Protocol and statistical analysis plan for the phase 3 randomised controlled Treatment of Invasively Ventilated Adults with Early Activity and Mobilisation (TEAM III) trial

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ABSTRACT

Objective: To describe the protocol and statistical analysis plan for the Treatment of Invasively Ventilated Adults with Early Activity and Mobilisation (TEAM III) trial.

Design: An international, multicentre, parallel-group, randomised controlled phase 3 trial.

Setting: Intensive care units (ICUs) in Australia, New Zealand, Germany, Ireland, the United Kingdom and Brazil.

Patients: 750 adult patients expected to receive mechanical ventilation for more than 48 hours.

Interventions: Early activity and mobilisation delivered to critically ill patients in an ICU for up to 28 days compared with standard care.

Main outcome measures: The primary outcome is the number of days alive and out of hospital at 180 days after randomisation. Secondary outcomes include ICU-free days, ventilator-free days, delirium-free days, all-cause mortality at 28 and 180 days after randomisation, and functional outcome at 180 days after randomisation.

Results: Recruitment at 46 research sites passed 576 patients in March 2021. Final collection of all 180-day outcome data for the target of 750 patients is anticipated by May 2022.

Conclusions: Consistent with international guidelines, a detailed protocol and prospective analysis plan has been developed for the TEAM III trial. This plan specifies the statistical models for evaluating primary and secondary outcomes, defines covariates for adjusted analyses, and defines methods for exploratory analyses. Application of this protocol and statistical analysis plan to the forthcoming TEAM III trial will facilitate unbiased analyses of the clinical data collected.

Trial registration: ClinicalTrials.gov identifier NCT03133377.

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The quality of survival for patients after intensive care unit (ICU) admission is a major health challenge that has been described as the defining challenge for critical care in the 21st century.[1] ICU survivors may have delayed and compromised functional recovery, which can persist for months or years.[2,3] Preliminary evidence suggests that critically ill patients admitted to an ICU who are expected to require prolonged mechanical ventilation may benefit from early activity and mobilisation.[4-6] The Treatment of Invasively Ventilated Adults with Early Activity and Mobilisation (TEAM III) trial (ClinicalTrials.gov identifier NCT03133377) is a phase 3 randomised controlled trial of patients who are expected to receive mechanical ventilation for more than 48 hours. In these patients, we will evaluate whether, compared with standard care, early mobilisation and rehabilitation commenced in the ICU increases the number of days alive and out of hospital at 180 days ($DAOH_{180}$) after randomisation. In this article, we describe the protocol and statistical analysis plan, which was finalised before completion of trial patient recruitment.

Methods

Study design and setting

TEAM III is an international, multicentre, prospective, parallel-group, randomised controlled phase 3 superiority trial evaluating the safety and efficacy of an early activity and mobilisation protocol compared with standard care.[7] The first patient was randomly assigned in February 2018 and patient recruitment is estimated to be completed by October 2021. Final collection of all 180-day outcome data is anticipated by May 2022. The total recruitment target of 750 patients will be enrolled from sites in Australia, New Zealand, Germany, Ireland, the United Kingdom and Brazil.

Study population

The inclusion and exclusion criteria are shown in Table 1. Eligible patients will be randomly assigned to early activity

Table 1. Inclusion and exclusion criteria

Inclusion criteria

- Aged 18 years or older
- Intubated and expected to remain on invasive mechanical ventilation for more than 48 hours
- Sufficient cardiovascular stability to make mobilisation potentially possible, as indicated by:
  - the absence of current bradyarrhythmia requiring pharmacological support
  - a current ventricular rate ≤ 150 beats/min
  - most recent lactate level ≤ 4.0 mmol/L
  - current combined noradrenaline/adrenaline infusion rate of ≤ 0.2 μg/kg/min or, if noradrenaline/adrenaline infusion rate has increased by more than 25% in the preceding 6 hours, dose must be < 0.1 μg/kg/min
  - most recent cardiac index ≥ 2.0 L/min/m^2 (where measured)
  - no current requirement for venoarterial ECMO
- Sufficient respiratory stability to make mobilisation potentially possible, as indicated by:
  - current FiO_2 ≤ 0.6
  - current positive end expiratory pressure ≤ 16 cmH_2O
  - an absence of current requirement for nitric oxide, prone ventilation, neuromuscular blockers, prostacyclin, venovenous ECMO or high-frequency oscillation ventilation
  - current respiratory rate ≤ 45 breaths/min

Exclusion criteria

- Dependent for activities of daily living in the month before the current ICU admission (gait aids are acceptable)
- Documented cognitive impairment
- Proven or suspected acute primary brain injury (eg, traumatic brain injury, stroke, hypoxic brain injury)
- Proven or suspected spinal cord injury or other neuromuscular disease that will result in permanent or prolonged weakness (not including ICU-acquired weakness)
- Has rest-in-bed orders and/or bilateral non-weight bearing orders for the lower limbs
- Life expectancy < 180 days owing to a chronic or underlying medical condition
- Death is deemed inevitable as a result of the current illness, and the patient, treating clinician or substitute decision maker are not committed to full active treatment
- Unable to communicate in the official local language
- This is not the first ICU admission in the index hospital admission
- Fulfilled all inclusion criteria and none of the exclusion criteria ≥ 72 hours ago

FiO_2 = fraction of inspired oxygen. ICU = intensive care unit. ECMO = extra corporeal membrane oxygenation.

and mobilisation, to the highest suitable level as assessed daily by a physiotherapist face to face during the ICU admission up to 28 days, or physiotherapy care that is standard for that hospital.

Randomisation

A web-based interface (https://www.teamtrial.org.au) will be used to confirm that patients fulfil all the inclusion criteria and no exclusion criteria. Randomisation between trial mobilisation and control interventions will be performed on this website using a computer-generated randomised treatment allocation schedule stratified by participating hospital site with a permuted scheme with blocks of varying sizes.

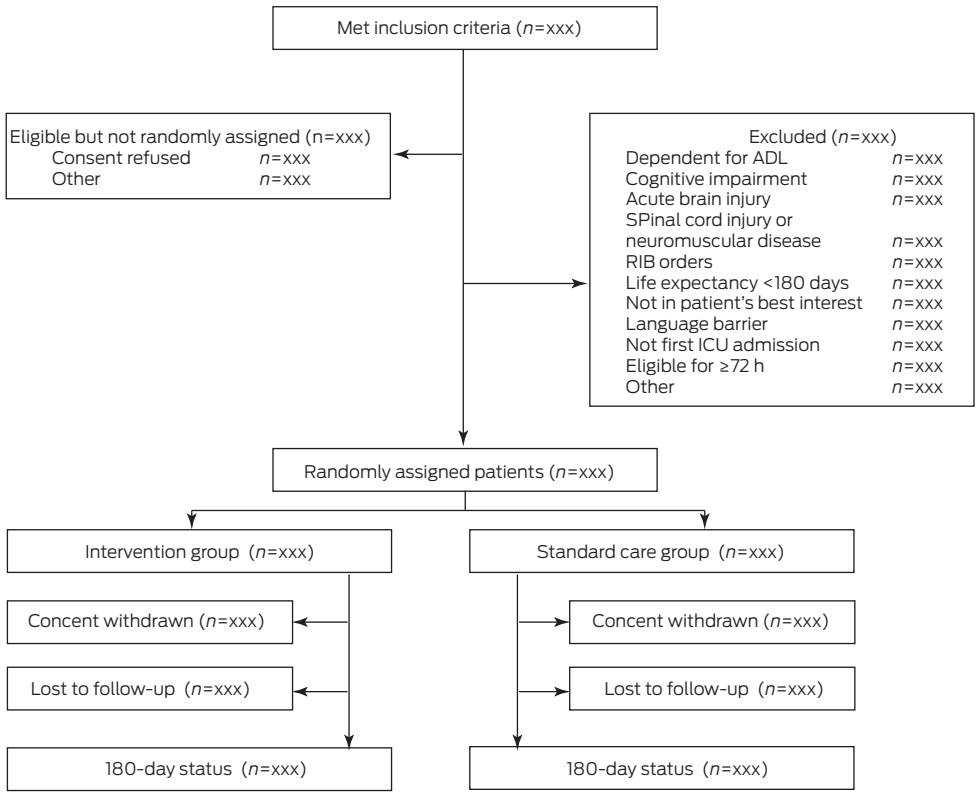
Treatment masking (blinding)

Patient mobility while receiving mechanical ventilation is obvious, so it is not possible to blind patients or clinical staff to treatment allocation. Bias will be minimised by concealed treatment allocation before randomisation, protocolised treatment of the intervention group,[7] and assessment of the primary outcome by centralised, blinded and trained research staff in each region. In the United Kingdom, minimisation of bias will be augmented by data linkage. The primary outcome measure — number of $DAOH_{180}$ after randomisation, with any days spent in a rehabilitation facility or nursing home counted as days in hospital — is subject to minimal ascertainment bias.

Intervention

We followed the UK's Medical Research Council guidelines for developing and evaluating a complex intervention and the template for intervention description and replication (TIDieR) checklist and guide (Online Appendix, D).[8,9] Each patient allocated to the intervention group will receive physiotherapist-directed, functional rehabilitation comprising active exercises and mobilisation conducted as early as possible and at the highest level of ICU mobility scale activity possible for them (Figure 1; Online Appendix, E).[10,11] The first full day will be considered Day 1 and the intervention will occur daily for the duration of the ICU stay up to Day 28. Each patient allocated to the control group will receive standard care from physiotherapy staff not involved in delivering the intervention, which in most cases will involve no active exercise out of bed.[12] For both groups, concomitant care will be guided by the treating

Figure 1. Intervention protocol



IMS = intensive care unit mobility scale.

clinician and all post-ICU patient management will be at the discretion of the patient's ward-based treating physicians. The intervention and study tools were designed to facilitate updates to clinical practice if the TEAM III trial results support such implementation.[13]

Primary outcome

The trial primary outcome variable will be $DAOH_{180}$.[14-16] For each patient, days during the index hospitalisation, hospital readmission, inpatient rehabilitation or in a nursing home between randomisation and Day 180 will be subtracted from 180 to calculate their $DAOH_{180}$ result (Table 2). Patients who die before Day 180 will be defined as having the worst possible outcome of zero $DAOH_{180}$.

Secondary outcomes

Secondary outcome measures will be evaluated at 28 days and 180 days after randomisation (Table 2). Outcomes at Day 28 include: all-cause mortality; ICU-free days; ventilator-free days; and delirium-free days measured using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) and Richmond Agitation–Sedation Scale (RASS). Patients who die before Day 28 will be assigned zero ICU-free, ventilator-free and delirium-free days. Outcomes at Day 180 include: all-cause mortality; time to death; DAOH in patients who die before Day 180; DAOH in patients alive at Day 180; days in hospital, a rehabilitation facility or a nursing home to Day 180 according to 180-day survival status; quality of life and health status measured using the five-level EuroQol five dimensions questionnaire (EQ-5D-5L); independent activities of daily living scores measured using the Barthel activities of daily living (ADL) index and the Lawton instrumental activities of daily living (IADL) scale; generic function and disability measured using the 12-level World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0 12L); cognitive function measured using the Montreal Cognitive Assessment (MOCA)–Blind; and psychological function measured using the Hospital Anxiety and Depression Scale (HADS) and Impact of Event Scale – Revised (IES-R).

Table 2. Primary and secondary outcomes

Primary outcome

- DAOH score to Day 180 ($DAOH_{180}$)
  - out of hospital refers strictly to days at home or accommodation that is not health care related, but not days in rehabilitation facilities or nursing homes
  - calculation: $DAOH_{180}$ = 180 – (sum of days in hospital to end of Day 180 in one or more admission episode + days not at home [ie, in rehabilitation facility or nursing home] to Day 180).
  - $DAOH_{180}$ is defined as zero for deaths before Day 180.
  - example: for a patient with a 21-day first hospital admission in January who was discharged directly home, then readmitted to hospital in April for a total of 12 days, then discharged directly home, and then admitted in May from home to a rehabilitation facility for 10 days before returning home, the calculation would be: $DAOH_{180}$ = 180 – (21 + 12 + 10) = 137

Secondary outcomes at 28 days

- ICU-free days from randomisation, defined as days alive and discharged from ICU*
- Ventilator-free days from randomisation, where extubation for > 48 hours is successful†
- Delirium-free days (CAM-ICU and RASS score, from randomisation, censored at ICU discharge)‡
- Time from randomisation until death
- Process-of-care measures
  - tracheostomy in ICU
  - neuromuscular blockers by continuous infusion
  - reintubation during index ICU admission
  - vasopressor-free days during index ICU admission from randomisation
  - corticosteroids during index ICU admission
  - new post-randomisation renal replacement therapy in ICU
  - daily RASS sedation score
  - ICU mobilisation outcomes (censored at ICU discharge if before Day 28)[7,11]
  - highest daily ICU mobility scale in ICU
  - total duration of active mobilisation in ICU

Secondary outcomes at 180 days

- All-cause mortality
- DAOH in patients who die before Day 180
- DAOH in patients alive at Day 180
- Time from randomisation until death
- Time from randomisation to ICU and hospital discharge, overall, and with death as a competing outcome
- ICU-free days, defined as days alive and discharged from ICU*
- Ventilator-free days from randomisation, where extubation for > 48 hours is successful†
- Quality of life and physical function
  - EQ5D-5L score[17,18]
  - generic function and disability score (WHODAS 2.0 12L)[19,20]
  - independent activities of daily living scores (Barthel ADL index and Lawton IADL scale)[21,22]
- Cognitive and psychological function
  - MOCA-Blind score[3,23]
  - HADS score[24]
  - IES-R score[25]

Economic outcome

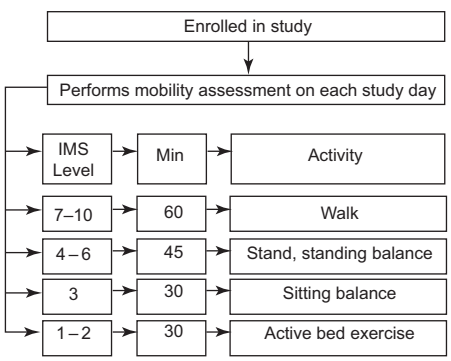
- Cost-effectiveness at 6 months

ADL = activities of daily living. CAM-ICU = Confusion Assessment Method for the Intensive Care Unit. DAOH = days alive and out of hospital. EQ5D-5L = five-level EuroQol five dimensions questionnaire. HADS = Hospital Anxiety and Depression Scale. ICU = intensive care unit. IES-R = Impact of Event Scale – Revised. IADL = instrumental activities of daily living. MOCA-Blind = Montreal Cognitive Assessment – Blind. RASS = Richmond Agitation–Sedation Scale. WHODAS 2.0 12L = 12-level World Health Organization Disability Assessment Schedule 2.0. * Patients who die at any time are assigned zero ICU-free days. † Patients who die at any time are assigned zero ventilator-free days. ‡ Patients who die at any time are assigned zero delirium-free days.

Statistical analyses

Effect estimates for all outcomes will be accompanied by a 95% confidence interval (CI), consistent with a two-sided type 1 error of 5%. There will be no adjustment for multiplicity of testing among effect estimates and corresponding 95% CIs for non-primary outcomes, which therefore should be interpreted cautiously as hypothesis-generating results.[26] Descriptive and summary statistics will be calculated by treatment group and overall. Continuous data will be summarised as means (standard deviations [SDs]) if about normally distributed, and otherwise as medians (interquartile ranges). Categorical data will be summarised as counts and proportions. Unadjusted differences between groups will be assessed initially using two-sample *t* tests or Wilcoxon rank-sum tests, or Fisher exact tests for proportions, as appropriate. The number of screened patients who fulfil the inclusion criteria, the numbers included in the primary and secondary analyses and all reasons for exclusion from the primary and secondary analyses will be reported according to CONSORT guidelines (Figure 2). The full analysis set for the main primary and secondary analyses will retain participants in their original randomly assigned groups, and include all randomly assigned patients except those who withdraw consent for use of trial data.[27,28] Wherever possible and appropriate, statistical inference will account for potential dependency in patient clusters formed by each participating ICU or hospital site. Linear and generalised linear model diagnostics, outlier assessment and remedial measures will follow standard approaches.[29,30] Proportional hazards assumptions across treatment arms in time-to-event analyses will be evaluated using scaled Schoenfeld residuals and visual assessment of log–log plots.[31] Whenever needed, the proportional odds assumption for cumulative logistic models will be assessed by visual assessment of relevant plots for clinically important departures from proportionality.

Figure 2. Consolidated Standards of Reporting Trials (CONSORT) diagram for the TEAM III trial



ADL = activities of daily living. ICU = intensive care unit. RIB = rest in bed.

Primary outcome

The primary outcome, $DAOH_{180}$, is expected to have a bimodal and asymmetric frequency distribution. A linear quantile regression analysis will be used because this approach models selected conditional quantiles of a continuous response.[32] Also, this is potentially more robust to outliers and misspecification of an error distribution compared with traditional least squares linear (mean) regression. $DAOH_{180}$ will be modelled as a continuous random variable, with a null hypothesis of equality in the median (quantile = 0.5) $DAOH_{180}$ between the full analysis set of patients according to randomised treatment group. The magnitude of the differential primary outcome according to randomised treatment group will be derived from the treatment group effect estimate returned by a simple linear median quantile model with a term for binary treatment group. The number needed to treat for benefit or harm will also be reported if strong evidence of a difference between treatment groups is found. Model fitting will use published software for linear quantile models. At the time of writing, within the R statistical environment, the quantile regression package quantreg offers a bootstrapped procedure for construction of cluster-robust standard errors with associated 95% CIs to support cluster-robust inference (Online Appendix, 2 — Calculation of primary outcome).[33-35] Specification of either simplex (exterior point) or interior point median regression methods showed satisfactory relative power compared with several alternative analysis methods in simulated data scenarios (Online Appendix, 3 — Relative power of alternative methods for analysis of the primary outcome).

Sensitivity analyses of the primary outcome

Baseline covariate imbalance. In the event of baseline variable imbalance ($P < 0.05$) between randomisation arms despite the randomisation process, a sensitivity analysis of the primary outcome will be used to report the effect of the trial intervention on median $DAOH_{180}$, with unbalanced baseline variable(s) included as fixed term(s) with the treatment term within that supplementary linear quantile regression (Online Appendix, 2 — Calculation of primary outcome).[36]

Missing data. If more than 5% of the primary outcome data are missing, complete case analyses will be accompanied by further sensitivity analyses using two SD best–worst case, two SD worst–best case, and multiple imputation under the assumption of data missing at random.[37-40]

Grid of quantiles. The quantile regression TEAM intervention effect estimate, adjusted according to the covariate(s) included in the primary outcome model, will

be computed on a selected discrete set of quantiles within the $0.01 \le \tau \le 0.99$ range to summarise any non-constant TEAM intervention effect within the $DAOH_{180}$ upper and lower tails. These results will be reported graphically and/or in tables that also show, for comparison, the mean TEAM intervention effect estimate across all quantiles returned from a similarly constructed linear mixed-effect model.[35,40,41]

Results at each research site. The differential primary outcome according to randomised treatment group will be tabulated according to research site.

Ordinal categorical analysis. The differential effect of treatment will be estimated within a proportional odds cumulative logistic model treating $DAOH_{180}$ as an ordinal categorical random variable.[42] The wide range of $DAOH_{180}$ categories may be collapsed to a convenient and clinically meaningful smaller number of ordered categories without important loss of statistical information.[43-45]

Secondary outcomes

Because no adjustment for multiple comparisons will be performed in the analyses of trial secondary outcomes, these outcomes and their reported unadjusted 95% CIs will be considered hypothesis-generating.[26]

Time-to-event analyses. The time to events of interest, including mortality to 180 days, will be assessed using Kaplan–Meier plots and log-rank tests. These will be supplemented by Cox proportional hazard regression models including variables as for the primary outcome model, with the proportional hazards assumption assessed using Schoenfeld residuals,[31] as described above. The time to discharge according to treatment group will be assessed using a competing risks model with death before discharge treated as a competing risk.[46]

Other binary outcomes. Other binary variables, including adverse events, will be analysed with logistic regression models to estimate odds ratios with 95% CIs.

Pre-specified subgroup analyses of the primary outcome. Possible heterogeneity of treatment effect in the following pre-specified subgroups will be evaluated by tests of interaction between each subgroup and the study treatment in the models described above:[47]

- baseline WHODAS 2.0 category (no and mild disability versus moderate, severe and complete disability);
- age (dichotomised at the full analysis set median age);
- diagnosis (sepsis versus trauma versus other);
- severity of illness (dichotomised at the full analysis set median APACHE [Acute Physiology and Chronic Health Evaluation] III score); and
- frailty (a binary reduction of the seven-point Clinical Frailty Scale at 1–4 [well and vulnerable] versus 5–7 [frail]).[48]

The new appearance of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection across the world during the coronavirus disease 2019 (COVID-19) pandemic introduces the possibility that these patients may be enrolled in TEAM III in substantial numbers. These patients may have experienced a different clinical trajectory from other ICU patients recruited so far, including prolonged durations of mechanical ventilation accompanied by days of pharmacological paralysis and treatment with glucocorticoid medication.[42,49] Using the full analysis set, the primary outcome will also be evaluated according to SARS-CoV-2/COVID-19 status subgroup (known positive versus negative or unknown).

Outcomes at 28 days. Outcomes at 28 days are listed in Table 2. The scores of ICU-free, ventilator-free and delirium-free days evaluated at 28 days after randomisation will be modelled as continuous random variables in the same way as for the primary analysis. These scores will be zero for patients who die before Day 28.

Health-related quality of life. Health-related quality of life (HRQOL), health problems in each domain of the EQ-5D-5L and functional outcomes assessed at 180 days will be summarised as means (with SDs), medians (with interquartile range) or as proportions. Unadjusted differences in HRQOL between groups will be assessed initially using the two-sample *t* test or Wilcoxon rank-sum test, or the Fisher exact test for proportions, as appropriate. HRQOL measures will further be evaluated using multivariable linear regression (or quantile regression where normality assumptions are violated) with adjustment for clustering by site and potential baseline imbalance ($P < 0.05$). These outcomes include the EQ-5D-5L utility score, EuroQol visual analogue scale (EQ-VAS) score (range, 0–100), ADL score (range, 0–20), IADL score (range, 0–8), WHODAS 2.0 12L score (percentage), MOCA-Blind score (range, 0–22), HADS score (range, 0–21 for either anxiety or depression), and the IES-R score (range, 0–88). EQ-5D-5L utility scores will be calculated using an Australian or UK value set if available at the time of analysis, or a crosswalk value set where an appropriate EQ-5D-5L value set is not available. The WHODAS 2.0 12L percentage scores will be used to categorise patients into five mutually exclusive disability categories at 180 days: no disability (0–4%); mild disability (5–24%); moderate disability (25–49%); severe disability (50–95%); and complete disability (96–100%).[50] In addition, patients will be classified as having no or mild disability if their WHODAS score was < 25%, and classified as moderate, severe or complete disability if their WHODAS score was ≥ 25%.

Cost-effectiveness analyses. Cost-effectiveness analyses will be conducted from a health care payer perspective using

a within-trial time horizon. Incremental cost-effectiveness ratios will be calculated as a cost per additional quality-adjusted life-year and cost per additional day alive and out of hospital gained at Day 180 for early activity and mobilisation compared with standard care. The EQ-5D-5L, administered 6 months after randomisation, will enable utilities to be determined and subsequent calculation of quality-adjusted life-years (QALYs). Costs will be determined based on resource use during the intensive care, acute care and post-acute care periods up to Day 180 and will include costs of the intervention where appropriate. To address the issue of transferability in multinational trials, we will adjust for heterogeneity across geographic regions (which may arise, for example, owing to differences in treatment patterns) and obtain estimates for costs and effects in specific regions of the study.

All costs will be converted to a common currency using purchasing power parity statistics from the Organisation for Economic Co-operation and Development. Health care costs will be compared between regions using the same methods as used in previous economic evaluations of multinational clinical trials by our group.[51]

Per-protocol analyses. It is well understood that trial protocols may not be followed fully for some trial participants.[52] Following completion of the main primary and secondary outcome analyses, there will be an option to repeat a selection of those analyses using a per-protocol analysis set, whereby the subset of protocol-compliant patients assigned to early activity and mobilisation is compared with all patients assigned to the control group.[7,27,53] Protocol-compliant patients will be determined retrospectively; this will exclude patients for whom there were major protocol violations (eg, violation of entry criteria leading to random assignment of ineligible patients), patients who were not assessed by a physiotherapist for possible early activity and mobilisation on every day from randomisation to ICU discharge (to a maximum of 28 days), and patients for whom the primary outcome variable is not available.

Data management

All trial data will be collected by trained staff at each participating site and entered into a secure database (using electronic case report forms) by site staff using a web interface. Data management will be coordinated by project managers at the Australian and New Zealand Intensive Care (ANZIC) Research Centre, including programming (online study database design) and data management support (data monitoring, database questions, technical issues, data queries, query resolution). Data collection methods are detailed in the Online Appendix, E. All numerical data fields in the trial database have upper and lower review limits based on biologically unlikely thresholds to help identify possible data entry errors. Also, all data entered by European Union (EU) countries will be pseudonymised to align with EU data regulations.

Study monitors from the ANZIC Research Centre, the Medical Research Institute of New Zealand and Intensive Care National Audit and Research Centre in the UK will monitor all research sites in person, with the assistance of a German-speaking trial monitor at sites in Germany, a Portuguese-speaking monitor at sites in Brazil and a trial monitor from the Irish Critical Care Clinical Trials Network at sites in Ireland. During monitoring visits, multiple aspects of data validity are checked, including consent documents, inclusion and exclusion criteria, adverse events, and all admission and discharge dates required to calculate primary outcome data and important daily data. An independent data and safety monitoring committee (DSMC) continues to oversee the quality of the trial and has access to trial outcome and accumulated safety data, including the differential proportions of total mortality. Further details are available in the Online Appendix, C.

Sample size, power and interim analysis schedule

Conservative inflation factors were applied to a standard parametric calculation for sample size in this quantile regression. Estimated mean and SD $DAOH_{180}$ were derived from a published pilot TEAM randomised controlled trial and systematic review, assuming overall mean ± SD days alive and out of hospital of 143 ± 21 (control group) versus 156 ± 27 (intervention group).[7,16] Using a type I error proportion of 0.05 and a 7-day difference between the groups in $DAOH_{180}$ (being about half the point estimate found in the pilot randomised controlled trial), recruiting 313 patients in each group would achieve 90% power to detect a difference. The recruitment goal was set at 750 patients. This final trial size incorporated an inflation of 15% to account for a non-parametric distribution of the primary end point and up to a 5% loss to follow-up; in comparison, previous studies by the ANZICS Clinical Trials Group have yielded losses to follow-up of ≤ 2%.[54,55]

Interim analysis

There has been one interim analysis assessing efficacy and safety by the DSMC located in Ireland, the UK and the US, with no early stopping option planned for futility. A time point of 1 month after the first 400 patients reached their 28-day follow-up (3 June 2020) was set so that the interim analysis was conducted in a timely manner. At that point, the DSMC had access to:

- differential all-cause mortality at hospital discharge, censored at Day 28;

- the differential number of days alive and not in hospital to Day 28, with a score of zero allocated to any survivors who remained in hospital at Day 28; and
- the differential number of days alive and not in hospital to Day 180 for those with available data.

The DSMC's interim evaluation of Day 28 censored accumulated differential all-cause mortality at hospital discharge was supported by symmetrical ± 3 SD Haybittle–Peto boundaries, with this interim analysis "spending" a total of 0.0031 of the available type 1 error at that point.[56] To preserve an overall type 1 error no greater than 0.05, the final analysis of the primary trial outcome at full recruitment should be conducted at a two-sided *P* value of 0.0491 (Z = ± 1.967), which in practice will be assumed unchanged from 0.05.[57] On 2 September 2020, the DSMC confirmed that the TEAM III trial was approved to continue recruitment to the final target sample size.

Analysis software

Data capture and processing will initially be done by Research Path. Data will then be exported in relevant formats for statistical analyses using current versions of R software, SAS software or Stata software.[33,58,59]

Safety and adverse event analyses

Safety and tolerability implications will be summarised using descriptive statistical methods, supplemented by calculation of 95% CIs where appropriate. Patients with protocol deviations, adverse events and missing values will be identified, and a descriptive analysis that includes their relationship to treatment will be undertaken.

Ethics and informed consent

Ethics approval for the study was obtained from the responsible local and national human research ethics committees before recruitment at each study site commenced. By virtue of the inclusion criteria, none of the patients who are eligible for this study will be competent to provide prospective informed consent. The approach to consent in this study will be based on that developed from the guidelines in Chapter 4.4 of the 2013 edition of the National Health and Medical Research Council's *National statement on ethical conduct in human research*. Informed consent to participate will comply with requirements of relevant local and national human research ethics committees.

Compliance with Good Clinical Practice requirements

The trial is being conducted, and accumulating data are being monitored, according to the standard requirements of Good Clinical Practice.[60]

Discussion

Invasive mechanical ventilation is a life-saving intervention, but patients receiving this intervention are typically confined to bed with no active exercise. This immobilisation may contribute substantially to the development of muscle weakness and wasting in many such patients, with these undesirable events associated with increased hospital length of stay, increased mortality after hospital discharge, and poor long-term functional recovery. At present, there are no specific proven therapies available for this common clinical scenario.

The potential benefits of a bundle of activities comprising early activity and mobilisation during prolonged invasive mechanical ventilation are supported by scientific rationale. This intervention has the potential to shorten ventilator dependence, decrease mortality, and reduce physical and cognitive functional decline associated with illnesses needing prolonged mechanical ventilation in an ICU.

The TEAM III trial is designed to detect an important beneficial effect of early activity and mobilisation, if one exists, while minimising potential risks. Application of the statistical analysis plan within this TEAM III trial protocol will facilitate evaluation of these important clinical data and support confidence in the subsequent generalisation of its findings. The aim of the TEAM III trial is to provide definitive guidance for clinicians regarding the true efficacy and safety of a bundle of activities comprising early activity and mobilisation in the management of critical illness in adults.

Trial status

The TEAM III trial began in November 2017, with patient recruitment estimated to be completed by about October 2021 with a total of 750 participants, and final collection of all 180-day outcome data anticipated by May 2022. The trial recruitment at a total of 46 research sites passed 576 patients in March 2021.

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and the TEAM trial sites and investigators are listed in the Online Appendix, A and B respectively).

Competing interests

No relevant disclosures.

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