

Study protocol 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

Nutrition is routinely provided to all patients who are mechanically ventilated and remain in the intensive care unit (ICU) for more than a few days. It may be provided by the enteral or intravenous route, but the enteral route is preferred and is recommended by nutrition guidelines as first-line therapy.¹⁻⁵ Accordingly, enteral nutrition (typically via a nasogastric tube) is usually initiated within 24 hours of admission using a formula with an energy content of 1 kcal/mL and prescribed at an approximate rate of 1 mL/kg/h.⁶ However, due to gastric intolerance, fasting for procedures, and unplanned removal of the nasogastric tube, standard enteral nutrition practice typically delivers less than 60% of the recommended energy goals (calories).⁶⁻⁹

The literature addressing the effects of energy delivery on outcomes after critical illness remains divided. Some studies support the concept that increasing energy delivery will improve outcomes.^{6,10-16} Others suggest that short term energy delivery below the recommended goals, “permissive underfeeding” (around 1000 kcal/day), or well below the recommended goals, “trophic feeding” (around 400 kcal/day), is well tolerated without a detrimental effect on outcomes.¹⁷⁻¹⁹ Finally, there are trials that suggest that increased energy delivery may be harmful;^{20,21} however, in these trials, energy was supplemented intravenously rather than provided solely by the enteral route. The data currently available are limited by a lack of power to demonstrate an effect on mortality, the likelihood of bias (there are no blinded studies), and the fact that most studies have not delivered 100% of energy goals to either study arm. The proposed study was designed to determine if increased energy delivery via the enteral route can improve clinical outcomes.

The Augmented versus Routine Approach to Giving Energy Trial (TARGET) feasibility study showed that patients receive about 46% more energy (around 2000 total kcal/day) when receiving an energy-dense formula (1.5 kcal/mL) instead of standard nutrition (1 kcal/mL) both administered at the same rate (1 mL/kg ideal body weight [IBW]/h). The absolute risk reduction for 90-day mortality was 17% (95% confidence interval [CI], 0.6–33%; $P = 0.056$). No adverse effects were observed in either treatment group.²² Importantly, the feasibility study also showed efficient and effective recruitment and randomisation and administration of the intervention in a blinded fashion.

The purpose of this article is to document the protocol for TARGET. This trial, funded by the National Health and

ABSTRACT

Background: Nutrition is routinely provided to critically ill patients who are mechanically ventilated and remain in the intensive care unit for more than a few days. Nasogastric feeding, which is standard practice for patients who are unable to tolerate oral nutrition, typically delivers less than 60% of the recommended energy requirements. It remains uncertain whether the delivery of about 100% of the recommended energy goals via the enteral route will affect survival and other important clinical outcomes.

Objective: To describe the protocol for a large-scale, multicentre, double-blind, randomised, controlled, parallel-group, phase 3 clinical trial to determine if augmentation of calorie delivery using an energy-dense enteral nutrition formulation in mechanically ventilated patients increases 90-day survival when compared with routine care.

Methods: 4000 patients who are mechanically ventilated and are expected to receive enteral nutrition for more than 2 days are to be randomised to an energy-dense formulation (1.5 kcal/mL) or routine enteral feed formulation (1 kcal/mL), given at the same rate. The primary outcome is 90-day all-cause mortality. Secondary outcomes include cause-related mortality up to Day 90; all-cause mortality at hospital discharge and at Days 28 and 180 after randomisation; and ventilator-, vasopressor- and renal replacement-free days to Day 28. Health-related quality of life and functional assessments will be conducted at Day 180 after randomisation.

Results and conclusions: The results of this trial are expected to determine whether increased energy delivery, using an energy-dense formula can improve clinically meaningful outcomes, including survival.

Crit Care Resusc 2018; 20 (1): 6-14

Medical Research Council of Australia (project grant no. 1078026) and the Medical Research Institute of New Zealand (project grant no. 15.141), aims to establish whether 90-day survival and functional outcomes after critical illness are improved by increased energy delivery. The trial is registered on ClinicalTrials.gov (NCT02306746) and is endorsed by the Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group (CTG).

Methods

Study design and participants

TARGET is a multicentre, double-blinded, randomised, controlled, parallel-group, phase 3 clinical trial to determine if augmentation of calorie delivery using an energy-dense enteral nutrition formulation in 4000 patients who are mechanically ventilated increases 90-day survival compared with routine care, which typically delivers less than 60% of the recommended energy goals.⁶⁻⁹

Approval was obtained from the responsible local or national human research ethics committees before study commencement. It was given for patients to be enrolled without consent on the basis that the two treatment options are acceptable as current management. The consent process is as follows: when identified as suitable, patients are enrolled and randomised to the study intervention and, at the first available opportunity, the next of kin or the patient (when deemed competent) are given an information sheet regarding the trial and are able to choose to either continue in the trial or opt-out. If the next of kin or the patient request that they not be enrolled (or be withdrawn), standard nutrition therapy is provided and patient data are not used, unless consent to do so is obtained.

Patient recruitment commenced in nine sites in June 2016 and, currently, 46 ICUs in Australia and New Zealand are actively recruiting. It is anticipated that the 4000 patients will be enrolled over about 18 months, finishing in late 2017. Investigators can co-enrol patients in TARGET and other trials as long as the intervention in the other trials is unrelated to nutrition. The studies that have been allowed to co-enrol with TARGET are shown in Table 1, and patients' inclusion and exclusion criteria are listed in Table 2.

Outcomes

Table 3 lists the primary and secondary study outcomes. Health-related quality of life and functional assessments are conducted at 180 days after randomisation by individual site investigators. In addition to the five-level EuroQol five dimensions questionnaire,²⁴ assessments using the World Health Organization Disability Assessment Schedule 2.0,²⁵ the labour force questions from the Australian Labour Force Survey,²⁶ or the Adelaide Activities Profile^{27,28} are undertaken (online Appendix, available at cicm.org.au/Resources/Publications/Journal, Sections 2–5 for all assessment tools). The assessment tools used are dependent on age, employment status or level of independence as assessed at study baseline (Table 4). The rationale for this approach is provided elsewhere.^{29,30}

Intervention

Both TARGET protocol enteral nutrition formulations are supplied by Fresenius Kabi Deutschland, Germany,

in identical 1000 mL bags with study specific labels not disclosing the content. The energy-dense formulation (1.5 kcal/mL) is Fresubin energy fibre tube feed, and the routine enteral nutrition formulation (1 kcal/mL) is Fresubin 1000 complete tube feed. The protein content by volume in both formulations is similar, thus protein delivery on a g/kg/day basis does not differ between treatment groups. Table 5 summarises product information for both formulations.

Enteral nutrition distribution and logistics

The TARGET protocol enteral nutrition is shipped to Australia and stored at the Fresenius Kabi local warehouse. Delivery to participating sites is coordinated by the Australian and New Zealand Intensive Care Research Centre. Each consignment is temperature-monitored during transport. Management, including tracking of deliveries, allocation of enteral nutrition at randomisation, inventory of boxes allocated, and bags administered at both the sites and the coordinating centre is via a web-based database designed by Spiral Web Solutions (New Zealand).

Treatment assignment and allocation concealment

Eligible patients are randomised 1:1 to either a 1.5 kcal/mL or 1 kcal/mL enteral nutrition formulation using a permuted block randomisation method with variable block sizes, stratified by site. Central randomisation is performed by trained staff using a secure, password-protected, web-based database available 24 hours a day, 7 days a week. Both TARGET protocol formulations are identical in colour and packaging and blinding is conducted by Fresenius Kabi Deutschland before delivery in Australia. Each bag of the TARGET protocol enteral nutrition is identified by a unique identification number and packed in boxes that also have a unique identification number.

Patients, clinical and research staff, and staff at the trial management centre in New Zealand (Medical Research Institute of New Zealand) and the coordinating centre in Australia (Australian and New Zealand Intensive Care Research Centre) are blinded to the intervention allocation. Samples of random bags of TARGET protocol enteral nutrition will be tested at a central site laboratory for osmolality, sodium and glucose concentrations on completion of recruitment, and the results will be made available to the investigators after the database lock to ensure that the delivery of allocated enteral nutrition feed was correct as per the randomisation schedule.

Enteral nutrition administration

The TARGET protocol enteral nutrition is commenced as soon as possible after randomisation. If the patient has commenced non-study enteral nutrition within the 12 hours before randomisation, it is changed to TARGET protocol enteral nutrition at randomisation. The weight used to

Table 1. Studies approved for co-enrolment with the Augmented versus Routine Approach to Giving Energy Trial (TARGET)

Study acronym	Study title
Any observational study	
ADRENAL	Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock
Angiotensin II	Angiotensin II for the Treatment of Vasodilatory Shock
ART-123	Phase 3 Safety and Efficacy Study of ART-123 in Subjects with Severe Sepsis and Coagulopathy
AYA-ALL (protocol ALL06)	A phase 2 trial of an intensive paediatric protocol incorporating post-induction stratification based on minimal residual disease levels for the treatment of adolescents aged 15 years and above, and young adults aged up to 40 years, with newly diagnosed ALL
CYCLIST	A randomised controlled trial of in-bed cycling with critically ill patients on maintaining quadriceps muscle mass
DAL-301	Effect of Dalcetrapib versus Placebo on CV Risk in a Genetically Defined Population with a Recent ACS (dal-GenE)
ICU-ROX	A phase 2b, multicentre, randomised, single blinded clinical trial parallel groups comparing liberal versus conservative oxygen therapy in mechanically ventilated adults in the ICU
IMPACT	Improving Partnerships with Family Members of ICU Patients: the IMPACT trial
Nebulised heparin	A phase 2 randomised blinded trial of nebulised heparin in patients requiring mechanical ventilation for more than 48 hours
PATCH	Pre-hospital antifibrinolytics for traumatic coagulopathy and haemorrhage
PEPTIC	A multicentre, cluster cross-over, randomised registry trial comparing the safety and efficacy of proton pump inhibitors with histamine-2 receptor blockers for ulcer prophylaxis in intensive care patients
PHARLAP	A multicentre RCT of open lung strategy including permissive hypercapnia, alveolar recruitment and low airway pressures in patients with ARDS
PLUS	The Plasma-Lyte 148 versus Saline study
POLAR	Prophylactic Hypothermia to Lessen Traumatic Brain Injury
PREVENT	Prophylaxis of thromboembolism in critically ill patients using combined intermittent pneumatic compression and pharmacologic prophylaxis versus pharmacologic prophylaxis alone: a multicentre RCT
Pro-MEDIC	Prophylactic Melatonin for Delirium in Intensive Care: a randomised placebo controlled trial
PROTECT-ICD	Programmed Ventricular Stimulation to Risk Stratify for Early Cardioverter-Defibrillator Implantation to Prevent Tachyarrhythmias following Acute Myocardial Infarction
PROTECTIN	A randomised, feasibility, safety and biological efficacy placebo-controlled trial of aspirin in ICU patients with the systemic inflammatory syndrome
REACTOR	Randomised evaluation of active control of temperature versus ordinary temperature management
REMAP-CAP	Randomised, Embedded, Multifactorial, Adaptive Platform Trial for Community-Acquired Pneumonia
SPICE	Sedation practice in intensive care evaluation RCT
STARRT-AKI	Standard versus accelerated initiation of renal replacement therapy in acute kidney injury
SuDDICU	A cluster RCT of the clinical effectiveness and cost-effectiveness with a contemporaneous study of the ecological impact of selective decontamination of the digestive tract in critically ill patients treated in ICUs
TRANSFUSE	A multicentre randomised double blinded phase 3 trial of the effect of standard issue red blood cell blood units on mortality compared with freshest available red blood cell units
TRICS-III	Transfusion Requirements in Cardiac Surgery III
TTM-TBI-Feasibility	A feasibility study on the effect of target temperature management on patient temperature in patients with traumatic brain injury

ACS = acute coronary syndrome. ALL = acute lymphoblastic leukaemia. ARDS = acute respiratory distress syndrome. CV = cardiovascular. ICU = intensive care unit. RCT = randomised controlled trial.

calculate the enteral nutrition goal rate is the IBW, calculated from patient height, determined in the supine position³¹ (ie, for men, $IBW = 50 + 0.91 [\text{height in cm} - 152.4]$; and for women, $IBW = 45.5 + 0.91 [\text{height in cm} - 152.4]$). This height-related calculation has been used in previous nutrition studies in critically ill patients to determine energy

goals.¹⁷ The goal rate for the administration of the TARGET protocol enteral nutrition is 1 mL/kg IBW/h. This rate was chosen as it would provide 24 kcal/kg IBW/day if the full daily volume of 1 kcal/mL is delivered and reflects routine practice. To avoid possible overfeeding, the maximum goal rate is 100 mL/h. To further prevent the risk of overfeeding,

Table 2. Inclusion and exclusion criteria for enrolment in the Augmented versus Routine Approach to Giving Energy Trial (TARGET)

Inclusion criteria	<ul style="list-style-type: none"> The patient is aged 18 years or older The patient is intubated and receiving mechanical ventilation The patient is about to commence enteral nutrition or enteral nutrition commenced within the previous 12 hours The patient is expected to be receiving enteral nutrition in ICU until at least the day after tomorrow
Exclusion criteria	<ul style="list-style-type: none"> Any enteral or parenteral nutrition received for > 12 hours in this ICU admission Treating clinician considers the enteral nutrition goal rate (ie, 1 mL/kg IBW/h) to be clinically contraindicated (eg, requirement for fluid restriction) Requirement for 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) 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 The patient has an underlying disease that makes survival to 90 days unlikely The patient has ≥ 15% acute burns The patient was previously enrolled in this study

IBW = ideal body weight. ICU = intensive care unit.

Table 4. Outcome assessments at 180 days after randomisation

Baseline category*	Day 180 questionnaires
Patient aged < 65 years and in the labour force	EQ-5D-5L ²⁴ WHODAS 2.0 ²⁵ Labour force questions from the ALFS ²⁶
Patient aged < 65 year and not in the labour force	EQ-5D-5L WHODAS 2.0
Patient aged ≥ 65 years and living at home without essential supports	EQ-5D-5L Adelaide Activities Profile ^{27,28}
Patient aged ≥ 65 years and living at home with essential supports	EQ-5D-5L WHODAS 2.0
Patient aged ≥ 65 years and living in long term care facility	EQ-5D-5L WHODAS 2.0
Any age — unable to categorise	EQ-5D-5L

EQ-5D-5L = five-level EuroQol five dimensions questionnaire. ALFS = Australian Labour Force Survey. WHODAS = World Health Organization Disability Assessment Schedule. * Patients are assigned to categories at baseline to determine which questionnaire they complete at the 180-day follow-up in addition to the EQ-5D-5L.

Table 3. Study outcomes

Primary outcome	<ul style="list-style-type: none"> All-cause mortality at Day 90 after randomisation
Secondary outcome	<ul style="list-style-type: none"> Cause-related mortality at 90 days after randomisation²³ All-cause mortality at hospital discharge All-cause mortality at 28 days after randomisation Time from randomisation until death Number of days alive and not in the ICU to Day 28 after randomisation Number of days alive and not in hospital to Day 28 after randomisation Ventilator-free days to Day 28 after randomisation*† Proportion of patients receiving any vasopressors to Day 28 after randomisation Vasopressor-free days to Day 28 after randomisation* Proportion of patients receiving any renal replacement therapy up to Day 28 after randomisation† Renal replacement-free days to Day 28 after randomisation** Proportion of patients with positive blood cultures to Day 28 after randomisation Proportion of patients requiring intravenous antimicrobials to Day 28 after randomisation All-cause mortality at 180 days after randomisation Functional outcomes at 180 days after randomisation[§]

ICU = intensive care unit. * Patients who die prior to Day 28 are assigned zero organ support-free days. † This refers to invasive ventilation only. ‡ Does not include patients receiving chronic dialysis prior to this ICU admission § Functional outcomes are assessed 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 as applicable.²⁴⁻²⁸

Table 5. The Augmented versus Routine Approach to Giving Energy Trial (TARGET) protocol enteral nutrition formulation product information*

Nutritional composition	Energy-dense enteral nutrition formulation	Routine enteral nutrition formulation
	Fresubin energy fibre 1000 mL bag	Fresubin 1000 complete 1000 mL bag
Per 1000 mL		
Energy, kcal	1500	1000
Protein, g	56	55
Carbohydrate, g	180	125
Fat, g	58	27
Fibre, g	15	20
Water, mL	760	830
Sodium, mmol	43	67
Osmolarity, mosmol	325	300

* Table supplied by Fresenius Kabi Deutschland, Germany.

if a patient receives the full volume of the TARGET protocol enteral nutrition (ie, 1 mL/kg IBW/h) prescribed for 5 consecutive days and the clinician is concerned about possible overfeeding, the clinician may consider ceasing the study intervention and prescribe (unmasked) non-study enteral nutrition formulations from that time. Dietitian or clinician assessments of energy requirements are made at baseline when possible, but are not used to determine goal rate and energy delivery.

All aspects of nutrition management, other than formula choice and hourly goal rate, are according to individual unit practice. These include the rate at which the TARGET protocol enteral nutrition is commenced and incremented, and strategies to increase nutrient delivery. It is recommended that goal rate is achieved within 48 hours of commencement. If supplemental parenteral nutrition, rather than parenteral nutrition only, is deemed necessary by the treating clinician (eg, feeding intolerance), it is assumed that the patient is receiving a formula containing 1.25 kcal/mL to calculate total energy goals and to determine the amount of parenteral nutrition to administer. Where possible, patients should remain on the allocated TARGET protocol enteral nutrition for the period of supplemental parenteral nutrition, unless this becomes contraindicated.

TARGET protocol enteral nutrition is administered up to 28 days after randomisation or until the patient ceases enteral nutrition (eg, starts oral nutrition), dies or is discharged from the ICU, whichever occurs first. The TARGET protocol enteral nutrition may also be ceased by the clinician if the patient develops a contraindication to enteral nutrition,

nutritional supplements (other than vitamin supplements) are commenced, the treating clinician determines that it is not in the best interest of the patient (eg, is concerned about the risk of cumulative over or underfeeding), or consent is withdrawn. All patients requiring enteral nutrition after cessation of study intervention are converted to unmasked non-study formulations according to the individual unit's usual protocol. Patients discharged and readmitted to the ICU within 28 days of trial enrolment and requiring enteral nutrition are recommenced on TARGET protocol enteral nutrition as per the previous treatment allocation.

Data collection and management

Table 6 lists data collection. Randomised patients are followed up until death or 180 days after randomisation, whichever occurs first. Full data are collected for all randomised patients, including patients who do not receive TARGET protocol enteral nutrition for the full study period, and analysed on an intention-to-treat principle. If consent for participation is withdrawn or if the patient or the family wishes to opt-out, data are not used unless consent to do so is obtained.

Data are entered into a web-based database by trained staff at each participating site. Patients that meet all inclusion criteria are recorded on a screening log, including patients who meet one or more exclusion criteria and those who do not meet an exclusion criterion but are not randomised for other reasons. Data management is coordinated by the project managers at the Australian and New Zealand Intensive Care Research Centre and the Medical Research Institute of New Zealand, including programming and data management support (eg, source data verification, database questions, technical issues, data queries, query resolution).

Adverse events are collected from randomisation until 48 hours after cessation of the TARGET protocol enteral nutrition. Serious adverse events are collected from randomisation until Day 90 after randomisation. Events that constitute serious adverse events in the TARGET protocol are considered by the site investigator to be of concern or related to the study or the intervention.

Protocol deviations

Pre-specified protocol deviations are categorised into major and minor deviations. Major deviations include:

- randomisation of ineligible patients;
- failure to receive any TARGET protocol enteral nutrition;
- non-protocol enteral nutrition administration during the study period;
- administration of the wrong type of TARGET enteral nutrition; and
- administration > 10% above the goal volume for at least a 24-hour period.

Table 6. Data collection

Baseline data	<ul style="list-style-type: none"> • Demographics (age, sex, weight [ideal and actual], height, body mass index) • Usual residence • Source of admission (ICU and hospital) • ICU admission category (medical, elective or emergency surgical) • ICU admission diagnosis (as defined by the APACHE III severity of illness scoring system) • Comorbidities (as defined by the APACHE II severity of illness scoring system) • ICU admission APACHE II severity of illness score • Presence of sepsis (known or suspected infection, SOFA score and lactate) • Biochemistry: potassium, magnesium, phosphate, albumin concentrations • Receipt of vasopressors • Receipt of acute RRT • Nutritional requirements (calculated by dietitian or clinician) • Categorisation for Day 180 functional outcomes • Ethnicity (for patients enrolled in New Zealand only)
ICU data*	<p>Daily data collected while receiving TARGET protocol EN</p> <ul style="list-style-type: none"> • TARGET protocol EN bag identification numbers • Volume delivered in 24 hours • Reason for interruption of protocol EN • EN tube position • Gastric residual volumes • Highest and lowest blood glucose • Insulin administration <p>Daily data collected while receiving TARGET protocol EN and mechanically ventilated</p> <ul style="list-style-type: none"> • Highest Paco₂ • Minute ventilation and respiratory rate <p>Daily data collected while receiving TARGET protocol EN on Days 1–7</p> <ul style="list-style-type: none"> • Complications of EN (eg, regurgitation or vomiting) • Number of bowel actions • Proton pump inhibitors • Biochemistry: potassium, magnesium, phosphate concentrations <p>Daily data collected during the ICU admission up to Day 28 or to death or ICU discharge, whichever occurs first</p> <ul style="list-style-type: none"> • Non-protocol EN • Parenteral nutrition • Other calories — glucose, propofol • Other calories — citrate (if the patient is receiving RRT) <p>Daily data collected during the ICU admission up to Day 28 or to death or ICU discharge or receiving oral nutrition, whichever occurs first</p> <ul style="list-style-type: none"> • Infective complications (intravenous antimicrobial prescription or positive blood cultures) • Receipt of mechanical ventilation • Receipt of vasopressor support • Receipt of RRT <p>Data collected on Days 1, 7, 14, 21 and 28 of ICU admission or on death or ICU discharge, whichever occurs first</p> <ul style="list-style-type: none"> • Albumin concentration
TARGET protocol EN	<ul style="list-style-type: none"> • Calculated TARGET protocol EN goal rate • Date and time started • Date and time ceased • Reason for cessation of TARGET protocol EN

Table 6. Data collection (continued)

Follow-up data	<ul style="list-style-type: none"> • ICU admission and discharge dates • Hospital admission and discharge dates • Hospital discharge destination • ANZICS-CORE adult patient database number (for subsequent data linkage) • Vital status at ICU discharge • Vital status at hospital discharge • Vital status and location at 28 days after randomisation • Vital status and location at 90 days after randomisation • Vital status and location at 180 days after randomisation • Cause-specific mortality • Quality of life assessment at 180 days after randomisation (EQ-5D-5L)²⁴ • Functional outcome assessments[†] at 180 days after randomisation (WHODAS 2.0, the ALFS and the Adelaide Activities Profile as applicable)²⁵⁻²⁸
Consent or opt-out data	<ul style="list-style-type: none"> • Date and time consent granted or date the study brochure presented • Date of consent withdrawal or opt-out

ALFS = Australian Labour Force Survey. ANZICS-CORE = Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation. APACHE = Acute Physiology and Chronic Health Evaluation. EN = enteral nutrition. EQ-5D-5L = five-level EuroQol five dimensions questionnaire. ICU = intensive care unit. $Paco_2$ = arterial partial pressure of carbon dioxide. RRT = renal replacement therapy. SOFA = Sequential Organ Failure Assessment. TARGET = the Augmented versus Routine approach to Giving Energy Trial. WHODAS = World Health Organization Disability Assessment Schedule. * Collected for up to 28 days after randomisation while patient was present in the ICU. † Patients are assigned to categories at baseline to determine which questionnaire they complete at the 180-day follow up in addition to the EQ-5D-5L.

Minor deviations include using a bag of TARGET protocol enteral nutrition for > 24 hours, and continuing TARGET protocol enteral nutrition after the patient has commenced oral nutrition.

Statistical methods

The full details of the statistical methodology are described in the statistical analysis plan published in this issue of the Journal.³²

Using a type I error rate of 0.05, the trial will achieve 80% power with 1887 in each group ($n = 3774$ fully evaluable patients) to detect a difference of between 3.8–4.3%, depending on an expected baseline mortality of 20–30%, for 90-day mortality. The desired trial recruitment total was inflated to 4000 patients to account for the small effect of the interim analysis and loss to follow-up. The primary outcome of all-cause mortality at 90 days and the secondary mortality outcomes will be compared between treatments with unadjusted risk ratios with corresponding 95% CIs and tested using uncorrected χ^2 tests. Adjusted analyses of mortality outcomes will be conducted to adjust for research site and pre-specified clinical covariates. Other secondary outcomes will be analysed with ordinal logistic regression (functional outcomes), Cox proportional hazards regression (duration of survival) and χ^2 , rank sum or Student t tests as appropriate. Subgroup analyses will assess the differential effect of calorie delivery on outcome across pre-specified patient groups using tests of interaction.

Monitoring

An independent data safety monitoring committee was established before patient enrolment commenced. A planned interim safety analysis was undertaken when 1500/4000 patients completed a 90-day follow-up. The interim analysis compared the standardised statistic representing differential all-cause 90-day mortality against symmetrical O'Brien–Fleming boundaries for safety and efficacy. There was no intention to cease trial recruitment for “futility”. The data safety monitoring committee advised that recruitment continue to the planned sample size of 4000 patients.

The study is monitored by quality control reviews of protocol compliance, data queries, safety reporting, and protocol deviations. On-site monitoring of data quality is performed on 10% of the data.

Conclusion

This trial will provide important information to inform clinicians as to whether the provision of increased energy delivery can alter clinical outcomes, including survival.

Acknowledgements

The TARGET trial is funded by a project grant from the National Health and Medical Research Council (project grant no 1078026), the Health Research Council of New Zealand (project grant no.

15.141) and supported by the Centre of Research Excellence in Translating Nutritional Science to Good Health, the University of Adelaide, Adelaide, South Australia. The enteral nutrition was supplied and blinded by Fresenius Kabi Deutschland, Germany. Neither funding agencies nor Fresenius Kabi Deutschland had any role in the trial design, data collection or analysis. The trial is endorsed by the ANZICS CTG. 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. The members of the Working Party, Management Committee, participating sites, principal investigators, co-investigators and research coordinators are listed in the online Appendix, Section 1.

Competing interests

None declared.

Author details

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

The TARGET Management Committee (Appendix, Section 1) are responsible for the writing and content of this article

Correspondence: Patricia Williams; tricia.williams@sa.gov.au

References

- Heyland DK, Dhaliwal R, Drover JW, et al. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. *JPEN* 2003; 27: 355-73.
- McClave SA, Martindale RG, Vanek VW, et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN). *JPEN* 2009; 33: 277-316.
- Kreymann KG, Berger MM, Deutz NE, et al. ESPEN Guidelines on Enteral Nutrition: intensive care. *Clin Nutr* 2006; 25: 210-23.
- Nguyen N, Bryant LK, Burgstad C, et al. Delayed enteral feeding impairs intestinal carbohydrate absorption in critically ill patients. *Crit Care Med* 2011; 40: 50-4.
- MacFie J, Reddy BS, Gatt M, et al. Bacterial translocation studied in 927 patients over 13 years. *Br J Surg* 2006; 93: 87-93.
- Alberda C, Gramlich L, Jones N, et al. The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study. *Intensive Care Med* 2009; 35: 1728-37.
- Doig GS, Simpson F, Finfer S, et al. Effect of evidence-based feeding guidelines on mortality of critically ill adults: a cluster randomized controlled trial. *JAMA* 2008; 300: 2731-41.
- de Beaux I, Chapman M, Fraser R, et al. Enteral nutrition in the critically ill: a prospective survey in an Australian intensive care unit. *Anaesth Intensive Care* 2001; 29: 619-22.
- Finfer S, Chittock DR, Su SY, et al, NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009; 360: 1283-97.
- Villet S, Chiolero RL, Bollmann MD, et al. Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients. *Clin Nutr* 2005; 24: 502-9.
- Rubinson L, Diette GB, Song X, et al. Low caloric intake is associated with nosocomial bloodstream infections in patients in the medical intensive care unit. *Crit Care Med* 2004; 32: 350-7.
- Petros S, Engelmann L. Enteral nutrition delivery and energy expenditure in medical intensive care patients. *Clin Nutr* 2006; 25: 51-9.
- Taylor SJ, Fettes SB, Jewkes C, Nelson RJ. Prospective, randomized, controlled trial to determine the effect of early enhanced enteral nutrition on clinical outcome in mechanically ventilated patients suffering head injury. *Crit Care Med* 1999; 27: 2525-31.
- Heidegger CP, Berger MM, Graf S, et al. Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. *Lancet* 2013; 381: 385-93.
- Creutzberg EC, Wouters EF, Mostert R, et al. Efficacy of nutritional supplementation therapy in depleted patients with chronic obstructive pulmonary disease. *Nutrition* 2003; 19: 120-7.
- Singer P, Anbar R, Cohen J, et al. The tight calorie control study (TICACOS): a prospective, randomized, controlled pilot study of nutritional support in critically ill patients. *Intensive Care Med* 2011 37: 601-9.
- Rice TW, Wheeler AP, Thompson BT, et al, National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. *JAMA* 2012; 307: 795-803.
- Arabi YM, Aldawood AS, Haddad SH, et al. Permissive underfeeding or standard enteral feeding in critically ill adults. *N Engl J Med* 2015; 372: 2398-2408.
- Parikh HG, Miller A, Chapman M, et al. Calorie delivery and clinical outcomes in the critically ill: a systematic review and meta-analysis. *Crit Care Resusc* 2016; 18: 17-24.
- Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. *N Engl J Med* 2011; 365: 506-17.
- Braunschweig CA, Sheean PM, Peterson SJ, et al. Intensive nutrition in acute lung injury: a clinical trial (INTACT). *JPEN* 2015; 39: 13-20.
- Peake SL, Davies AR, Deane AM, et al. Use of a concentrated enteral nutrition solution to increase calorie delivery to critically ill patients: a randomized, double-blind, clinical trial. *Am J Clin Nutr* 2014; 100: 616-25.
- Ridgeon E, Bellomo R, Myburgh J, et al. Validation of a classification system for causes of death in critical care: an assessment of inter-rater reliability. *Crit Care Resusc* 2016; 18: 50-4.



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The National University Health System (NUHS) is an integrated Academic Health System and Regional Health System in Singapore that delivers value-driven, innovative and sustainable healthcare. Institutions in the NUHS group include three hospitals – National University Hospital, Ng Teng Fong General Hospital and Jurong Community Hospital; three National Specialty Centres – National University Cancer Institute, Singapore, National University Heart Centre, Singapore and National University Centre for Oral Health, Singapore; a polyclinic group – the National University Polyclinics; one medical centre – Jurong Medical Centre; and three academic health sciences institutions – National University of Singapore (NUS) Yong Loo Lin School of Medicine (including the Alice Lee Centre for Nursing Studies), NUS Faculty of Dentistry and NUS Saw Swee Hock School of Public Health.

Intensivist

The National University Heart Centre, Singapore is seeking candidates who are highly motivated and willing to join us for a challenging and fulfilling appointment as an Intensivist. Clinical responsibilities would be in the cardiothoracic intensive care unit, a 19 bed unit that looks after adult patients with cardiac, thoracic or vascular surgical problems. A full range of services, with the exception of transplantation, is offered including extracorporeal life support and echocardiography. Other clinical responsibilities would be individually negotiated depending on the skills and experience of the candidate, and might include working in other intensive care units of the hospital, in Anaesthesia or Medicine.

Candidates must possess a basic Medical Degree that can be registered with the Singapore Medical Council and recognised intensive care postgraduate qualifications. Commencing salary will be competitive, depending on qualifications and experience.

Successful candidates must possess a good record in clinical excellence and commitment to medical education and research. We are expanding our Department's services as well as research initiatives.

Please submit a full CV including personal particulars, names of 3 referees, professional qualifications, career history, e-mail address, telephone and fax numbers, and expected salary, together with medical testimonials and certificate of registration to:

Medical Affairs (HR) Department
National University Health System Pte Ltd
1E Kent Ridge Road, Singapore 119228
Fax: (65) 6779 7453. E-mail: medical@nuhs.edu.sg
Website: <http://www.nuhs.edu.sg>

(We regret that only shortlisted candidates will be notified.)

- 24 EuroQol Group. EuroQol — a new facility for the measurement of health-related quality of life. *Health Policy* 1990; 16: 199-208.
- 25 Ustün TB, Chatterji S, Kostanjsek N, et al. Developing the World Health Organization disability assessment schedule 2.0. *Bull World Health Organ* 2010; 88: 815-23.
- 26 Australian Bureau of Statistics. Labour Force Survey. Cat. No. 6202.0. Canberra: Commonwealth of Australia; 2014. <http://www.abs.gov.au/Ausstats/abs@.nsf/0/C8EA41B567B547C1CA257927000DBE89?OpenDocument> (accessed Dec 2017).
- 27 Clark MS, Bond MJ. The Adelaide Activities Profile: a measure of the life-style activities of elderly people. *Aging (Milano)* 1995; 7: 174-84.
- 28 Bond MJ, Clark MS. Clinical applications of the Adelaide Activities Profile. *Clin Rehabil* 1998; 12: 228-37.
- 29 Iwashyna TJ, Deane AM. Individualizing endpoints in randomized clinical trials to better inform individual patient care: the TARGET proposal. *Critical Care* 2016 20: 218.
- 30 Deane AM, Hodgson CL, Young P, et al. The rapid and accurate categorisation of critically ill patients (RACE) to identify outcomes of interest for longitudinal studies: a feasibility study. *Anaesth Intensive Care* 2017; 45: 476-84.
- 31 Brower RG, Matthay MA, Morris A, et al, Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; 342: 1301-8.
- 32 TARGET Investigators on behalf of the Australian and New Zealand Intensive Care Society Clinical Trials Group. Statistical analysis plan for the Augmented versus Routine Approach to Giving Energy Trial (TARGET). *Crit Care Resusc* 2018; 20: 15-21. □