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Protocol summary and statistical analysis plan for Intensive Nutrition Therapy comparEd to usual care iN criTically ill adults (INTENT): a phase II randomised controlled trial

Emma J Ridley ,[1,2] Michael Bailey,[1,3] Marianne Chapman,[4,5] Lee-anne S Chapple,[4,5] Adam M Deane,[3] Carol Hodgson,[1,6] Victoria L King,[1] Andrea Marshall,[7,8] Eliza G Miller,[1] SP McGuinness,[1,9] Rachael Parke,[9,10] Andrew A Udy,[1,6] and the Australian and New Zealand Intensive Care Society Clinical Trials Group

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For numbered affiliations see end of article.

Correspondence to
Dr Emma J Ridley;
emma.ridley@monash.edu

ABSTRACT

Introduction It is plausible that a longer duration of nutrition intervention may have a greater impact on clinical and patient-centred outcomes. The Intensive Nutrition care Therapy comparEd to usual care iN criTically ill adults (INTENT) trial will determine if a whole hospital nutrition intervention is feasible and will deliver more total energy compared with usual care in critically ill patients with at least one organ system failure.

Methods and analysis This study is a prospective, multicentre, unblinded, parallel-group, phase II randomised controlled trial (RCT) conducted in 23 hospitals in Australia and New Zealand. Mechanically ventilated critically ill adult patients with at least one organ failure who have been in intensive care unit (ICU) for 72–120 hours and meet all of the inclusion and none of the exclusion criteria will be randomised to receive either intensive or usual nutrition care. INTENT started recruitment in October 2018 and a sample size of 240 participants is anticipated to be recruited in 2022. The study period is from randomisation to hospital discharge or study day 28, whichever occurs first, and the primary outcome is daily energy delivery from nutrition therapy. Secondary outcomes include daily energy and protein delivery during ICU and in the post-ICU period, duration of ventilation, ventilator-free days, total bloodstream infection rate and length of hospital stay. All other outcomes are considered tertiary and results will be analysed on an intention-to-treat basis.

Ethics and dissemination Ethics approval has been received in Australia (Alfred Hospital Ethics Committee (HREC/18/Alfred/101) and Human Research Ethics Committee of the Northern Territory Department of Health (2019-3372)) and New Zealand (Northern A Health and Disability Ethics Committee (18/NTA/222). Results will be disseminated in an international peer-reviewed journal(s), at scientific meetings and via social media.

Trial registration number NCT03292237.

Strengths and limitations of this study

- This is the first randomised controlled trial to investigate the feasibility of a whole hospital nutrition intervention in critically ill patients.
- It is a multicentre study, increasing generalisability.
- It will test the methodology for providing a nutrition intervention in two distinct periods (in intensive care unit (ICU) and post-ICU).
- The overall concept and methodology could be applied in other populations if feasible.
- Due to the nature of the intervention, it is unblinded and this is a limitation.

INTRODUCTION

Nutrition is a commonly provided therapy in critical illness, but randomised controlled trials (RCTs) varying the amount of energy delivery have failed to demonstrate clinical benefit to date. Based on observational evidence only, best practice guidelines recommend delivery of energy and protein in amounts close to predicted requirements in critical illness. Despite these recommendations, the largest and most recent analysis of observational data from 923 hospitals and including 17 154 patients reported mean (SD) energy and protein adequacy from artificial nutrition of 56%±30% and 52%±30%, respectively, as part of standard care.[1] This is consistent with other international data sets.[2 3]

No difference in clinical outcomes have been shown in large RCTs investigating standard care energy provision compared with either energy provision matched to energy expenditure or trophic energy provision, and one has shown harm with greater energy provision using an estimated requirement.[4–7] A common characteristic of these trials is

the short nutrition intervention duration (provided for around 5–7 days) in the early period of critical illness. This is an important consideration for a nutrition intervention, where short-term provision in the early phase of illness may not plausibly affect outcomes.

The timing of nutrition delivery may be important for its impact. There is evidence that early delivery of some enteral nutrition (EN) is likely to have a number of benefits including on subsequent gut function, stress ulcer disease and possibly bacterial translocation.[8] Early delivery of EN to meet estimated energy requirements can result in gut dysfunction and glucose intolerance.[6] Later in intensive care unit (ICU) stay and throughout the subsequent hospital admission may be a time when the amount of energy and protein is important for recovery, with metabolism changing to allow exogenous nutrition to be processed. Although it is plausible that nutrition may be important, the limited data available indicate that both energy and protein intake during this period is worse than in the early ICU period for factors relating to patients, clinicians and system issues.[9–15] A cumulative energy deficit because of inadequate energy delivery after ICU discharge, coupled with the deficits observed during the ICU period, may be an explanation for the lack of benefit observed in critical care nutrition trials to date.

The Intensive Nutrition Therapy comparEd to usual care iN criTically ill adults (INTENT) trial aims to address this evidence gap, by determining if a whole hospital nutrition intervention is feasible and will result in the delivery of more total energy than usual care in critically ill adults.

METHODS AND ANALYSIS

Trial design, setting and population

INTENT is a multicentre prospective, unblinded, parallel, phase II RCT and will include 240 critically ill adult patients from 23 ICUs in Australia and New Zealand. Recruitment started 15 October 2018 with completion of primary recruitment expected in 2022. The reporting of the INTENT protocol follows the Standard Protocol Items: Recommendations for Interventional Trials checklist.[16] The INTENT research team comprises research coordinators/nurses, dietitians and intensivists at each participating site.

Screening, randomisation and blinding

Patients aged ≥18 years and who are between 72 and 120 hours of their index ICU admission will be screened for eligibility. Those who require invasive mechanical ventilation (MV), have at least one specified organ system failure and are at a nutritional deficit (<80% of energy provision for any reason via EN in the previous 24 hours) at the time of screening will be eligible for inclusion. Those that meet all the inclusion and none of the exclusion criteria and for whom consent is obtained (in Australia) will be randomised. The complete inclusion and exclusion criteria are listed in table 1.

Table 1 Eligibility criteria

Inclusion criteria	
Patients in intensive care who meet all of the following will be eligible:	
1.	Admitted to any intensive care unit for between 72 and 120 hours
2.	Receiving invasive ventilator support
3.	At least 18 years of age
4.	Have central venous access suitable for PN solution administration
5.	Have one or more organ system failure (respiratory, cardiovascular or renal) related to their acute illness defined as:
a)	$PaO_2/FiO_2 \leq 300$ mm Hg
b)	Currently on one or more continuous inotrope/vasopressor infusion which were started at least 4 hours ago at a minimum dose of: ► Norepinephrine≥0.1 mcg/kg/min ► Epinephrine≥0.1 mcg/kg/min ► Any dose of vasopressin ► Milrinone>0.1 mcg/kg/min
c)	Renal dysfunction defined as: ► Serum creatinine 2.0–2.9 times baseline or ► Urine output 0.5 mL/kg/hour for ≥12 hours or ► Currently receiving renal replacement therapy
d)	Currently has an intracranial pressure monitor or ventricular drain in situ
Exclusion criteria	
Patients will be excluded if:	
1.	Both EN and PN cannot be delivered at enrolment
2.	Currently receiving PN
3.	Clinician believes a specific parenteral formula is indicated
4.	Death is imminent in the next 96 hours or there is a current treatment limitation in place or the patient is unlikely to survive to 180 days due to underlying/chronic illness
5.	More than 80% of energy requirements have been satisfactorily delivered via the enteral route in the last 24 hours
6.	Dialysis dependent chronic renal failure
7.	Suspected or known pregnancy
8.	Product contraindication
9.	The treating clinician does not believe the study to be in the best interest of the patient

EN, enteral nutrition ; PN, parenteral nutrition.

The randomisation schedule was generated by the study statistician with an allocation ratio of 1:1, stratified by site and in permuted blocks of variable size (2 and 4). Randomisation occurs by INTENT research teams via a dedicated, secure, password protected internet-based website designed by Research Path Pty Ltd. An email notification is provided on randomisation of each participant

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to the INTENT research and project management team detailing the site of randomisation, the participants' study identification number, study energy requirement and treatment arm. The study period continues until hospital discharge, death or study day 28 (whichever occurs first). The flow of participants through the study is presented in figure 1.

Intervention and comparator

The intervention comprises delivery of an individualised intensive nutrition care strategy from randomisation to hospital discharge or study day 28, whichever occurs first, aiming for energy provision between 80% and 100% of predicted requirements at all times. In ICU, a previously tested, tailored supplemental parenteral nutrition (PN) intervention is provided whenever daily energy provision is less than 80% of the study energy requirement.[17] This is followed by a tailored, individualised nutrition intervention in the late ICU phase and onto the hospital ward, delivered by an INTENT dietitian and based on clinical indication. The comparator is usual nutrition care, with provision and management of nutrition care in accordance with local protocols at each site for the period of hospitalisation.

Determining energy requirements

To determine individual energy requirements, a standardised calculated body weight (CBW) is determined for the duration of the ICU stay. To determine CBW, actual or estimated weight and height are required to allow calculation of body mass index (BMI). Actual height will be used if available, otherwise it will be estimated using demi arm span.[18] CBW will equal actual body weight for participants with a BMI <25 kg/m^2 if under 65 years of age (or <30 kg/m^2 if aged ≥65 years). Otherwise, an adjusted body weight will be calculated per the method detailed in online supplemental appendix 1. Once set, the individualised energy requirement of 25 kcal/kg CBW will not be altered for the duration of the ICU admission (online supplemental appendix 2).

Interventional products

The interventional PN is Olimel N12E with a multitrace element solution (10 mL), multivitamin (Cernevit, Baxter Healthcare Corporation, 5 mL) and ascorbate (125 mg) for stability, manufactured and supplied by Baxter Healthcare Corporation (interventional PN composition is available in online supplemental appendix 3).

Once oral intake is started, two study oral nutrition supplements are prescribed per day to intervention participants (Fortisip Compact Protein or Forticreme Complete where a modified fluid product is required, manufactured by Nutricia Australia Pty Ltd). These are provided to sites within the study budget. The supplements are charted at a recommended dose of 60 mL four times per day or as appropriate for the participant. Study oral nutrition supplement composition is provided in online supplemental appendix 4.

ICU procedures common to both arms

Once randomised, the target rate (mL/hour) for continuous EN delivery is calculated by the treating clinical team to match the study energy requirement set by the database. The choice of EN formula, protein requirement estimation and management of blood glucose levels occurs in accordance with local hospital protocols. When participants are prescribed an oral diet, strict food record charts are to be completed. To increase compliance with completion of food record charts, the INTENT research team will provide regular reminders and bedside visits to patients and treating nursing staff, as well as request family assistance where appropriate. It will be recorded if the food record chart is incomplete despite these measures.

Intensive nutrition intervention in ICU

The intensive nutrition intervention is implemented by the bedside nurse, ICU medical team and clinical dietitians under the guidance of the INTENT research team.

Day of randomisation

The interventional PN is administered within 2 hours of randomisation at the rate determined by the study database, via a central venous catheter (including long-term central catheters if already in situ) or a peripherally inserted central catheter. Care of the line is per the participating hospital's usual procedure including schedule for removal or change. On the day of randomisation, the rate of interventional PN is based on the amount of energy received from EN in the previous 24 hours (figure 2a). EN must continue to be optimised and is not to be reduced based on the amount of interventional PN being administered in the first 24 hours. For every intervention participant, there are three available rates of interventional PN based on the study energy requirement from randomisation until ICU discharge (or removal of central access, whichever occurs first); off, rate based on 10 kcal/kg CBW/day, or rate based on 20 kcal/kg CBW/day.

Daily review for Intensive nutrition intervention

From study day 2 until ICU discharge, the amount of energy provided from EN, oral nutrition, glucose ≥25% and propofol in the previous 24 hours is entered into the study database at the same time each day by a member of the INTENT research team. The database calculates the proportion of the participants study energy requirements met in the previous 24 hours and determines the need for, and rate of, interventional PN delivery for the subsequent 24 hours, based on the three rates determined at randomisation (figure 2b). While in ICU, nutrition management for participants allocated to the intervention will aim to provide ≥80% of energy requirements and avoid overfeeding (defined as ≥110% of the study energy requirement). Participants are reviewed daily by the INTENT research team to ensure the nutrition management plan is appropriate, EN and interventional PN are being delivered correctly and the combination of EN and propofol is not leading to provision of ≥110% of the study

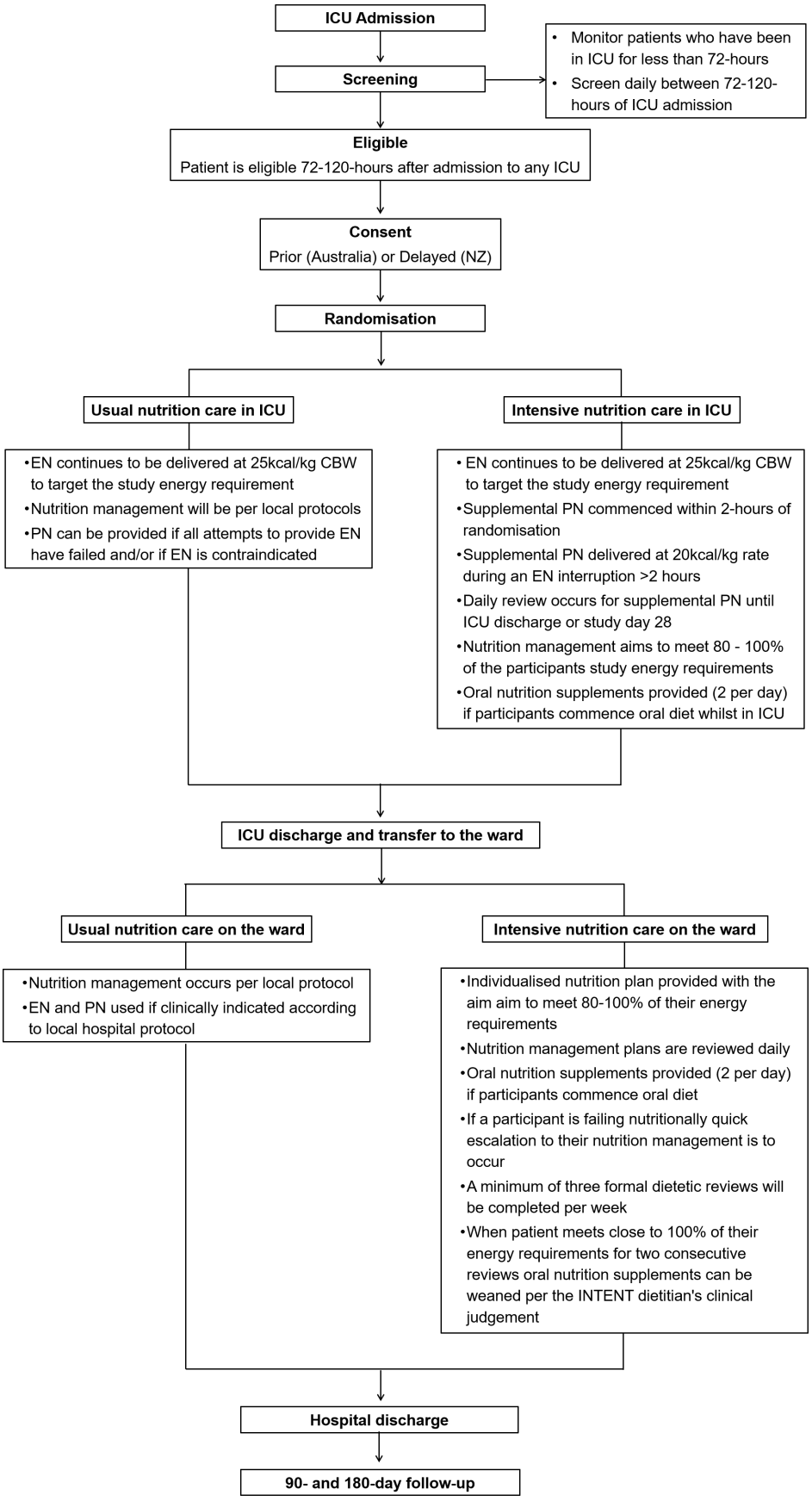

Figure 1 Study processes from screening to study completion. CBW, calculated body weight; EN, enteral nutrition; INTENT, Intensive Nutrition care Therapy comparEd to usual care iN criTically ill adults; EN, enteral nutrition; ICU, intensive care unit; NZ, New Zealand; PN, parenteral nutrition.

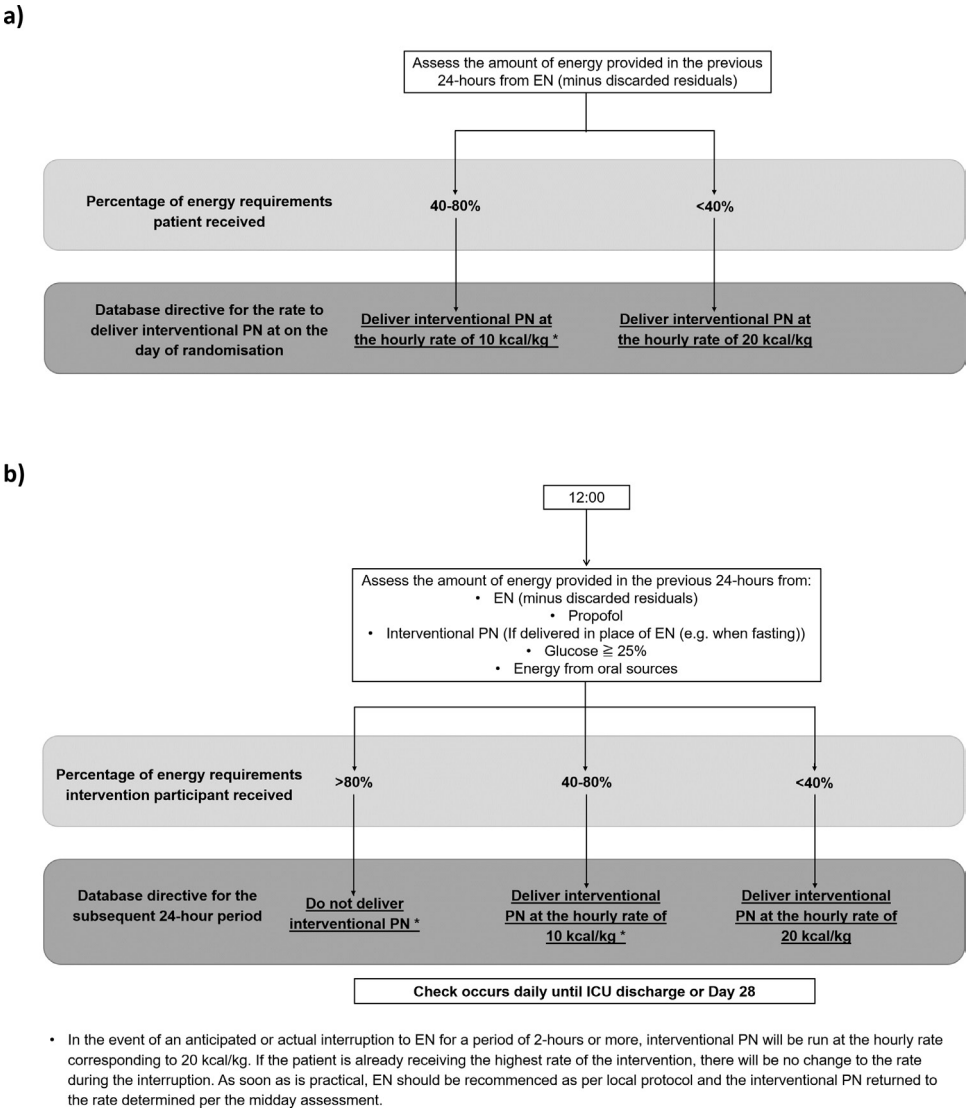

Figure 2 Management of interventional parenteral nutrition (PN) in the intensive nutrition care arm. (A) Determining the rate of interventional PN delivery on the day of randomisation. (B) Daily adjustment of interventional PN rate.
EN, enteral nutrition; PN, parenteral nutrition.

energy requirement. Interventional PN will continue at the set rate for the following 24 hours and will only be altered by the treating team when there is an interruption to EN or if deemed a safety concern as outlined in the study procedures.

Management of EN

Where an anticipated or actual interruption to EN occurs for a period of 2 hours or more, interventional PN is provided at the hourly rate corresponding to 20 kcal/kg CBW/day to minimise the energy deficit that accrues during interruptions to EN. If the participant is already receiving the highest rate of the intervention, the PN rate will not change during the interruption period. As soon as it is practical, EN is to be restarted as per local protocol and the interventional PN will revert to the rate determined by the midday assessment (figure 2b).

Where it is anticipated that EN will be required on the ward, it is recommended that a fine bore nasogastric tube (NGT) replace a wide bore NGT at time of tracheal extubation for participant comfort and to enable energy delivery from all sources be maintained at 80%–100% of requirements during this transition period. Final decisions regarding this treatment are at the discretion of the treating team and reasons for clinician or participant refusal are collected.

Strategies to minimise the risk of overfeeding in the intensive nutrition arm

Safety features of the intervention to minimise the risk of overfeeding include:

- Energy requirements are set using an adjusted body weight for participants who are overweight or obese (online supplemental appendix 1).
- Inclusion of all energy sources (EN, propofol, glucose (>25%), any oral nutrition, and PN delivered during any EN interruption(s)) when determining the daily need for interventional PN following randomisation.

- The maximum amount of energy provided by the interventional PN is 20 kcal/kg CBW/day or equivalent to 80% of the study energy requirement.
- Revision of EN rates to ensure 80%–100% of the participants' study energy requirement is provided where propofol and EN collectively provide >110% of the participants study energy requirements.

Cessation of the interventional PN

Provision of the interventional PN ceases when the participant no longer has access for PN delivery (determined by the treating medical team based on local practice) or on ICU discharge (whichever occurs first). If PN is clinically indicated following ICU discharge, the decision is at the discretion of the treating clinical team and the formula will change to the hospital's usual PN solution.

Start of oral intake

Oral diet will start in the intervention arm according to usual practice at the site with two study oral nutrition supplements prescribed per day. Additional oral nutrition supplements can be added at the study dietitian's discretion where the participant is meeting <80% of their study energy requirements from all sources. When EN is received with oral diet, EN will be titrated to prevent overfeeding and can be ceased when oral intake (including oral supplements) provides >75% of energy requirements for at least 48 hours.

Escalation of nutrition care

After cessation of the interventional PN, escalation of nutrition care may occur at any time when energy intake drops below 80% of the study requirement. Escalations include (but are not limited to) modification of the diet prescription and/or addition of oral nutrition supplements and/or insertion of an NGT and recommencement of EN. Recommencement of the interventional PN may be requested where all other options have been exhausted and energy intake has not improved above 80% of the study requirement. The choice of escalation will be based on available site options, be clinically appropriate for the individual participant and implementation at the discretion of the treating team. Reasons for clinician or participant refusal are collected.

ICU discharge and transfer to the ward

An INTENT nutrition discharge summary will be completed for all intervention participants within 48 hours of ICU discharge and will form part of the patient handover documentation between ICU and the treating medical team on the ward (online supplemental appendix 5).

Usual care arm in ICU

Participants allocated to the usual care arm will start or continue to receive EN via an NGT at a rate of 25 kcal/kg CBW/day, with the aim to provide the individualised study energy requirement. All other aspects of nutrition therapy provision will occur in accordance with local hospital protocols, including NGT management. Every attempt is to be made based on usual practice at the site to obtain adequacy of EN prior to the use of PN. If these strategies fail or an absolute contraindication to EN develops, the interventional PN will be provided with the aim to provide the individualised study energy requirements. Similar to intervention participants, and with the aim of preventing overfeeding, it is recommended that the rate of EN be lowered where propofol and EN collectively provide >110% of the participants' study energy requirement.

Ward procedures common to both arms

After ICU discharge and transfer to the hospital ward, the energy requirement set at randomisation can continue to be followed or a new requirement can be estimated by clinical staff. The choice of EN formula, rate of delivery, protein requirement estimation, management of blood glucose levels and NGT care will occur per local protocols. The decision to start or continue PN in either arm is at the discretion of the treating clinical team and the formula prescribed will be the hospital's usual PN solution. When oral diet commences, strict food record charts will be completed for all participants with documentation including diet code prescription, diet satisfaction, meal provision and consumption and nutrition impacting symptoms where <50% of a participant's study energy requirement is consumed orally (up to three symptoms per day). To increase compliance with the completion of food record charts, the same strategies implemented by the INTENT research team in ICU will be implemented on the ward (refer to the ICU procedures common to both arms section).

Intensive nutrition care ward management

During the post-ICU period, the objective of the intervention is to provide ≥80% of study energy requirements on all study days without overfeeding. The recommendation is to continue EN on the hospital ward while oral intake is being established, with any other form of nutrition therapy provided when safe and clinically appropriate (including oral diet fortification, oral supplements, and/or PN). If oral diet has not started in ICU, two study oral nutrition supplements will be prescribed per day on commencement. EN should be titrated and ceased when oral intake (including oral supplements) provides >75% of energy requirements for 48 hours as determined by the INTENT dietitian.

Participants are to be reviewed daily by the INTENT dietitian to ensure the nutrition management plan is appropriate and no escalations in care are required (with a minimum of three formal nutrition reviews for data collection per week). Escalations to nutrition care will be completed where a participant is failing to meet 80% of their study energy requirements. Such escalations may include, but are not limited to, prescribing an additional oral nutrition supplement(s), food fortification

or modification of the diet prescription, and/or recommencement of EN or PN.

Study oral nutrition supplements and any other hospital provided supplements may be titrated or ceased if oral intake provides approximately 100% of energy requirements for two consecutive reviews at the discretion of the INTENT dietitian.

Usual care ward management

All aspects of nutrition care are according to local protocols including timing and frequency of nutrition reviews, escalation of care and removal/reinsertion of NGTs.

Outcomes

Primary outcome: Daily energy delivered from nutrition therapy

Secondary outcomes:

- Nutrition intake
  - Daily protein intake
  - Energy and protein intake by location (ICU and ward)
- Duration hospital stay (survivors and non-survivors)
- Ventilator-free days (VFDs) at study day 28
- Total blood stream infection rate

Tertiary outcomes:

- Duration of ICU stay (survivors and non-survivors)
- Duration of MV to study day 28 (survivors and non-survivors)
- ICU mobility scale at ICU discharge
- Blood stream infections:
  - Number of blood stream infections to day 28
  - Time to any blood stream infection
- In-hospital and 28-day mortality
- Weight at hospital discharge
- Cost per quality-adjusted life year (QALY)
- Cost per life year gained (LYG)
- 90-day and 180-day outcomes
  - Survival
  - Health-related quality of life (assessed using the European Quality of Life 5 Dimension 5 Level questionnaire (EQ-5D-5L), European Quality of Life Visual Analogue Scale (EQ VAS), World Health Organisation Disability Assessment Schedule 2.0: 12-item version (WHODAS 2.0)
  - Frailty as assessed by the Clinical Frailty Score
  - Additional healthcare resource utilisation

Follow-up will be conducted by study research personnel from the hospital of participation either via telephone, or in person if the participant is attending an outpatient appointment. Participants may also be contacted for follow-up through the post if the previous two methods of contact are unsuccessful.

Sample size and power

A recent study conducted in six ICUs in Australia and New Zealand enrolling 100 patients using a similar inclusion and exclusion criteria and coordinated by the Australian and New Zealand Intensive Care Research Centre (ANZIC-RC) found that the mean (SD) energy delivered to the standard nutrition arm throughout their hospital stay (median 22 days) was 1540 (410) kcal/day.[17] Based on a minimum acceptable clinical difference of 15% (215 kcal/day), with 190 subjects, this study will have a 95% power (two-sided p value of 0.05). To account for a potential loss to follow-up of 20% due to the longitudinal nature of the study intervention, the sample size has been inflated to recruit a total of 240 participants (120 in each group). This loss to follow-up rate is based on previous work conducted by the investigators and has been observed in other studies with longitudinal follow-up.[14 17 19]

Statistical analysis plan

Statistical analysis will be performed on a modified intention-to -basis excluding only participants who withdraw consent. While formal comparison of baseline variables will not be presented, to establish baseline imbalance for sensitivity analyses, informal comparisons will be performed using χ^2 tests for equal proportion, Student's t-test for normally distributed outcomes and Wilcoxon rank-sum tests otherwise with results reported as numbers (percentages), means (SD) or medians (IQR), respectively.

Longitudinal analysis of daily total energy (and protein) will be performed using hierarchical mixed linear modelling with patients nested within sites and patients and sites treated as random effects, fitting main effect for treatment and time and an interaction between the two to determine if treatment behaves differently over time, with results reported as least square means (95% CI). To determine if total energy (or protein) differs significantly between pre and post ICU discharge, a dichotomous variable for location (ICU or ward) will also be included in the model with heterogeneity determined by fitting an interaction between treatment and location. Sensitivity to baseline imbalance will be performed using covariate adjustment for known covariates (age, BMI, clinical frailty score, admission diagnosis, illness severity) and imbalanced variables ($p<0.2$), while sensitivity to missingness will be performed using multiple imputation.

Segmented linear regression (interrupted time series) will further be used to evaluate whether there is a stepwise change in the daily total energy intake before and after ICU discharge, and whether there was a difference in the rate of change of energy delivery before and after ICU discharge. Autocorrelation between consecutive days will be determined using a Durban Watson test and where there is evidence of significant autocorrelation ($p<0.05$), an appropriate autoregressive error structure will be employed.

Times to extubation, ICU discharge and hospital discharge will be analysed using frailty models (Cox proportional hazards regression with robust errors clustered at a site level) to account for the competing risk of death with results reported as sub-distributional hazard ratios (95% CI) and presented as cumulative incidence

graphs with comparison using Gray's test. Model assumptions will be assessed through the analysis of the Schoenfeld residuals against time.

Binomial outcomes (mortality and infections) will be assessed using hierarchical generalised modelling with relative risk (95% CI) determined using a binomial distribution with an identity link and ORs (95% CI) determined using a logistic binomial model.

Patient survival will be analysed using Cox proportional hazards regression including clustering for site with results reported as HRs (95% CI) and presented as Kaplan-Meier survival curves with comparison using a log-rank test.

Continuous longitudinal data (EQ-5D-5L, EQ VAS and WHODAS 2.0) will be analysed using the hierarchical mixed modelling process previously described with results presented as least square means (95% CI) and differences (95% CI).

VFDs and ICU mobility at discharge will be compared between groups using hierarchical quantile regression with results reported as median (IQR) and difference of medians (95% CI).

Frailty trajectory will be determined for each patient using linear regression fitted to baseline, day 90 and day 180 clinical frailty scores. Differences in trajectory will then be compared using hierarchical linear or quantile regression in accordance with the underlying distribution.

Where sufficient data exist, subgroup analysis will be performed for the primary outcome on four subgroups determined at baseline:

- High risk of malnutrition defined as a score of 2 or more using the Malnutrition risk assessment (MUST).[20]
- Frailty at baseline (dichotomised by Clinical Frailty Score 1–4 and 5–8).
- Age>65 years.
- Cardiac surgery at ICU admission.

Heterogeneity between subgroups will be determined by fitting main effects for treatment, subgroup and an interaction between treatment and subgroup, with results reported as forest plots.

Longitudinal analysis of binomial process of care measurements will be performed using logistic regression with robust SEs clustered at individual patient level and results reported as odds ratios (95% CI).

Analysis will primarily be performed using SAS V.9.4 (SAS Institute) and a two-sided p value of 0.05 will be used to indicate statistical significance. No adjustment will be made for multiple comparisons with all non-primary outcomes considered as hypothesis generating.

A formal economic evaluation will be conducted. The primary cost-effectiveness analysis will be conducted from the Australian healthcare payer's perspective using an analytical time horizon of 180 days. Costs will be determined by multiplying resource use by cost using local site costs where available or published national resource costs otherwise (eg, ICU bed day cost, ward readmissions and staffing costs). QALYs will be calculated using information from the EQ-5D-5L and EQ VAS collected at 90-day and 180-day post randomisation, combined with information on vital status. We will present the overall ICU costs, ward costs and total costs, including the intervention costs as means and SD. Total QALYs to 180 days will be presented as means and SD. Incremental cost-effectiveness ratios will be calculated, including the cost per additional QALY and cost per LYG for the intensive nutrition care arm compared with usual nutrition care. To increase the robustness of the sampling distribution, we will use non-parametric bootstrapping with unrestricted random sampling to produce cost and effectiveness replications, and confidence intervals for the cost-effectiveness ratios. These will be represented graphically on a cost-effectiveness plane. In addition, each QALY will be valued at a willingness to pay threshold for a QALY gain of $50 000, in conjunction with the costs of each treatment strategy to report the incremental net benefits of intensive nutrition care compared with usual nutrition care. We will also present the data on a cost-effectiveness acceptability curve to enable determination of cost-effectiveness at various willingness to pay thresholds.

Presentation of outcome data

Table 2 lists the proposed tables and figures for inclusion in the main manuscript, and online supplemental appendix 6 presents the proposed table format and variables. Figure 3 presents how the flow of participants through the study will be reported. Outcome data at 90 and 180 days and the economic evaluation will be published separately from the primary publication.

Data collection and management

This trial is coordinated by ANZIC-RC, Monash University, Melbourne, Australia. A site research staff training session will be held for all sites by the project manager and chief investigator prior to the initiation of the study and dedicated study tools provided to participating sites to support the implementation of the protocol and associated study procedures. All study-related data will be collected by trained site research staff and entered in the web-based case report form by site research staff. Data collection will continue until study day 28, hospital discharge or death (whichever occurs first). Automatic validation occurs in the web-based case report form to ensure accuracy of data entered with ad hoc checks of data also performed by the project manager. These checks will be supplemented by monitoring visits by trained project managers from the coordinating centre. All sites will receive an initial monitoring visit after two to four patients have been recruited (at least one in each study arm) where 100% source data will be verified. Additional monitoring visits will be completed based on recruitment rates and any identified issues which need review. It is preferred that monitoring visits are conducted on site, but due to the COVID-19 pandemic, some of this process may need to be conducted remotely. A full list of the data being collected is shown in table 3.

Table 2 Planned tables and figures

Proposed tables and figures for the main manuscript	
Table 1	Baseline participant characteristics
Table 2	Daily nutrition delivery, process and intervention data over the 28-day study period
Table 3	Energy and protein delivery by location over the 28-day study period
Table 4	Clinical outcomes over the 28-day study period
Figure 1	CONSORT diagram
Figure 2	Daily energy delivery for duration of the 28-day study period: (A) Energy from nutrition only (kcal); (B) Energy from nutrition (kcal/kg CBW/day); (C) Energy from all sources (kcal); (D) Energy from all sources (kcal/kg CBW/day).
Figure 3	Daily protein delivery for the duration of the 28-day study period: (A) Grams delivered; (B) g/kg CBW/day.
Proposed tables and figures for the online supplemental appendix of the main publication	
Online supplemental table S1	Extended baseline participant characteristics
Online supplemental table S2	Daily extended nutrition information, energy and protein delivery over the 28-day study period
Online supplemental table S3	Daily extended clinical information, energy and protein delivery in ICU
Online supplemental table S4	Daily extended clinical information, energy and protein delivery on the ward
Online supplemental table S5	Nutrition process and intervention data over the 28-day study period
Online supplemental table S6	Nutrition process and intervention data in ICU
Online supplemental table S7	Nutrition process and intervention data on the ward
Online supplemental table S8	Extended clinical data over the ICU period
Online supplemental table S9	Extended outcome data
Online supplemental figure S1	Daily energy delivery for duration of the 28-day study period: (A) energy from nutrition only (kcal/kg actual body weight/day); (B) Energy from all sources (kcal/kg actual body weight/day)
Online supplemental figure S2	Daily energy delivered by location (ICU and ward): (A) Energy from nutrition only (kcal); (B) Energy from nutrition (kcal/kg CBW/day); (C) Energy from all sources (kcal); (D) Energy from all sources (kcal/kg CBW/day)
Online supplemental figure S3	Daily protein delivery by location (ICU and ward): (A) Grams delivered; (B) g/kg CBW/day; (C) g/kg actual body weight/day
Online supplemental figure S4	Kaplan-Meier survival curve
Online supplemental figure S7	Segmented regression-energy delivery over time
Online supplemental figure S6	Cumulative incidence for time to extubation, time to ICU discharge and time to hospital discharge.
Online supplemental figure S7	Forest plot for subgroups: (A) High risk of malnutrition; (B) Frailty at baseline; (C) Age >65 years; (D) Cardiac surgery at ICU admission

CBW, calculated body weight; CONSORT, Consolidated Standards of Reporting Trials; ICU, intensive care unit; REMOVE, REMOVE.

The INTENT management committee are responsible for the conduct of the trial. Monthly teleconferences are held to monitor study progress, quality of conduct, site issues and discuss any adverse or serious adverse events. Sites are further supported by either onsite, web-based or teleconference meetings with the chief investigator and/or project manager through the recruitment period.

Data safety monitoring committee

As this is a phase II RCT with energy delivery as the primary outcome, no interim analysis will be conducted and there are no stopping rules for feasibility. A data safety monitoring committee (DSMC) has been formed to act as an advisory body to the INTENT management committee, to safeguard the interests of trial participants, assess the safety of the interventions during the trial and for monitoring the overall feasibility and conduct of the trial. This includes approval/review of the study protocol, all protocol amendments and reported serious adverse events (SAEs). A safety and protocol compliance report was provided and accepted by the DSMC after the first 12 months of recruitment. Reports will be provided after 150 participants have 28 days of data collected (or 12 monthly, whichever occurs first).

Adverse events

Events that are part of the participants' natural history of the primary disease process or which are expected complications of critical illness will not be reported as SAEs. This practice is consistent with recommendations

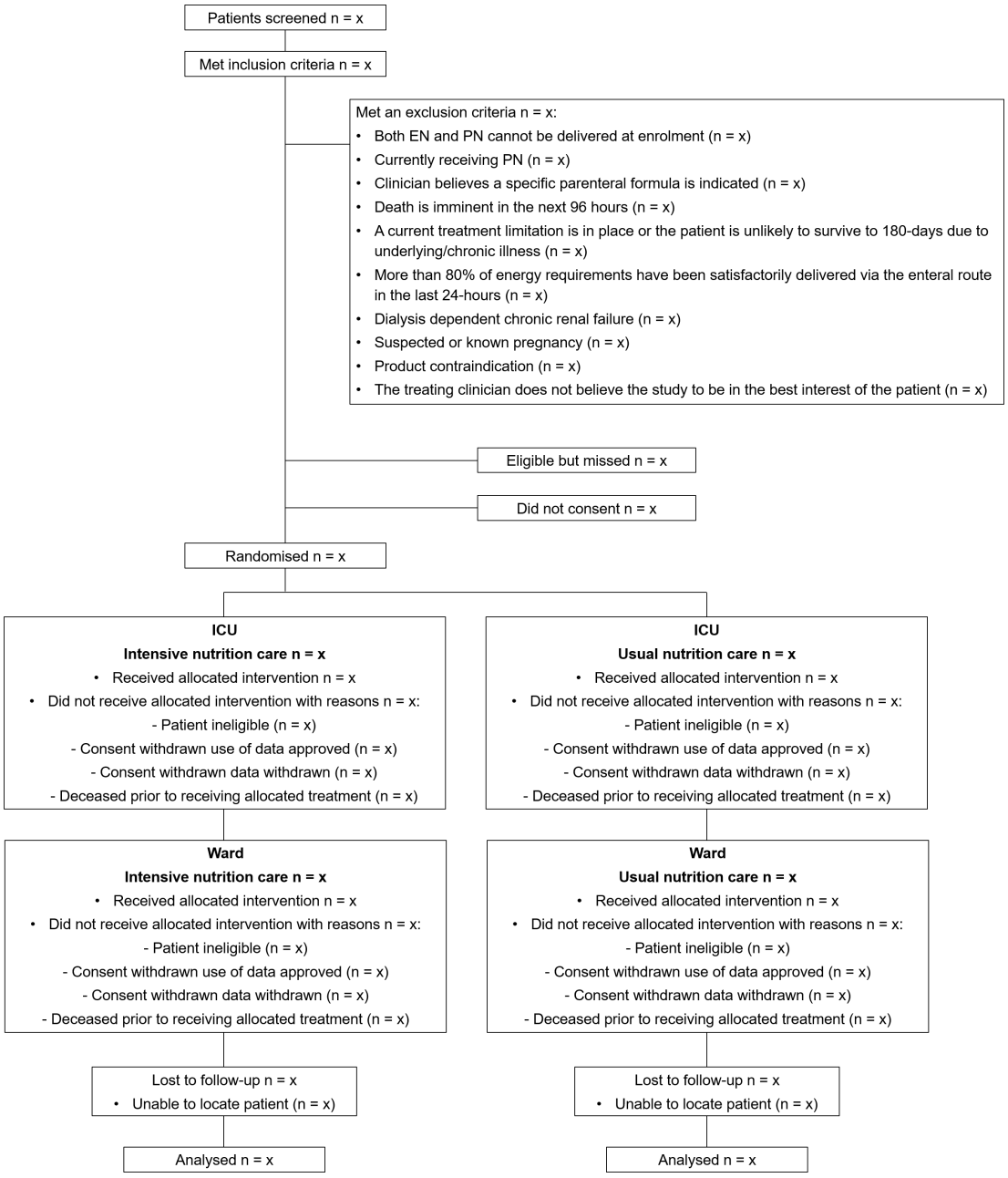

Figure 3 Proposed reporting of the flow of participants through the trial. ICU, intensive care unit.

specific to adverse event reporting in trials including critically ill participants.[21] All SAEs considered to be potentially causally related to the study intervention or are of concern in the investigator's judgement will be reported to Baxter Healthcare Corporation (the funding body), the respective ethics committee and the DSMC.

Protocol deviations

Prespecified protocol deviations will be categorised into major and minor (table 2). Major protocol deviations include (1) patients randomised but deemed ineligible; and (2) delivery of the incorrect rate of PN resulting in greater than 120% of a participants' energy requirements met.

Changes to the protocol

The original protocol was approved on 31 July 2018. A minor protocol amendment which consisted of minor wording changes and improvements for clarity was approved on 8 January 2020. A further protocol amendment that consisted of reclassifying selected secondary outcomes as tertiary outcomes was approved on 10 December 2020. The approved amended protocol (Version 1.2, 27 October 2020) was disseminated to all participating sites following its approval.

Patient and public involvement

This trial addresses several of the major existing evidence gaps in critical care nutrition, as outlined in a recent

Table 3 Table of events: intensive nutrition intervention and usual nutrition care arms

Data collected	Baseline	Day 1 —ICU D/C	Days 3, 7, 14, 21, 28	Days 7, 14, 21, 28	ICU D/C	Ward	Hospital D/C	90-day and 180-day follow-up
Screening, patient demographics and baseline data*	X							
SOFA	X		X					
Biochemistry†	X			X				
ICU daily data‡		X						
ICU discharge information§					X			
Ward data¶						X		
Weekly data**				X				
Hospital discharge information††					X			
Follow-up data‡‡								X
Escalations to nutrition care for intervention patients	All requested escalations to nutrition care for intervention patients should be recorded every day until hospital discharge, regardless of whether they were conducted or not							
Adverse events/serious adverse events	Description, timing, causality and resolution of adverse events from randomisation until day 90							
Protocol deviations	Major protocol deviations: ► Randomisation of ineligible patient ► Greater than 120% of an intervention participants study energy requirements delivered due to an incorrect rate of interventional PN provided Minor protocol deviations: ► Non-interventional PN being provided when interventional PN should have been provided ► Interventional PN not commenced within 2 hours of randomisation ► Incorrect rate of interventional PN provided ► Interventional PN not provided during a fasting period ► Study oral nutrition supplements not prescribed when oral diet commenced ► Study energy requirement not targeted (EN delivered higher than 25 kcal/kg CBW) ► Failure to complete the daily nutrition review in ICU ► <3 days of data collected per week on the ward							

X denotes must be collected on specified time point.
*Screening, patient demographics and baseline data: Patient and nutrition characteristics collected at screening will include: length of stay in the intensive care unit; patient initials; gender; height; weight; date of birth; enteral nutrition volume delivered during the 24 hours prior to screening. Patient information collected at baseline: Location prior to admission; ICU, hospital and time and date of commencement of mechanical ventilation; Acute Physiology and Chronic Health Evaluation (APACHE) II score; APACHE III diagnosis; comorbidities; Clinical Frailty Score; Malnutrition Universal Screening Tool; commencement of renal replacement therapy prior to randomisation; date and time of first central access insertion and other central access lines; energy and protein provision from hospital admission to time of randomisation; usual living location; Ethnicity (New Zealand sites only).
†Biochemistry variables if measured as part of routine practice: alanine aminotransferase; gamma-glutamyl transferase; alkaline phosphatase; bilirubin; triglycerides.
‡ICU daily data: Nutrition data: Study energy and protein requirements; energy and protein from nutrition and energy from non-nutrition sources; causes of and periods of fasting or interruptions to EN; if receiving oral diet: diet code and diet satisfaction, prescription and consumption of study oral nutrition supplements (intervention participants) and any other prescribed oral nutrition supplements (including intolerance issues), nutrition impacting symptoms if <50% of the intended oral intake was consumed. Clinical data: prokinetics; morning blood glucose and number of episodes of hypoglycaemia; units of insulin delivered; renal replacement therapy; changes in central line or new central access insertions; infectious complications; invasive mechanical ventilation.
§ICU discharge: nutrition data: mode of nutrition delivery; completion of INTENT nutrition discharge summary (intervention participants only). Clinical data: Survival; length of mechanical ventilation; ICU mobility scale; postdischarge location.
¶Ward data: nutrition data: study energy and protein requirements; energy and protein from nutrition; mode of nutrition and volumes where appropriate; if receiving oral diet: diet code and diet satisfaction, prescription and consumption of study oral nutrition supplements (intervention participants) and any other prescribed oral nutrition supplements (including intolerance issues), nutrition impacting symptoms if <50% of the intended oral intake was consumed; causes of and periods of fasting or interruptions to EN. Clinical data: weight (if recorded); use of antimemetics/antinausea medications; infectious complications.
**Weekly data: number of dietetic reviews per week (both groups); time spent implementing on the ward (intervention patients only).
††Hospital discharge: nutrition data: mode of nutrition delivery at discharge; length of time EN and PN delivered. Clinical data: survival; postdischarge location; weight; length of stay (ICU, ward hospital)
‡‡90-day and 180-day post randomisation: survival; Clinical Frailty Score; European Quality of Life 5 Dimension 5 Level and European Quality of Life Visual Analogue Scale; World Health Organisation Disability Assessment Schedule 2.0: 12-item version; resource utilisation.
CBW, calculated body weight; D/C, Discharge; ICU, intensive care unit; PN, parenteral nutrition; SOFA, Sequential organ failure assessment.

intensive care research agenda in nutrition and metabolism.[4] Patients have not been involved in the development of this trial. However, this trial will hopefully inform a programme of research that will evolve and assess both patient and clinician acceptability of the intervention, and patient opinion of nutrition and aspects of nutrition care following critical illness. Inclusion of patients and carers is critical in generation of evidence in this area.

ETHICS AND DISSEMINATION

In Australia, this study has been approved by the Alfred Hospital Ethics Committee (HREC/18/Alfred/101) and the Human Research Ethics Committee of the Northern Territory Department of Health (2019-3372). In New Zealand, the New Zealand Central Health and Disability Ethics Committee (18/NTA/222/AM01) reviewed and approved this study.

Patients will be unable to provide informed consent prior to randomisation/enrolment. Accordingly, the patient's medical treatment decision maker (relative/friend) or legal surrogate will be approached to provide consent for the patient to participate prior to enrolment in the study. In New Zealand, the respective ethics committee has approved the use of a deferred consent

model. Family/Whanau are approached as soon as possible to inform them about study enrolment and to seek their views on whether or not the patient would be agreeable to being included in the research study. In both countries, the patient will be approached to give consent for continued participation in the trial if they recover the ability to do so and the timing is appropriate. The master information and consent forms are available in online supplemental appendix 7. Results will be disseminated in international peer-reviewed journal(s), scientific meetings and via social media.

Author affiliations
[1]Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Department of Epidemiology and Preventative Medicine, Monash University, Melbourne, Victoria, Australia
[2]Nutrition Department, The Alfred Hospital, Melbourne, Victoria, Australia
[3]Department of Medicine and Radiology, University of Melbourne, Royal Melbourne Hospital, Parkville, Victoria, Australia
[4]Discipline of Acute Care Medicine, University of Adelaide, Adelaide, South Australia, Australia
[5]Intensive Care Unit, Royal Adelaide Hospital, Adelaide, South Australia, Australia
[6]Intensive Care Unit, The Alfred Hospital, Melbourne, Victoria, Australia
[7]Acute and Complex Care, Gold Coast Hospital and Health Service, Southport, Queensland, Australia
[8]Menzies Health Institute Queensland, Griffith University, Gold Coast Campus, Southport, Queensland, Australia
[9]Cardiothoracic and Vascular Intensive Care Unit, Auckland City Hospital, Auckland, New Zealand
[10]School of Nursing, The University of Auckland, Auckland, New Zealand

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Contributors EJR developed the original concept; EJR, MB, MC, LSC, AMD, CH, VLK, AM, EGM, SPM, RLP and AAU contributed to the design of the research and final protocol; EJR, EGM and VLK drafted the the first version of the paper; EJR, MB, MC, LSC, AMD, CH, VLK, AM, EGM, SPM, RLP and AAU contributed to further drafting and reporting of the protocol publication; MB is the study statistician and developed the statistical analysis plan; EJR, MB, MC, LSC, AMD, CH, VLK, AM, EGM, SPM, RLP and AAU approved the final manuscript.

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ORCID iD
Emma J Ridley http://orcid.org/0000-0002-7922-5717

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