

Statistical analysis plan for the Augmented versus Routine Approach to Giving Energy Trial (TARGET)

The TARGET Investigators on behalf of the Australian and New Zealand Intensive Care Society Clinical Trials Group

The Augmented versus Routine Approach to Giving Energy Trial (TARGET) is a multicentre, double-blind, randomised, controlled, parallel group, phase 3 clinical trial designed to evaluate whether enteral delivery of recommended energy (calorie) goals using an energy-dense formulation improves clinical outcomes, when compared with routine care, in critically ill patients receiving invasive mechanical ventilation.

The TARGET trial is funded by the National Health and Medical Research Council of Australia (project grant no. 1078026) and the Medical Research Institute of New Zealand (project grant no. 15.141) and is endorsed by the Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group (CTG). Recruitment commenced in June 2016, and 46 Australian and New Zealand intensive care units (ICUs) are recruiting participants (online Appendix, available at cicm.org.au/Resources/Publications/Journal). The TARGET trial is registered on ClinicalTrials.gov (NCT02306746). The full details of our trial methodology have been published in this issue of the Journal.¹

Here we describe the pre-specified statistical analysis plan developed by the chief investigators and trial statisticians before completion of patient recruitment and data collection into the TARGET trial. Our statistical analysis plan outlines the principles and methods of analysing and reporting the trial results. The use of a pre-specified plan aims to reduce the risk of analysis bias arising from knowledge of the trial results emerging during the conduct of the analyses.²⁻⁴

Aims and hypotheses

The primary aim of the TARGET trial is to determine whether augmentation of calorie delivery using an energy-dense enteral nutrition formulation in mechanically ventilated patients improves 90-day survival when compared with routine care, which typically delivers less than 60% of recommended energy goals.⁵⁻⁸ The null hypothesis is that the relative risk (RR) of 90-day all-cause mortality between mechanically ventilated patients randomised to receive either an energy-dense enteral nutrition formulation or a routine enteral nutrition formulation delivered at the same goal rate is one (H_0 , RR = 1), versus an alternative hypothesis that the RR is not equal to one (H_1 , RR \neq 1).⁹

ABSTRACT

Background: The Augmented versus Routine Approach to Giving Energy Trial (TARGET) is a 4000-patient randomised, double-blind controlled trial designed to evaluate whether enteral delivery of recommended energy goals using a 1.5 kcal/mL enteral nutrition formulation improves clinical outcomes, compared with a 1 kcal/mL enteral nutrition formulation delivered at the same goal rate, in critically ill patients receiving invasive mechanical ventilation.

Objective: In keeping with best practice, and in accordance with other trials conducted by the investigators, a pre-specified statistical analysis plan has been described and made public before completion of patient recruitment and data collection into the TARGET trial.

Methods: Our statistical analysis plan was designed by the TARGET chief investigators and statisticians and approved by the TARGET Management Committee. We reviewed the data collected as specified in the trial protocol and collected in the case report form. We present information pertaining to data collection, pre-specified subgroups, processes of care and trial outcomes. Primary and secondary outcomes are defined and methods for assessing functional outcomes (secondary outcomes) are described.

Results: We have developed a statistical analysis plan that includes our methods for presenting the trial profile, baseline characteristics, processes of care, outcomes and adverse events. Seven pre-specified subgroups and our methods for statistical comparisons between groups are described.

Conclusion: We have developed a pre-specified statistical analysis plan for TARGET. To minimise analytical bias, this plan has been developed and made available to the public domain before completing recruitment and data collection.

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Secondary aims will be assessed including whether augmentation of calorie delivery using an energy-dense enteral nutrition formulation in mechanically ventilated patients is associated with improved functional outcomes when compared with routine care.¹

Design

Population

Four-thousand critically ill adult patients meeting all the inclusion criteria and none of the exclusion criteria will be recruited to the study (Table 1).¹ A process of opt-out consent will apply — the full details are described in our methodology article.¹

Randomisation

A permuted block randomisation method with variable block sizes stratified by site allocates eligible patients to the TARGET protocol enteral nutrition, using an energy-dense (1.5 kcal/mL) or routine (1 kcal/mL) formulation, in a 1:1 ratio. The central web-based electronic randomisation is performed using secure study management software (<https://target.spinnakersoftware.com>) developed by Spinnaker Software — a clinical trial software company (<http://spinnakersoftware.co.nz>).

Study treatments and blinding

The TARGET enteral nutrition formulations are Fresubin energy fibre tube feed (Fresenius Kabi Deutschland, Germany) (1.5 kcal/mL) and Fresubin 1000 complete tube feed (Fresenius Kabi Deutschland, Germany) (1 kcal/mL) delivered at the same goal rate (1 mL/kg of ideal bodyweight per hour). The products are identical in colour and packaging. Patients and clinical, research and coordinating centre staff are blinded to the intervention allocation. Unblinding will occur after the last patient follow-up and the database lock. The intervention is delivered for up to 28 days after randomisation or until the patient ceases enteral nutrition,

dies or is discharged from the ICU, whichever occurs first. At any time, the treating clinician may determine that it is not in a patient's best interest to continue with the TARGET protocol enteral nutrition or consent to continue may be withdrawn.¹

Outcome definitions

Primary outcome

The primary trial outcome is all-cause mortality at Day 90 after randomisation. In keeping with previous ANZICS CTG trials, minimal loss to follow-up is anticipated and missing values will not be imputed.^{7,10}

Secondary outcomes

The secondary outcomes include:

- cause-related mortality at 90 days after randomisation. The primary cause of death will be classified as cardiovascular (arrhythmia, cardiogenic, septic or hypovolaemic shock), respiratory (hypoxic respiratory failure), metabolic, neurological (traumatic brain injury with or without brain death, no traumatic brain injury with or without brain death), or other;^{7,10,11}
- all-cause mortality at hospital discharge;
- all-cause mortality at 28 days after randomisation;
- the time from randomisation until death;
- the number of days alive and not in the ICU to Day 28 after randomisation;
- the number of days alive and not in hospital to Day 28 after randomisation;
- ventilator-free days to Day 28 after randomisation (patients who die before Day 28 will be assigned zero organ support-free days);¹²

Table 1. Eligibility criteria for enrolment in the Augmented versus Routine Approach to Giving Energy Trial (TARGET)

Inclusion criteria	<p>The patient is aged 18 years or older</p> <p>The patient is intubated and receiving mechanical ventilation</p> <p>The patient is about to commence enteral nutrition or enteral nutrition commenced within the previous 12 hours</p> <p>The patient is expected to be receiving enteral nutrition in ICU at least until the day after tomorrow</p>
Exclusion criteria	<p>The patient has received any enteral or parenteral nutrition for > 12 hours in this ICU admission</p> <p>The treating clinician considers the enteral nutrition goal rate (ie, 1 mL/kg IBW per hour) to be clinically contraindicated (eg, requirement for fluid restriction)</p> <p>The patient requires specific nutritional therapy, as determined by the treating doctor or dietitian (ie, TARGET protocol enteral nutrition not considered to be in the best interest of the patient)</p> <p>Death is deemed to be imminent or inevitable during this admission and either the attending physician, patient or substitute decision maker is not committed to active treatment</p> <p>The patient has an underlying disease that makes survival to 90 days unlikely</p> <p>The patient has ≥ 15% acute burns</p> <p>The patient was previously enrolled in this study</p>

IBW = ideal bodyweight. ICU = intensive care unit.

- the proportion of patients receiving any vasopressors to Day 28 after randomisation;
- vasopressor-free days to Day 28 after randomisation (patients who die before Day 28 will be assigned zero organ support-free days);
- the proportion of patients receiving any renal replacement therapy up to Day 28 after randomisation (excluding those receiving chronic dialysis before this ICU admission);
- renal replacement-free days to Day 28 after randomisation in patients not receiving chronic dialysis before ICU admission (patients who die before Day 28 will be assigned zero organ support-free days);
- the proportion of patients with positive blood cultures to Day 28 after randomisation;
- the proportion of patients requiring intravenous antimicrobials to Day 28 after randomisation;
- all-cause mortality at 180 days after randomisation; and
- the functional outcomes at 180 days after randomisation assessed, as applicable, using the five-level EuroQol five dimensions questionnaire; the World Health Organization Disability Assessment Schedule 2.0; the Australian Labour Force Survey and the Adelaide Activities Profile.^{13,14-17}

Data collection and follow-up

Full details of the data collected and the data collection schedule are described in our methodology article.¹ In addition to trial eligibility criteria, baseline measures are:

- demographics (age, sex, ideal and actual weight, height and body mass index [BMI]);
- usual residence;
- admission source (ICU, hospital);
- ICU admission category (medical, elective surgical, emergency surgical);
- ICU admission diagnosis;
- chronic comorbidities;
- ICU admission APACHE (Acute Physiology and Chronic Health Evaluation) II severity of illness score;
- presence of sepsis;
- electrolytes and serum albumin;
- receipt of vasopressors, acute renal replacement therapy;
- dietician or clinician assessment of nutritional requirements;
- categorisation for 180-day functional outcomes;¹⁸ and
- ethnicity (New Zealand participants only, categorised as European, Maori, Pacific peoples, Asian, Middle Eastern/Latin American/African, other).

The daily data include:

- administration of TARGET protocol enteral nutrition and non-study nutrition (enteral and parenteral nutrition, incidental calories);
- intolerance to enteral nutrition (gastric residual volumes, diarrhoea, administration of promotility agents);
- insulin administration and highest and lowest blood glucose levels;
- electrolytes and serum albumin (Days 1, 7, 14, 21, 28);
- respiratory parameters;
- intravenous antimicrobials and positive blood cultures; and
- receipt of mechanical ventilation, vasopressors or renal replacement therapy.

The follow-up data are:

- ICU and hospital admission and discharge date and hospital discharge destination;
- vital status at ICU and hospital discharge;
- vital status and location at Day 28, 90 and 180 after randomisation;
- cause-specific mortality; and
- quality of life and functional outcomes at Day 180 after randomisation.

Sample size

Our sample size calculation is based on data from our feasibility study (overall mortality 28%) and the ANZICS Centre for Outcome Resource Evaluation database.^{9,19} Using a type I error rate of 0.05 and an expected baseline mortality of 20–30%, recruiting 1887 per group ($n = 3774$, fully evaluable participants) will achieve 80% power to detect a difference of 3.8–4.3%, depending on baseline mortality, for 90-day mortality. A difference of around 4% (number needed to treat = 25) is a realistic and clinically meaningful minimum effect.^{20,21}

The 17% absolute 90-day mortality difference in the feasibility study has not been used to determine sample size due to the recognised potential for exaggeration of treatment effects in feasibility studies.^{22,23} A 6% sample size inflation has been applied to account for anticipated losses during follow-up, and for one planned interim safety and efficacy analysis on completion of the 90-day follow-up of the first 1500 participants recruited, leading to an overall recruitment goal of 4000 participants. Previous studies by the ANZICS CTG have yielded a loss to follow-up rate of $\leq 5\%$.^{7,10}

Statistical analysis

Principles

All analyses will be conducted on patient-level data. If consent for participation is withdrawn or consent to continue is not given, the data will not be used unless consent to do so is obtained, including for all mortality time points. Analyses will be performed by modified intention-to-treat according to the participants' randomly allocated group, regardless of treatment compliance. These analyses will include participants for whom consent to continue is refused but the use of data already collected is allowed, including the primary outcome, and will exclude patients who do not fulfil the study entry criteria and never received the intervention.²⁴ Per-protocol and as-treated sensitivity analyses from the main intention-to-treat dataset will be also performed for the primary and secondary outcomes.⁴

Missing data will not be imputed, including for 90-day vital status. Where there are missing observations, the number of observations used will be reported. Two-sided hypothesis testing at a significance level of 0.05 will be used. No adjustment for multiple tests will be made, with the interpretation of the significance of the tests being appropriate for the primary or secondary nature of the outcome. Analyses will primarily be conducted using SPSS Statistics version 22 or later (IBM) and Stata version 15.0 or later (StataCorp, Texas, USA).

Interim analysis

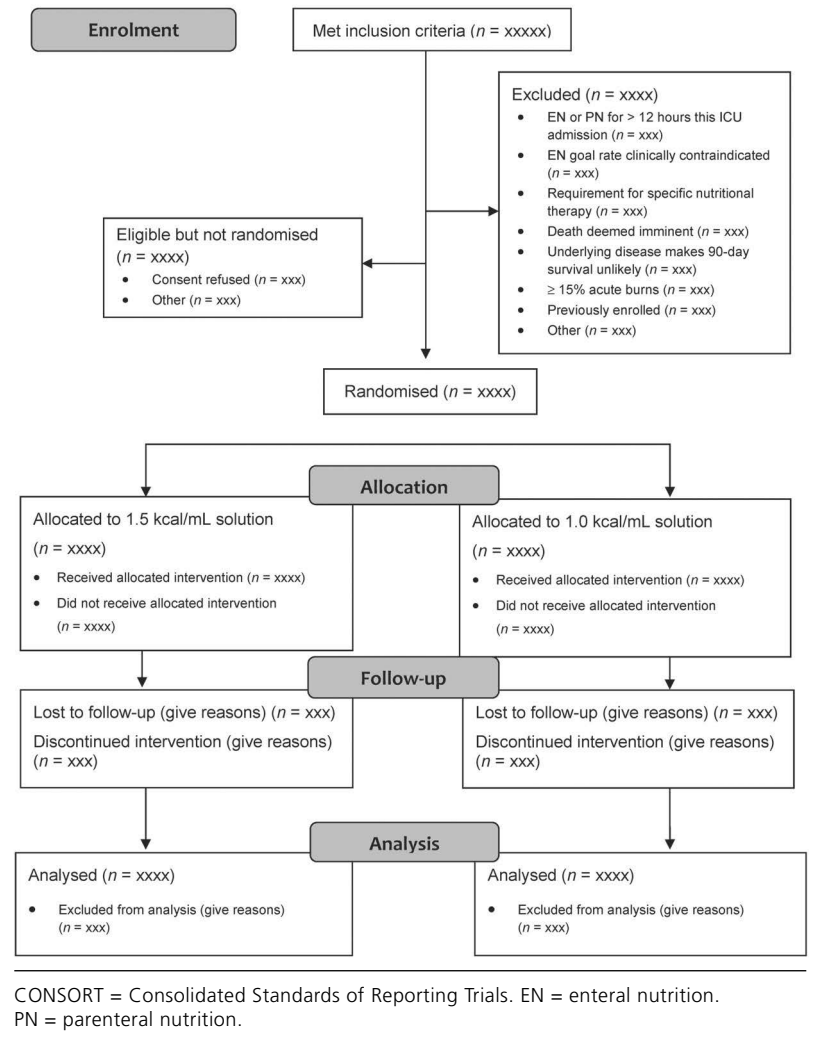
A planned interim safety analysis was conducted by an independent data safety and monitoring committee (DSMC), composed of experienced clinical researchers without other connection to the TARGET trial, on completion of follow-up to Day 90 after randomisation for the first 1500 participants recruited (37.5% recruitment, to accommodate a rapid rate of patient recruitment). The interim analysis compared the standardised statistic representing differential all-cause 90-day mortality against symmetrical O'Brien-Fleming boundaries, conventionally set at a standard deviation of ± 3.5 . With these boundaries, only a small amount (0.0005) of the 0.05 total α error is "spent". In the absence of early stopping, the final analysis at $0.05 - 0.0005 = 0.0495$ may be conducted accurately at full recruitment

using an unmodified $P = 0.05$. The data were analysed with the treatment group indicated by a blinded binary code. All codified data remained confidential to the DSMC and the independent trial statistician. After consideration of the interim analysis statistical report, the DSMC recommended continuation of recruitment to the planned 4000 patient sample size.

Trial profile

Patient flow through the trial will be presented in a Consolidated Standards of Reporting Trials diagram (Figure 1).²⁵ We will report the number of patients who meet the trial eligibility criteria, the number of patients randomised, and the number of patients in the modified intention-to-treat dataset for whom 90-day mortality data are available for evaluation of the primary outcome.

Figure 1. CONSORT diagram of participants in the Augmented versus Routine Approach to Giving Energy Trial



Participant characteristics and baseline comparisons

Patient characteristics at baseline will be tabulated by treatment group. The categorical variables will be presented as frequency counts (n) and as a proportion of the number of patients with available data (%). Continuous variables will be presented as summary statistics for location (mean or median) and variability (standard deviation or interquartile range). The total counts for variables with missing data will be indicated as footnotes to individual tables.

Processes of care

Details of the TARGET protocol enteral nutrition and non-study nutrition delivery, including calorie delivery, intolerance to enteral nutrition, blood glucose management and biochemical and respiratory changes, will be tabulated by treatment group. Categorical variables will be presented as frequency counts (n) and as a proportion of the number of patients with available data (%) and compared using an unadjusted χ^2 test or Fisher exact test, as appropriate. Continuous variables will be presented as summary statistics for location (mean or median) and variability (standard deviation or interquartile range) and compared using rank sum or Student t tests as appropriate. Total counts for variables with missing data will be indicated as footnotes to individual tables.

Analyses

Primary outcome

The numbers at risk in each group and the number and proportion of events will be reported. The primary outcome of all-cause mortality at 90 days after randomisation will be compared between treatments and presented as unadjusted RR with 95% confidence interval (CI). Differences between treatments in this 2×2 contingency table analysis will be assessed using an unadjusted χ^2 test.

Two adjusted analyses of the primary outcome will be conducted based on research site (stratification variable), via a random effect in a mixed model, and on baseline clinical covariates of age, ICU admission APACHE II score, BMI, region (Australia or New Zealand), gender and admission type (medical/elective or surgical/emergency surgical). Adjusted analyses will be performed via log-binomial regression and treatment comparison via RR and corresponding 95% CI. In the case of non-convergence or other numerical estimation problems with the log-binomial model, a modified Poisson regression approach will be used with robust standard errors.

Secondary outcomes

Secondary outcomes of all-cause mortality at hospital discharge and at 28 and 180 days after randomisation

will be analysed with the same unadjusted and adjusted analyses as described for the primary outcome. For secondary functional outcomes, we will use ordinal logistic regression. Time to mortality according to treatment, censored at 90 days, will be analysed with Cox proportional hazards regression and presented in a Kaplan–Meier plot. Other secondary outcomes will be compared with χ^2 , rank sum or Student t tests as appropriate.

Subgroup analyses

Subgroup analyses to assess the differential effect of calorie delivery on outcome will be performed on pre-specified subgroups, irrespective of whether there is evidence of a treatment effect for the primary outcome, and presented as forest plots. Subgroups of interest are:

- age (dichotomised at 65 years);
- diagnostic subgroups (trauma v no trauma, sepsis v no sepsis, neurological v non-neurological, medical v surgical);
- quintiles of absolute risk of death as determined by the Australian and New Zealand Risk of Death score from linkage to the ANZICS Centre for Outcome Resource Evaluation registry; and
- BMI on presentation using the WHO categories of < 18.5 , 18.5 – 24.9 , 25.0 – 29.9 and ≥ 30.0 kg/m^2 .^{19,26}

The non-linear effects of BMI and the absolute risk of death will be examined using the raw BMI scores and risk of death as continuous variables. Subgroup analyses will be undertaken by tests for interaction by adding terms to the regression models.

A separate exploratory analysis evaluating the interaction between ethnicity (in New Zealand) and treatment allocation will be reported after the main manuscript describing the primary 90-day all-cause mortality treatment effect is issued. This analysis will be performed using a logistic regression model, with results reported as odds ratios and 95% CIs.

Protocol compliance

Pre-specified protocol non-compliance is categorised into major and minor deviations. The major deviations are:

- randomisation of ineligible patients;
- failure to ever receive TARGET protocol enteral nutrition;
- non-protocol enteral nutrition administration (unless the treating clinician considers the TARGET protocol enteral nutrition no longer in the patient's best interest);
- administration of incorrectly assigned TARGET protocol enteral nutrition formulation; and
- rate delivered above goal rate ($> 10\%$ above goal rate for over 24 hours), including supplemental parenteral nutrition administered over and above TARGET protocol enteral nutrition delivered at goal rate.

The minor deviations are:

- incorrect bag administered, but correctly assigned TARGET protocol enteral nutrition formulation;
- rate delivered above goal rate, but < 10% over 24 hours;
- rate delivered less than goal rate, unless clinically indicated;
- TARGET protocol enteral nutrition bag hung for over 24 hours;
- TARGET protocol enteral nutrition not ceased when oral nutrition commenced; and
- TARGET protocol enteral nutrition not ceased after 28 days post-randomisation.

Protocol deviations will be tabulated by treatment group and reported as frequency counts (*n*) and proportion (%).

Safety outcomes and adverse events

Adverse events are categorised as “not related”, “unlikely”, “possibly”, “probably” or “definitely related” to treatment, as determined by site investigators and reviewed by an experienced clinical researcher without other connection to the TARGET trial. Events will be tabulated by treatment group and reported as frequency counts (*n*) and proportions (%).

Future analyses

We will consider conducting hypothesis-generating exploratory analyses other than those pre-specified above to further evaluate the impact of calorie delivery on outcomes in this large, clinically important, nutrition dataset. Any such analyses conducted after knowing the main results of the TARGET trial will be cautiously interpreted and clearly indicated in any subsequent publications.

Conclusion

Our pre-specified statistical analysis plan was prepared before completion of recruitment and data collection into the TARGET trial. The plan provides a detailed description of the principles and methods for analysing and reporting the trial results and is in keeping with best research practice.²⁷

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Zealand Intensive Care Society Clinical Trials Group. The trial is managed by the Australian and New Zealand Intensive Care Research Centre, Monash University, Melbourne, Australia, and coordinated in New Zealand by the Medical Research Institute of New Zealand, Wellington, New Zealand.

Competing interests

None declared.

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Appendix

This appendix was part of the submitted manuscript and has been peer reviewed. It is posted as supplied by the authors.

APPENDIX: The Augmented versus Routine approach to Giving Energy Trial investigators

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