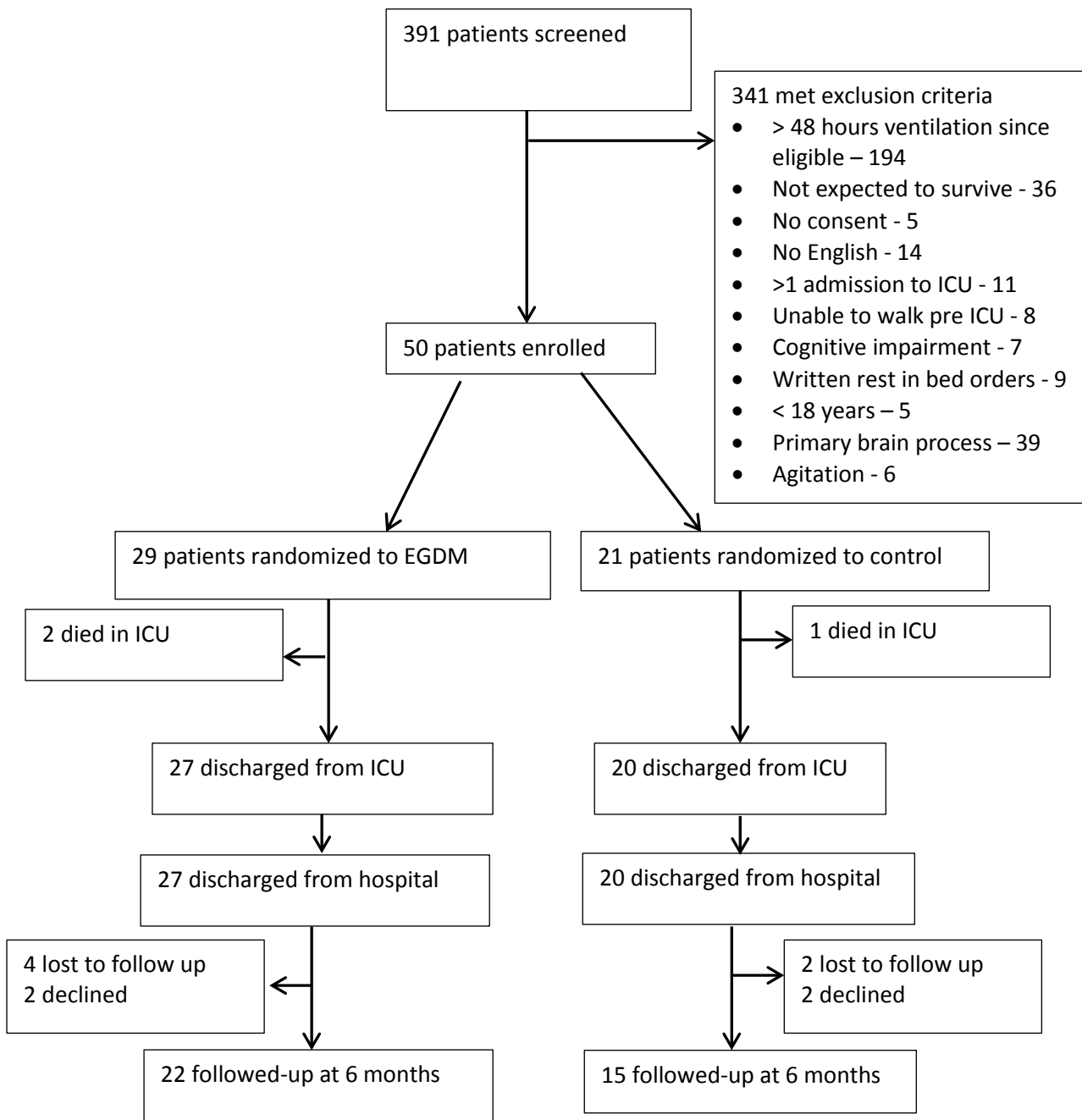


Figure 2. CONSORT diagram

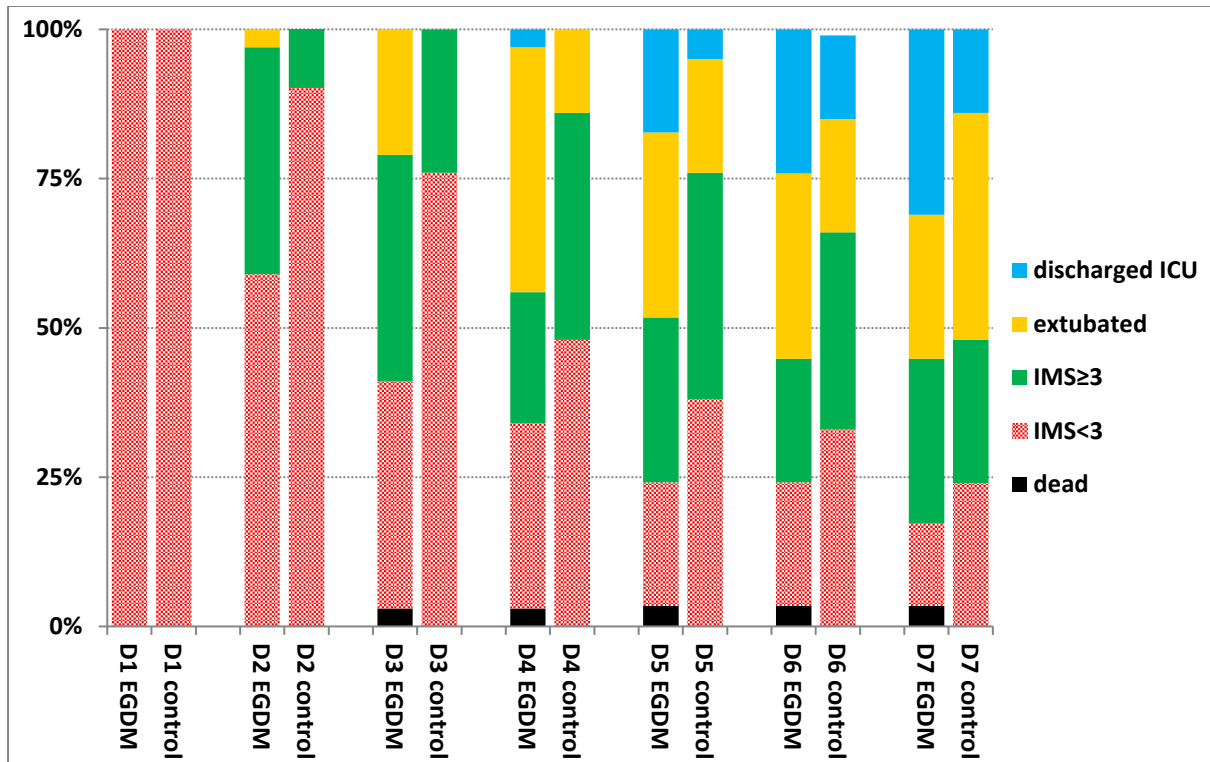


Figure 3. Percentage of patients (Y-axis) that are either dead, intubated and not mobilised out of bed, defined as ICU Mobility Score (IMS) < 3, intubated and achieving active out of bed exercises (IMS) ≥ 3, extubated but still admitted to the ICU, or discharged alive from ICU in the early goal-directed mobilization group (EGDM) versus the standard care group (control) for days 1-7 (X-axis).

The percentage of patients achieving out of bed exercise was significantly higher at day 3 (P<0.05).

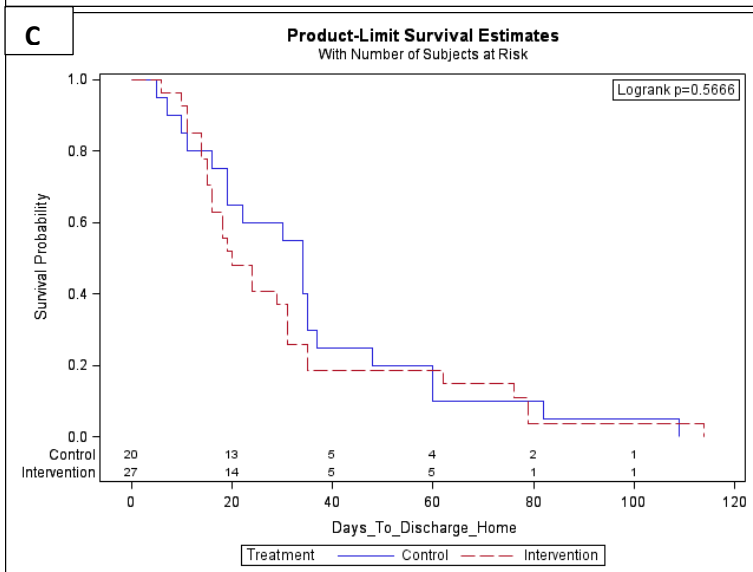
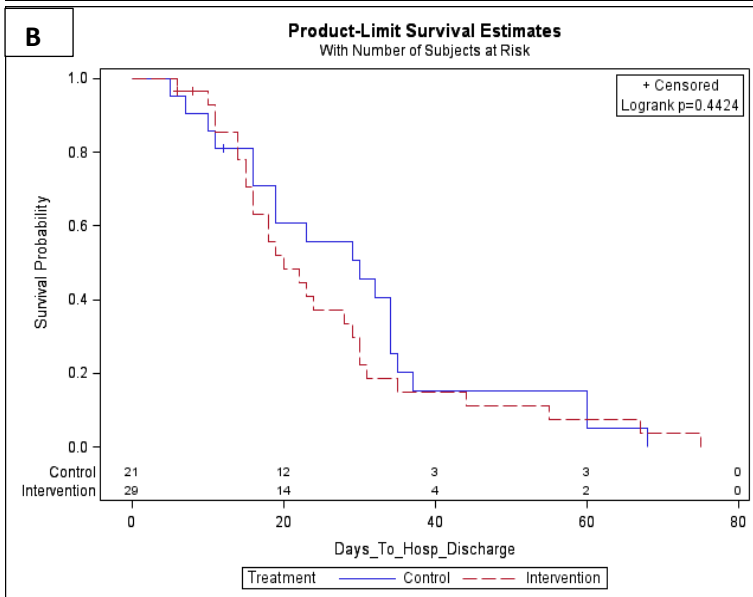
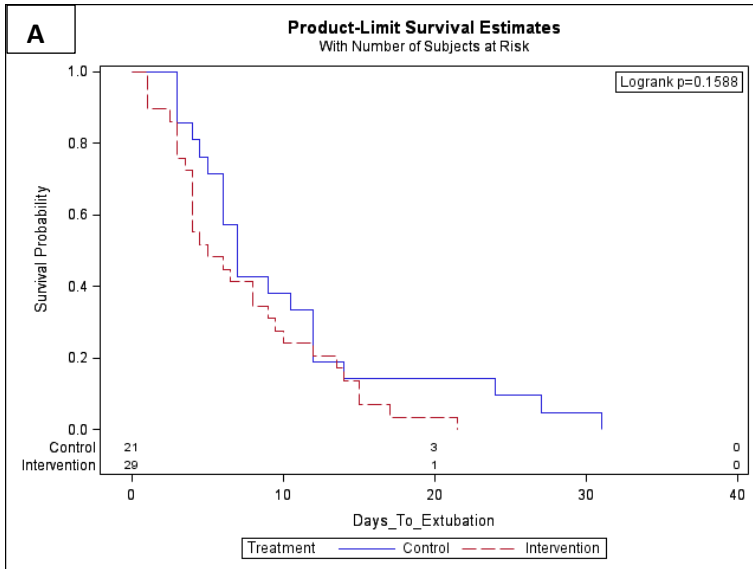


Figure 4. A. Time to extubation B. Time to acute hospital discharge C. Time to discharge home