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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

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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 17154 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

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

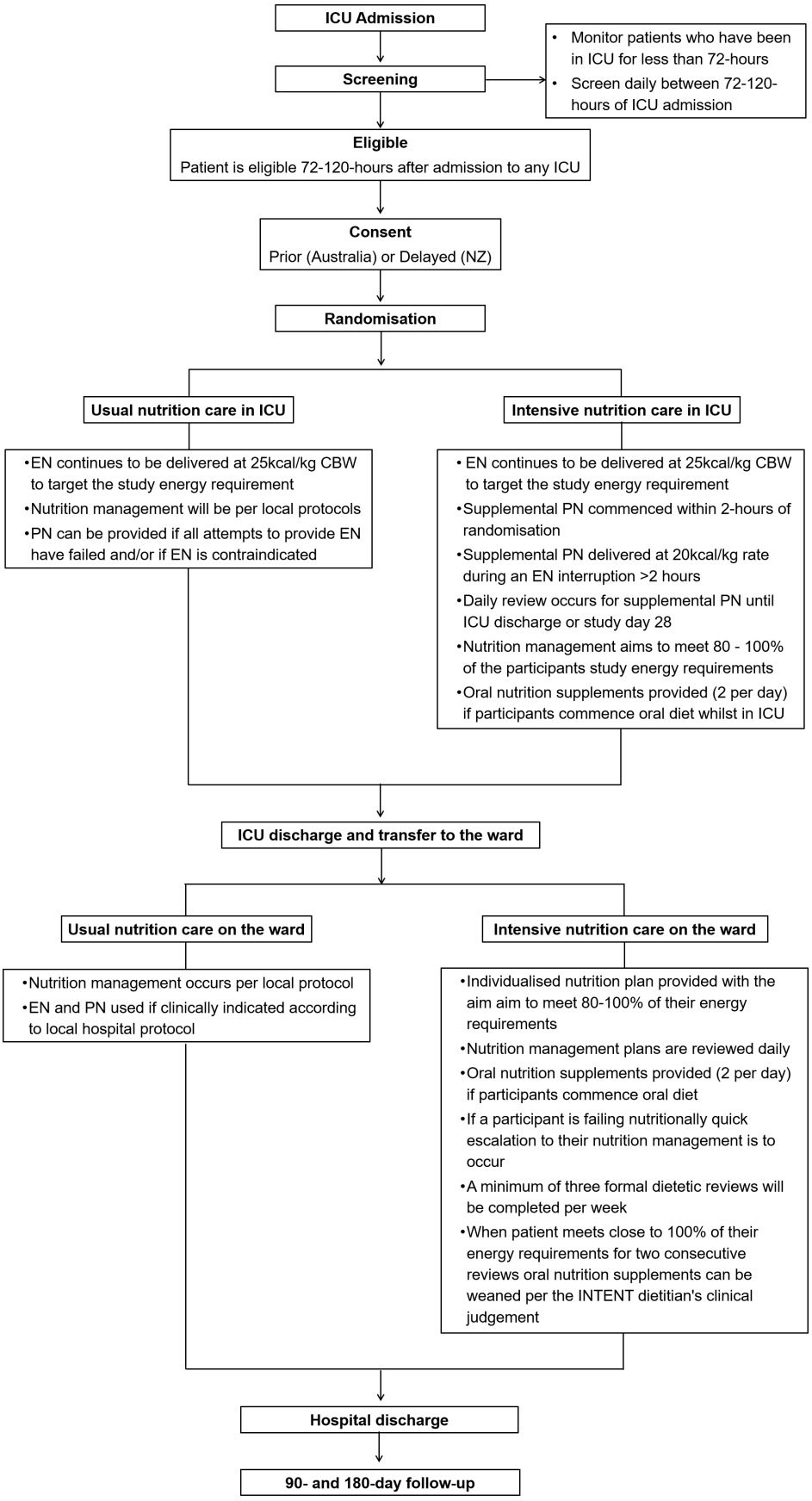

Figure 1 Study processes from screening to study completion. CBW, calculated body weight; EN, enteral nutrition; INTENT, Intensive Nutrition care Therapy comparEd to usual care iN criTically ill adults; EN, enteral nutrition; ICU, intensive care unit; NZ, New Zealand; PN, parenteral nutrition.

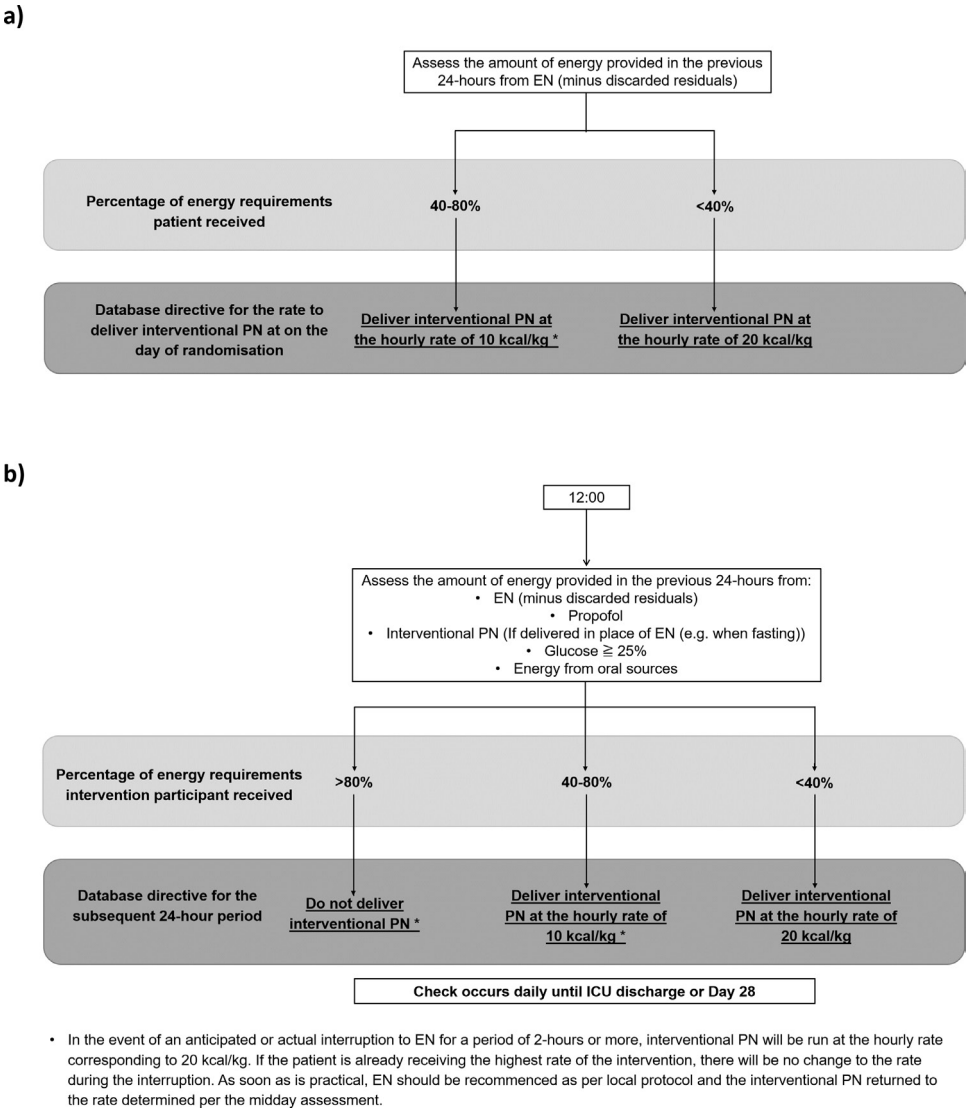

Figure 2 Management of interventional parenteral nutrition (PN) in the intensive nutrition care arm. (A) Determining the rate of interventional PN delivery on the day of randomisation. (B) Daily adjustment of interventional PN rate.
EN, enteral nutrition; PN, parenteral nutrition.

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

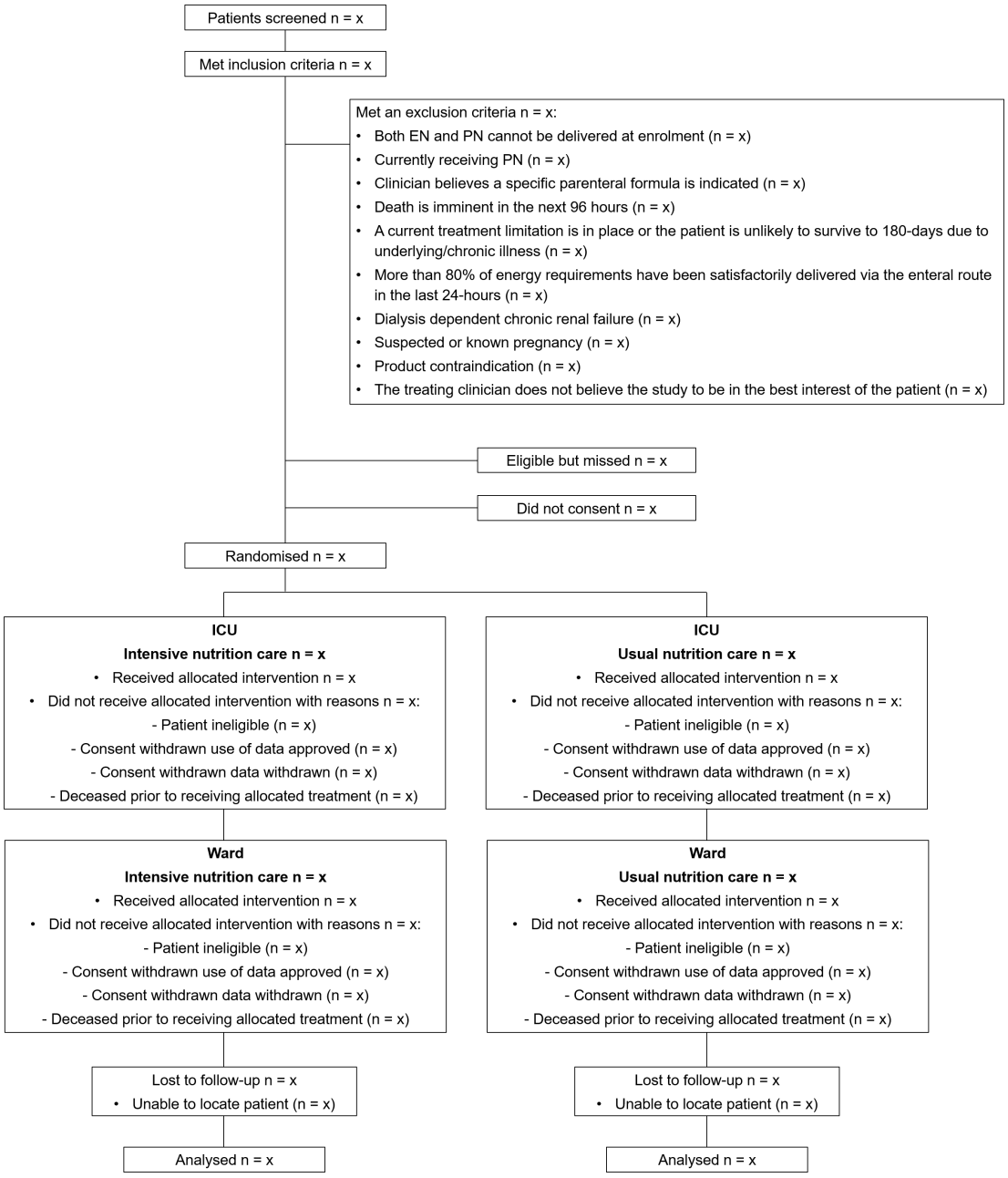

Figure 3 Proposed reporting of the flow of participants through the trial. ICU, intensive care unit.

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.

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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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Competing interests EJR has received honorarium from Baxter Healthcare (USA and Australia), Nestle and Nutricia (Australia). EJR is supported by a National Health and Medical Research Council (NHMRC) Emerging Leadership Fellowship. LSC is supported by a NHMRC Early Career Fellowship and has received honorarium from Nutricia (Australia and Global) and Fresenius Kabi. The institution that MC is employed by has received research funding for her work from Baxter Healthcare, Fresenius Kabi, Nutricia, Takeda and Theravance, unrelated to this study. The institution that AMD is employed by has received funding from Baxter Healthcare and Fresenius Kabi unrelated to this study. CLH is supported by a National Heart Foundation Fellowship and a National Health and Medical Research Council (NHMRC) Investigator Grant. APM has received honorarium from Baxter Healthcare (Australia) and received in-kind support from Danone (Australia) for work unrelated to this study. AAU is supported by a NHMRC Early Career Fellowship, and has received honorarium from Baxter Healthcare (Australia), in addition to in-kind support (trial consumables) from Integra Lifesciences, for work unrelated to this study.

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REFERENCES

1 Ridley EJ, Peake SL, Jarvis M, *et al*. Nutrition therapy in Australia and New Zealand intensive care units: an international comparison study. *JPEN J Parenter Enteral Nutr* 2018;42:1349–57.
2 Bendavid I, Singer P, Theilla M, *et al*. NutritionDay ICU: a 7 year worldwide prevalence study of nutrition practice in intensive care. *Clin Nutr* 2017;36:1122–9.
3 Cahill NE, Suurdt J, Ouellette-Kuntz H, *et al*. Understanding adherence to guidelines in the intensive care unit. *JPEN J Parenter Enteral Nutr* 2010;34:616–24.
4 Arabi YM, Aldawood AS, Al-Dorzi HM, *et al*. Permissive underfeeding or standard enteral feeding in high- and Low-Nutritional-Risk critically ill adults. post hoc analysis of the permit trial. *Am J Respir Crit Care Med* 2017;195:652–62.
5 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.
6 TARGET Investigators, for the ANZICS Clinical Trials Group, Chapman M, Peake SL, *et al*. Energy-Dense versus routine enteral nutrition in the critically ill. *N Engl J Med* 2018;379:1823–34.
7 National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Rice TW, Wheeler AP, *et al*. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. *JAMA* 2012;307:795–803.
8 Reintam Blaser A, Starkopf J, Alhazzani W, *et al*. Early enteral nutrition in critically ill patients: ESICM clinical practice guidelines. *Intensive Care Med* 2017;43:380–98.
9 Chapple L-AS, Deane AM, Heyland DK, *et al*. Energy and protein deficits throughout hospitalization in patients admitted with a traumatic brain injury. *Clin Nutr* 2016;35:1315–22.
10 Jarden RJ, Sutton-Smith L, Boulton C. Oral intake evaluation in patients following critical illness: an ICU cohort study. *Nurs Crit Care* 2018;23:179–85.
11 Merriweather JL, Salisbury LG, Walsh TS, *et al*. Nutritional care after critical illness: a qualitative study of patients' experiences. *J Hum Nutr Diet* 2016;29:127–36.
12 Moisey LL, Pikul J, Keller H, *et al*. Adequacy of protein and energy intake in critically ill adults following liberation from mechanical ventilation is dependent on route of nutrition delivery. *Nutr Clin Pract* 2021;36:201–12.
13 Peterson SJ, Tsai AA, Scala CM, *et al*. Adequacy of oral intake in critically ill patients 1 week after extubation. *J Am Diet Assoc* 2010;110:427–33.
14 Ridley EJ, Parke RL, Davies AR, *et al*. What happens to nutrition intake in the Post-Intensive care unit hospitalization period? an observational cohort study in critically ill adults. *JPEN J Parenter Enteral Nutr* 2019;43:88–95.
15 Rougier L, Preiser J-C, Fadeur M, *et al*. Nutrition during critical care: an audit on actual energy and protein intakes. *JPEN J Parenter Enteral Nutr* 2021;45:951–60.

16 Chan A-W, Tetzlaff JM, Altman DG, *et al*. Spirit 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200–7.
17 Ridley EJ, Davies AR, Parke R, *et al*. Supplemental parenteral nutrition versus usual care in critically ill adults: a pilot randomized controlled study. *Crit Care* 2018;22:12.
18 Estimating height in bedridden patients. Available: http://www.rxkinetics.com/height_estimate.html
19 McNelly AS, Bear DE, Connolly BA, *et al*. Effect of intermittent or continuous feed on muscle wasting in critical illness. *Chest* 2020;158:183–94.
20 Elia M. *Screening for malnutrition: A multidisciplinary responsibility. Development and Use of the Malnutrition Universal Screening Tool ('MUST') for Adults*. Redditch: British Association of Parenteral and Enteral Nutrition (BAPEN), 2003.
21 Cook D, Lauzier F, Rocha MG, *et al*. Serious adverse events in academic critical care research. *CMAJ* 2008;178:1181–4.

Appendix

Title: Protocol summary and statistical analysis plan for **I**ntensive **N**utrition **T**herapy compar**E**d to usual care i**N** cri**T**ically ill adults (INTENT): a phase II randomised controlled trial

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Contents:

Appendix 1: Calculated body weight determination and corresponding energy requirements

Calculated body weight (CBW) in kg will be used for the calculation of nutritional targets in the ICU, defined as follows;

For patients under 65 years of age:

a) The patient's actual weight if their body mass index (BMI) is deemed to be <25kg/m^2
b) BMI ≥ 25 kg/m^2 ≤ 40 kg/m^2 : CBW will be set at 'actual weight + ideal weight/2' where 'ideal weight' is equivalent to a BMI of 23 kg/m^2
c) BMI > 40 kg/m^2: CBW will be set at 'actual weight + ideal weight/2' where 'ideal weight' is equivalent to a BMI of 25 kg/m^2

For patients 65 years of age and over:

a) The patient's actual weight if their BMI is deemed to be < 30kg/m^2
b) BMI ≥30 kg/m^2: CBW will be set at 'actual weight + ideal weight/2' where 'ideal weight' is a weight equivalent to a BMI of 27 kg/m^2

The corresponding study energy requirements for a given CBW are provided in the table below.

Appendix 2: INTENT study energy requirement table

Patients calculated body weight (kg)	Daily requirement at 25 kcal/kg	Patients calculated body weight (kg)	Daily requirement at 25 kcal/kg	Patients calculated body weight (kg)	Daily requirement at 25 kcal/kg
40	1000	77	1925	114	2850
41	1025	78	1950	115	2875
42	1050	79	1975	116	2900
43	1075	80	2000	117	2925
44	1100	81	2025	118	2950
45	1125	82	2050	119	2975
46	1150	83	2075	120	3000
47	1175	84	2100	121	3025
48	1200	85	2125	122	3050
49	1225	86	2150	123	3075
50	1250	87	2175	124	3100
51	1275	88	2200	125	3125
52	1300	89	2225	126	3150
53	1325	90	2250	127	3175
54	1350	91	2275	128	3200
55	1375	92	2300	129	3225
56	1400	93	2325	130	3250
57	1425	94	2350	131	3275
58	1450	95	2375	132	3300
59	1475	96	2400	133	3325
60	1500	97	2425	134	3350

61	1525	98	2450	135	3375
62	1550	99	2475	136	3400
63	1575	100	2500	137	3425
64	1600	101	2525	138	3450
65	1625	102	2550	139	3475
66	1650	103	2575	140	3500
67	1675	104	2600	141	3525
68	1700	105	2625	142	3550
69	1725	106	2650	143	3575
70	1750	107	2675	144	3600
71	1775	108	2700	145	3625
72	1800	109	2725	146	3650
73	1825	110	2750	147	3675
74	1850	111	2775	148	3700
75	1875	112	2800	149	3725
76	1900	113	2825	150	3750

Appendix 3: Product information for Olimel N12E with electrolytes and additions

Contents	Compounded Ready To Use Parenteral Nutrition (per 1000ml bag)
Total nitrogen (g)	12.0
Amino acid (g)	75.9
Glucose (g)	73.3
Lipid as ClinOleic (g)	35.0
Total energy (kcal)	950
Non protein energy (kcal)	640
Glucose energy (kcal)	290
Lipid energy (kcal)	350
Sodium (mmol)	35
Potassium (mmol)	30
Magnesium (mmol)	4.0
Calcium (mmol)	3.5
Phosphate (including lipid) (mmol)	15.0
Acetate (mmol)	70
Chloride (mmol)	45
Osmolarity (mOsm/L)	1270
Additions per bag of PN	
Baxter's Multiple Trace Elements with Iron (mcg)	Per ml (10ml is added to each 1L PN bag)
Zinc	650
Copper	51.5
Manganese	5.5
Chromium	1.0
Selenium	8.0
Iodide	13
Molybdenum	1.9
Iron	110
Ascorbate (Vitamin C) for stability (mg per bag)*	120
Cernevit (ml per bag)	5

* Sodium Ascorbate in Australia, Ascorbate acid in NZ

Appendix 4: Nutrition information for Fortisip Compact Protein and Forticreme Complete*

	Fortisip Compact Protein (per 125 ml bottle)	Forticreme Complete (per 125 g pot)
Energy (kcal)	300	200
Energy (kJ)	1263	844
Protein (g)	18	11.9
Casein (g)	16.8	9.4
Whey (g)	1.3	2.6
Carbohydrates (g)	30.5	24
Sugars (g)	16.6	13.3
Lactose (g)	0.38	0.13
Fat (g)	11.8	6.3
Saturates (g)	1.1	0.9
Monounsaturates (g)	7.1	3.8
Polyunsaturates (g)	3.5	1.6
Omega 6 : Omega 3	5.1:1	5.1:1
Fibre (g)	0	0.13
Water (ml)	78.8	80
Sodium (mg)	50	78.8
Sodium (mmol)	2.1	3.4
Potassium (mg)	131	231
Potassium (mmol)	3.4	5.9
Calcium (mg)	43.8	163
Phosphorous (mg)	375	141
Magnesium (mg)	68.8	25
Chloride (mg)	75	80
Ca:P	1.2:1	1.1:1
Vitamin A (µg-RE)	325	256
Vitamin D (µg)	2.6	2.1
Vitamin E (mg α-TE)	4.6	3.4
Vitamin K (µg)	20	16.3
Vitamin C (mg)	37.5	20
Thiamin (mg)	0.56	0.46
Riboflavin (mg)	0.6	0.5
Niacin (mg NE)	4.5	3.5
Vitamin B6 (mg)	0.66	0.52

Vitamin B12 (µg)	1.4	0.64
Folic Acid (µg)	100	80
Pantothenic Acid (mg)	2	1.6
Biotin (µg)	15	8
Iron (mg)	2.6	3.3
Zinc (mg)	3	2
Manganese (mg)	0.79	0.8
Copper (µg)	438	540
Iodine (µg)	57.5	42.5
Molybdenum (µg)	25	22.5
Selenium (µg)	17.5	13.8
Chromium (µg)	16.3	13.8
Fluoride (mg)	0.24	0.23
Choline (mg)	138	110
Osmolality (mOsmol/kgH_20)	900	820

Mmol, millimole; µg, microgram; µg-RE, µg retinol equivalents; mg α-TE, milligram alpha- tocopherol equivalents; mg NE, milligram niacinamide; mOsmol/kgH20, milliosmols (one-thousandth of an osmole) per kilogram of water (mOsmol/kg)

* Please note the ingredients list and nutritional information is representative of the Vanilla flavour only for both products. There are minor variations between different flavours.

Appendix 5: INTENT ICU discharge summary

Patient Study No |__| |__| |__| - |__| |__|

Date Completed: ...../...../.....

Intensive **n**utrition **t**herapy compar**e**d to usual care i**n** cri**t**ically ill adults: A randomised pilot trial (INTENT)

This patient has been enroled to the INTENT randomised controlled trial (intervention arm).

The aim of the study is to optimise nutrition intake over the whole hospital period.

Please discuss any information or concerns regarding the patient's nutrition management with the Intervention Study Dietitian (details provided below) ***before*** making changes to the nutrition management plan for this patient.

ICU discharge summary

Summary of nutrition management in ICU and plan for ward management:

Patients calculated body weight in ICU: _____ kg

Energy requirement in the ICU (based on 25/kcal/kg): _____ kcal/ day

Average nutrition adequacy during ICU admission: _____

ICU mobility scale at discharge:...../10

At the time of discharge, the patient was receiving nutrition from (tick all boxes that apply):

Oral ☐ Enteral ☐ Parenteral ☐

Details of management plan: _____

_____

Recommended nutrition plan for the ward:

INTENT supplements: ☐ Y ☐ N Name: Dose:

Additional supplements: ☐ Y ☐ N _____

Enteral nutrition: ☐ Y ☐ N _____

_____

_____

_____

Intervention Dietitian name/ contact number: _____

Site Principal Investigator name/ contact number: _____

1

Summary of INTENT

INTENT is a multicentre, prospective, parallel, randomised controlled trial in 240 critically ill adults from 23 hospitals in Australia and New Zealand.

The primary aim is to determine whether the use of a pre-tested supplemental parenteral nutrition (PN) strategy in the Intensive Care Unit (ICU) and an intensive nutrition intervention after discharge to the hospital ward, will deliver more total energy than standard nutrition care over the entire hospital stay.

https://www.monash.edu/medicine/sphpm/anzicrc/research/intent-trial-intensive-nutrition-therapy-compared-to-usual-care-in-critically-ill-adults-a-pilot-randomised-trial

Appendix 6: Proposed presentation of tables and figures in the main results manuscript

Table 1: Baseline participant characteristics

	Intensive nutrition care (n=xxx)	**Usual nutrition care (n=xxx)**
Age, years	xx ± xx	xx ± xx
Sex, male, n (%)	xx (%)	xx (%)
Calculated body weight, kg	xx ± xx	xx ± xx
BMI, kg/m^2	xx ± xx	xx ± xx
APACHE II score	xx ± xx	xx ± xx
APACHE III diagnosis code, n (%)		
Cardiovascular	xx (%)	xx (%)
Trauma	xx (%)	xx (%)
Respiratory	xx (%)	xx (%)
Sepsis	xx (%)	xx (%)
Gastrointestinal	xx (%)	xx (%)
Musculoskeletal	xx (%)	xx (%)
Renal	xx (%)	xx (%)
Neurological	xx (%)	xx (%)
Unknown	xx (%)	xx (%)
CRRT commenced prior to randomisation, n (%)	xx (%)	xx (%)
Baseline SOFA score	xx ± xx	xx ± xx
MUST score	xx ± xx	xx ± xx
NUTRIC score	xx ± xx	xx ± xx
Clinical Frailty Score	xx ± xx	xx ± xx
Study energy requirement, kcal	xx ± xx	xx ± xx
Clinician estimated protein requirement, g	xx ± xx	xx ± xx
Energy received from hospital admission to randomisation from all sources, kcal	xxxx ± xxx	xxxx ± xxx
Time from hospital admission to randomisation, days	x.x ± x.x	x.x ± x.x
Time from randomisation to interventional PN commencement, hours	x.x ± x.x	x.x ± x.x

Continuous normally distributed data will be presented as mean ± SD, otherwise as median [IQR]. Where deemed appropriate, categorical variables with categories that contain small numbers (<10) will be collapsed for analysis. *Statistically significant differences in baseline characteristics between groups will be indicated by * for P <0.05, ** for P <0.01, and *** for P <0.001. Abbreviations: APACHE Acute physiology and chronic health evaluation; BMI body mass index; CRRT continuous renal replacement therapy; MUST malnutrition universal screening tool; NUTRIC Nutrition Risk in Critically ill; SOFA sequential organ failure assessment

Table 2: Daily nutrition delivery, process and intervention data over the 28 day study period

Variable	Intensive nutrition care (n=xxx)	Usual nutrition care (n=xxx)	Difference (95% CI) or OR (95% CI)
Daily energy and protein provision from EN, PN and oral sources			
Delivery of energy, kcal	xx ± xx	xx ± xx	xxx (xxx-xxx)
Energy, kcal/kg CBW	xx ± xx	xx ± xx	xxx (xxx-xxx)
Delivery of protein, g	xx ± xx	xx ± xx	xxx (xxx-xxx)
Protein, g/kg CBW	xx ± xx	xx ± xx	xxx (xxx-xxx)
Daily energy provision from all sources (nutrition and non-nutrition energy)			
Delivery of energy, kcal	xx ± xx	xx ± xx	xxx (xxx-xxx)
Energy, kcal/kg CBW	xx ± xx	xx ± xx	xxx (xxx-xxx)
Delivery of protein, g	xx ± xx	xx ± xx	xxx (xxx-xxx)
Protein, g/kg CBW	xx ± xx	xx ± xx	xxx (xxx-xxx)
Daily nutrition delivery data			
Volume of EN, ml	xx ± xx	xx ± xx	xxx (xxx-xxx)
Volume of PN, ml			
Interventional PN	xx ± xx	xx ± xx	xxx (xxx-xxx)
Non-study PN	xx ± xx	xx ± xx	xxx (xxx-xxx)
Days of nutrition mode, days/total number of days			
EN alone	n/N	n/N	xxx (xxx-xxx)

PN alone	n/N	n/N	xxx (xxx-xxx)
EN and PN	n/N	n/N	xxx (xxx-xxx)
EN and oral	n/N	n/N	xxx (xxx-xxx)
Oral	n/N	n/N	xxx (xxx-xxx)
GRV ml,	xx ± xx	xx ± xx	xxx (xxx-xxx)
Insulin, units	xx ± xx	xx ± xx	xxx (xxx-xxx)
Morning blood glucose level, mmol/L	xx ± xx	xx ± xx	xxx (xxx-xxx)
Blood glucose levels < 2.1 mmol/L per day, n/N	n/N	n/N	xxx (xxx-xxx)
Length of fasting, hours	xx ± xx	xx ± xx	xxx (xxx-xxx)
Nutrition process and intervention data			
Oral nutrition supplements, days/total number of days	n/N	n/N	xxx (xxx-xxx)
Less than 50% intended oral intake consumed, days/total number of days of oral nutrition	n/N	n/N	xxx (xxx-xxx)
INTENT oral nutrition supplements prescribed, days/total number of days	n/N	-	-
INTENT oral nutrition supplements consumption, percentage of prescribed volume	xx ± xx	-	-
Escalations to nutrition care requested, n/total study days	n/N	-	-
Nutrition care escalations performed, n/total study days	n/N	-	-

Top three escalations to nutrition care requested, n/total number of escalations			
Escalation 1	n/N	-	-
Escalation 2	n/N	-	-
Escalation 3	n/N	-	-
Time spent implementing the intensive nutrition intervention, hours per occasion	xx ± xx	-	-
Dietitian reviews for the ward admission, n/total number of reviews	n/N	n/N	x.xxx

Data is presented as mean ± SD unless otherwise specified. Abbreviations: CBW calculated body weight; EN enteral nutrition; PN parenteral nutrition

Table 3: Energy and protein delivery by location over the 28 day study period

Variable	Intensive nutrition care (n=xxx)	Usual nutrition care (n=xxx)	Difference (95% CI)
ICU			
Delivery of energy, daily, kcal	xx ± xx	xx ± xx	xxx (xxx-xxx)
Energy, daily, kcal/kg CBW	xx ± xx	xx ± xx	xxx (xxx-xxx)
Energy balance at ICU D/C (or D28), kcal	xx ± xx	xx ± xx	xxx (xxx-xxx)
Delivery of protein, daily, g	xx ± xx	xx ± xx	xxx (xxx-xxx)
Protein, daily, g/kg CBW	xx ± xx	xx ± xx	xxx (xxx-xxx)
Protein balance at ICU D/C (or D28), g	xx ± xx	xx ± xx	xxx (xxx-xxx)
Ward			
Delivery of energy, daily, kcal	xx ± xx	xx ± xx	xxx (xxx-xxx)
Energy, daily, kcal/kg CBW	xx ± xx	xx ± xx	xxx (xxx-xxx)
Energy balance at hospital D/C (or D28), kcal	xx ± xx	xx ± xx	xxx (xxx-xxx)
Delivery of protein, daily, g	xx ± xx	xx ± xx	xxx (xxx-xxx)
Protein, daily, g/kg CBW	xx ± xx	xx ± xx	xxx (xxx-xxx)
Protein balance at hospital D/C or D28, g	xx ± xx	xx ± xx	xxx (xxx-xxx)

Data is presented as mean ± SD unless otherwise specified. Abbreviations: ICU Intensive care unit; D/C discharge; CBW calculated body weight

Table 4: Clinical outcomes over the 28 day study period

Variable	Intensive nutrition care (n=xxx)	Usual nutrition care (n=xxx)	OR (95% CI)
Central line changes, changes/total number of patients	n/N	n/N	xxx (xxx-xxx)
RRT received, days	xx ± xx	xx ± xx	xxx (xxx-xxx)
SOFA score	xx ± xx	xx ± xx	xxx (xxx-xxx)
Blood stream infections			
Total, infections/ total number of patients	n/N	n/N	xxx (xxx-xxx)
Number to D28, infections/ total number of patients	n/N	n/N	xxx (xxx-xxx)
Time to any infection, days	xx ± xx	xx ± xx	xxx (xxx-xxx)
Weight change, kg	xx ± xx	xx ± xx	xxx (xxx-xxx)
Duration of EN delivery, days	xx ± xx	xx ± xx	xxx (xxx-xxx)
Duration of PN delivery, days	xx ± xx	xx ± xx	xxx (xxx-xxx)
Duration of EN and PN delivery, days	xx ± xx	xx ± xx	xxx (xxx-xxx)
Duration oral diet prescribed, days	xx ± xx	xx ± xx	xxx (xxx-xxx)
ICU			
Survival, n/total number of patients	n/N	n/N	xxx (xxx-xxx)
ICU mobility scale	xx ± xx	xx ± xx	xxx (xxx-xxx)
MV time to extubation, days[a]	xx ± xx	xx ± xx	xxx (xxx-xxx)
Ventilator free days at D28, days	xx ± xx	xx ± xx	xxx (xxx-xxx)
Length of stay (time to ICU D/C), days[a]	xx ± xx	xx ± xx	xxx (xxx-xxx)
Hospital			
Survival, n/total number of patients			
Total	n/N	n/N	xxx (xxx-xxx)
D28	n/N	n/N	xxx (xxx-xxx)
Length of stay (time to hospital discharge), days[a]	xx ± xx	xx ± xx	xxx (xxx-xxx)

Data is presented as mean ± SD unless otherwise specified. [a] Duration of MV, and lengths of stay is presented as Hazard Ratios (95%CI).
Abbreviations: D28 study day 28; D/C discharge; EN enteral nutrition; ICU intensive care unit; MV mechanical ventilation; PN parenteral nutrition; RRT renal replacement therapy; SOFA sequential organ failure criteria

Appendix 7: Master information and consent forms

Appendix 7A: Prior consent from person responsible/medical treatment decision maker

Insert Header with institution's name or institution's letterhead

Participant Information Sheet/Consent Form – Person Responsible/Medical treatment decision maker

Interventional Study - *Person responsible/Medical treatment decision maker consenting on behalf of participant*

[Insert site name]

Title	**I**ntensive **n**utrition **t**herapy compar**e**d to usual care i**n** cri**t**ically ill adults: A randomised pilot trial
Short Title	INTENT
Protocol Number	ANZIC-RC/ER001
Project Sponsor	ANZIC-RC
HREC Reference Number	HREC/18/Alfred/101
Coordinating Principal Investigator	Dr Emma Ridley
Site Principal Investigator	*[Site Principal Investigator]*
Associate Investigator(s)	*[Associate Investigator(s)]*

Part 1 What does participation involve?

1 Introduction

As the Person Responsible/Medical treatment decision maker you are invited to consider the patient's participation in this research project. This is because they have been admitted to an Intensive Care Unit (ICU), are connected to a ventilator (breathing machine) and have a medical condition that has led to at least one of their body systems (the lungs, heart or the kidneys) not working well enough on their own. The research project is aiming to see if an intensive nutrition feeding strategy is more effective in delivering adequate amounts of nutrition when compared to standard practice. The strategy will use a combination of intravenous nutrition (into the vein), enteral feeding (into the stomach or bowel) and/ or food (if the patient is able to eat) in the ICU and on the ward.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want the patient to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not the patient can take part, you might want to talk about it with a relative, friend or the patient's local doctor.

Participation in this research is voluntary. If you don't wish for the patient to take part, they don't have to. They will receive the best possible care whether they take part or not.

If you decide you want the patient to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:
• Understand what you have read
• Consent to the patient taking part in the research project
• Consent to the patient having the tests and treatments that are described
• Consent to the use of the patient's personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

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2 What is the purpose of this research?

People who are critically ill and treated in the ICU often do not receive sufficient amounts of nutrition. In most cases, patients aren't able to eat food (e.g. when they are connected to a breathing machine) or if they are able to eat, they often have poor appetites and do not eat sufficient amounts. In this situation, the standard treatment is to supply them with food dripped into their stomach or bowel through a feeding tube (termed enteral nutrition). However, even when enteral nutrition is used, it is difficult to meet the nutrition needs of patients because they are sick and can't always tolerate it. Sometimes, ICU doctors use alternative strategies to try and give patients more nutrition. One such strategy is to deliver parenteral (intravenous) nutrition in addition to enteral nutrition and/ or food. This is usually only started after the patient has had several days of insufficient nutrition from enteral nutrition and/ or food. It is referred to as supplemental parenteral nutrition.

Difficulty meeting the nutrition needs of patients often continues after patients are transferred from the ICU to the hospital ward. However, there is very little research that has looked at the amount of nutrition patients receive following ICU discharge and whether delivering increased amounts of nutrition in this setting assists with recovery and rehabilitation.

The aim of this study is to test a nutrition strategy to increase the amount of nutrition given to patients, both in ICU and on the ward. The nutrition strategy will use supplemental (intravenous) parenteral nutrition, enteral (feeding tube into the stomach) nutrition and/or food. In a pilot study, we found that the use of supplemental parenteral nutrition was safe and led to the delivery of higher amounts of nutrition compared to standard practice. However, in this study the strategy only ran for 7 days and did not continue on the ward. This larger trial will enrol 240 participants admitted to ICUs across Australia and New Zealand and will allow us to make a stronger conclusion on whether the use of supplemental nutrition across the whole hospital stay assists in delivering higher amounts of nutrition compared to standard practice. This study will help to establish whether supplemental nutrition should be introduced for all patients who require treatment in an ICU and whether an intensive nutrition strategy may be beneficial for delivering more nutrition on the ward.

This research has been initiated by Senior Research Fellow, Dr Emma Ridley and has been funded by Baxter Healthcare, who are manufacturers of several parenteral nutrition products. In this study we will use a recently developed mixture of parenteral nutrition that contains carbohydrates, lipids (fats), protein, water and various other salts, vitamins and minerals. This research is being managed by the Australian and New Zealand Intensive Care Research Centre (ANZIC-RC) at Monash University.

3 What does participation in this research involve?

This type of study is called a randomised controlled trial. When intensive care clinicians do not know which is the best treatment for a condition, this type of study is done to help find the answer. All patients are 'randomised' (like flipping a coin) to receive one of two treatments – in this case, either standard nutrition or an intensive nutrition strategy. Patients have an equal chance of being assigned to each group and neither the treating doctors, the patient, nor you will be able to decide what treatment they receive. At the end of the study we will compare the two groups of patients to see if one treatment is better than the other.

The study will continue for 28 days or until hospital discharge - whichever occurs first.

In the intensive care unit

The patient will be randomised to one of the following groups:

- Intensive nutrition group: The patient's nutritional intake will be assessed by the study team daily. If their nutritional needs are not being met with enteral nutrition and/or food, supplemental parenteral nutrition will be given. All other care will be according to ICU best practice guidelines.

OR

- Standard nutrition (control) group: The patient will be reviewed daily. Nutrition therapy will be based on unit protocols developed according to best practice guidelines. Enteral nutrition and/or food will be used to meet nutrition needs. Parenteral nutrition may be given if this is considered necessary by the ICU treating team.

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We will closely monitor the body systems (including heart, lungs, kidneys and liver) in both groups of patients. We will also carefully measure how much nutrition (from food, enteral and parenteral sources) is actually delivered to the patient. As part of usual practice for patients receiving parenteral nutrition, routine blood samples will be reviewed weekly when patients are receiving parenteral nutrition to look at liver function and level of blood fats. The blood samples will be taken from a line (drip) that is already in place as part of standard ICU care.

On the ward

- Intensive nutrition group: Patients will be monitored closely by a dietitian and a combination of nutrition strategies will be used to meet the nutrition needs. This may include fortified food, nutrition supplement drinks and enteral nutrition if required. Parenteral nutrition will only be used if the participant is unable to meet their nutrition needs by eating and/ or receiving enteral nutrition.

OR

- Standard nutrition (control) group: Nutrition therapy will be as per usual ward best practice.

For both groups of patients, we will carefully measure and record how much nutrition (from food, enteral and parenteral sources) is received by the patient 3 times a week.

Follow-up

At 3 and 6 months after the study started, we would like to contact you or the patient by telephone to see how they have recovered. The phone call will be from the hospital ICU research coordinator whom you may have already met. The questions relate to the patient's health, well-being, physical activities and mental function and should take approximately 15 minutes. If we are unable to reach you or the patient by telephone we will post the follow-up form to be completed.

There are no additional costs associated with participating in this research project, nor will you or the patient be paid. All nutrition care required as part of the research project will be provided free of charge.

4 Does the patient have to take part in this research project?

Participation in any research project is voluntary. If you do not wish for the patient to take part, they don't have to. If you decide that the patient can take part and later change your mind, you are free to withdraw them from the project at any stage. If you decide that the patient can take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether the patient can take part or not take part, or take part and then be withdrawn, will not affect the patient's routine treatment, you or the patient's relationship with those treating them, or the patient's relationship with the hospital.

The patient does not have to take part in this research project to receive treatment at this hospital. If you choose not to enrol the patient in this research study, they will receive standard best practice to manage their nutritional needs.

5 What are the possible benefits of taking part?

We cannot guarantee or promise that the patient will receive any benefits from this research; however, possible benefits may include:

- The receipt of greater amounts of nutrition during their ICU and hospital admission.
- Smaller amounts of weight loss and general loss of body condition.
- Improved function and/or quality of life at 3 and 6 months following hospital discharge.

6 What are the possible risks and disadvantages of taking part?

Medical treatments often cause side effects. The patient may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If the patient has any of these side effects, or you are worried about them, talk with the patient's study doctor. The patient's study doctor and research team will also be looking out for side effects.

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There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell the patient's study doctor immediately about any new or unusual symptoms.

Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, the participant's study doctor may need to stop the patient's treatment. The patient's study doctor will discuss the best way of managing any side effects with you.

Risk/Side effect	**Likelihood**	**Comment**
Overfeeding	Uncommon and unlikely to result in harm	By using up to three types of nutrition, some patients may receive overfeeding on some days. There are safeguards in the study protocol to avoid this and we think it is unlikely to lead to any problems in a short timeframe (few days to a week).
High sugar levels	Common but unlikely to result in harm	By using up to three types of nutrition, high blood sugars may occur on some occasions. This is common in ICU patients, even if they are not taking part in the study. Insulin is given to treat high blood sugars. This is a routine practice in ICU.
High blood fats	Uncommon and unlikely to result in harm	High blood fats may occur when using parenteral nutrition, however only very high levels have been linked to harm. Blood fat levels will be monitored closely during the study and the intervention will be ceased if blood fats reach levels associated with harm.
Abnormal liver test results	Common but unlikely to result in harm	People in the ICU frequently have abnormal liver tests and this may not be associated with the use of parenteral nutrition. Even so, we will monitor liver function closely and the intervention will be ceased if levels are of concern to the ICU treating team and if the increase is believed to be due to the use of parenteral nutrition.
Development of infections	Unlikely to be related to the study	Whilst some studies have shown that parenteral nutrition may increase infections, other studies have shown it may decrease infections. Infections are quite common in ICU patients even if they are not taking part in the study. We think the risk of infections directly related to parenteral nutrition will be low. We will measure how often infections occur in both groups.
Need for a catheter to deliver parenteral nutrition	No increased risk above standard practice	Patients will only be enrolled in this study if they already have the catheters (drips) needed to deliver the parenteral nutrition in place as part of their standard ICU care. If parenteral nutrition is needed on the ward (rare), there will be no increased risk linked to the insertion of a catheter above standard practice for these participants.

7 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, the patient's study doctor will tell you about it and discuss with you whether you want the patient to continue in the research project.

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Also, on receiving new information, the patient's study doctor might consider it to be in the patient's best interests to be withdrawn from the research project. If this happens, the doctor will explain the reasons and arrange for the patient's regular health care to continue.

8 What if I withdraw the participant from this research project?

If you decide to withdraw the patient from the project, please notify a member of the research team before you withdraw them. This will allow that person or the research team to discuss any health risks or special requirements linked to withdrawing. If you do withdraw the patient during the research project, the study doctor and relevant study staff will not collect additional personal information from the patient, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected up to the time you withdraw the patients will form part of the research project results. If you do not want them to do this, you must tell them. If the patient has an advanced care directive their wishes should be followed in relation to study involvement.

9 Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include lack of participants or change in staffing of the research team. It is extremely unlikely that this would occur.

10 What happens when the research project ends?

We plan to publish the results from this trial in peer-reviewed journals, present the findings at conferences and in a public lay press release. In any publication, information will be provided in such a way that patient cannot be identified.

If you would like a lay summary of the results of the research at the completion of the study, please contact the researcher Dr Emma Ridley, via e-mail, Emma.Ridley@monash.edu or telephone 03 9903 0350. It is expected that this project will be completed and the results will be available by July 2022.

Part 2 How is the research project being conducted?

11 What will happen to information about the participant?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about the patient for the research project. The patient's information will only be used for the purpose of this research project and it will only be disclosed with your permission, or in compliance with the law. Any information obtained in connection with this research project that can identify the participant will remain confidential. The participant's information will be stored in coded form (labelled with a unique study number, not the participant's name or hospital number) and will be linked to them by a master code list. The information will be stored in a locked cabinet with access restricted to staff involved in the research project. In addition, this data will be entered into a secure username and password protected database with access restricted to project staff, authorities and authorised representatives as described below. All information will be stored indefinitely.

The patient's health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities, the institution relevant to this Participant Information Sheet, ANZIC-RC, or as required by law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

It is anticipated that the results of this research project will be published and or presented in a variety of forums. In any publication and/or presentation, information will be provided in a de-identified format to ensure that the participant cannot be identified, except with your permission.

In accordance with relevant Australian and/or *[Name of state/territory]* privacy and other relevant laws, you have the right to request access to the patient's information collected and stored by the

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study team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access the patient's information.

12 What happens if an injury occurs as a result of participating in the research project?

If the patient suffers any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment for the participant. If the patient is eligible for Medicare, they can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

13 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of the Alfred Hospital and Monash University.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

14 Further information and who to contact

The person you may need to contact will depend on the nature of your query. If you want any further information concerning this project or if the participant has any medical problems which may be related to their involvement in the project (for example, any side effects), you can contact the principal study doctor on 03 9903 0350 or any of the following people:

Clinical contact person

Name	*[Name]*
Position	*[Position]*
Telephone	*[Phone number]*
Email	*[Email address]*

For matters relating to research at the site at which the participant is participating, the details of the local site complaints person are:

Site complaints contact person

Name	*[Name]*
Position	*[Position]*
Telephone	*[Phone number]*
Email	*[Email address]*

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC/Complaints contact person

Position	Complaints Officer, Office of Ethics & Research Governance, Alfred Health
Telephone	(03) 9076 3619
Email	research@alfred.org.au

Please quote the following HREC Reference Number: 294/18

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Consent Form – Person Responsible/ Medical treatment decision maker

Title	Intensive nutrition **t**herapy compared to usual care i**n** cri**t**ically **i**ll adults: A randomised pilot trial
Short Title	INTENT
Protocol Number	ANZIC-RC/ER001
Project Sponsor	ANZIC-RC
HREC Reference Number	HREC/18/Alfred/101
Coordinating Principal Investigator	Dr Emma Ridley
Principal Investigator	*[Principal Investigator]*
Associate Investigator(s)	*[Associate Investigator(s)]*

Consent Agreement

I am the Person Responsible/ medical treatment decision maker for the patient.

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I believe that the participation of the patient in this study is not contrary to their best interests/their preferences and values and their social wellbeing.

I freely agree to the patient participating in this research project as described and understand that I am free to withdraw the patient at any time during the research project without affecting their future health care.

I am aware of my responsibilities as the Person Responsible/ medical treatment decision maker for the patient and I understand that I will be assisting the patient in meeting their responsibilities whilst they are participating in this study.

I understand that I will be given a signed copy of this document to keep on behalf of the patient.

I give permission for the patient's doctors, other health professionals, hospitals or laboratories outside this hospital to release information to *[Name of Institution]* concerning the patient's disease and treatment for the purposes of this research project. I understand that such information will remain confidential.

Declaration by Person Responsible/medical treatment decision maker who has read the information

Name of Participant (please print) _____

Name of Person providing consent (please print) _____

Relationship of Person providing consent to Participant _____

Signature of Person providing consent _____ Date _____

Time (please write in 24-hour time e,g, 5pm is 17:00) _____

Declaration by Person Responsible/medical treatment decision maker unable to read the information and consent form

Witness to the informed consent process
Name (please print) _____
Signature _____ Date _____
* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the person responsible/medical treatment decision maker has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

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Appendix 7B: Participant consent to continue following medical treatment decision maker consent

Insert Header with institution's name or institution's letterhead

Participant Information Sheet/Consent Form

Consent to continue after person responsible/medical treatment decision maker consent

Title	INTENT
Short title	Intensive nutrition therapy compared to usual care in critically ill adults: a randomised pilot trial
Protocol Number	ANZIC-RC/ER001
Site Principal Investigator	

Part 1 What does participation involve?

1 Introduction

You were enrolled in this research project by your person responsible/medical treatment decision maker. Now you have recovered, we would like to tell you about the study and make sure that you are happy to continue to participate.

You were eligible for this study as you were a patient in the Intensive Care Unit (ICU), were connected to a ventilator (breathing machine) and one of your body systems (lungs, heart or kidneys) were not working well enough on their own. At the time, you were not meeting your nutritional needs using traditional methods. The research project is aiming to see if an intensive nutrition feeding strategy is more effective in delivering adequate amounts of nutrition when compared to standard practice. The strategy will use a combination of intravenous nutrition (into the vein), enteral feeding (into the stomach or bowel) and/ or food (if the patient is able to eat) in the ICU and on the ward.

Continuing participation in this study is voluntary. If you choose to continue to participate in the study and later change your mind, you can withdraw from the study. Your decision will have no impact on the quality of care you receive or your relationship with this hospital.

This research has been initiated by Senior Research Fellow, Dr Emma Ridley. It is funded by Baxter Healthcare, who are manufacturers of several parenteral nutrition products. This research is being managed by the Australian and New Zealand Intensive Care Research Centre (ANZIC-RC) at Monash University.

2 What is the purpose of this research?

People who are critically ill and treated in the ICU often do not receive sufficient amounts of nutrition. This is usually because they have poor appetites, they are unwell and can not tolerate food, or are connected to a breathing machine. Normally, patients are fed via a tube into the stomach (called enteral nutrition), but sometimes nutritional needs are still not met for a variety of reasons. An alternative strategy is to deliver nutrition into the vein (called parenteral nutrition), in addition to standard methods. This is known as supplemental parenteral nutrition, and is often only started after several days on inadequate nutrition.

It can also be difficult to meet the nutritional needs of patients on the ward, however it is not well understood how much nutrition ward patients get and if it makes a difference to their recovery.

The aim of this study is to test a nutrition strategy to increase the amount of nutrition given to patients, both in ICU and on the ward. The nutrition strategy will use supplemental (intravenous) parenteral nutrition, enteral (feeding tube into the stomach) nutrition and/or food.

From previous research, we know that using supplemental parenteral nutrition was safe and resulted in increased nutrition compared to standard care, but the strategy only ran for 7 days and was in a small number of patients. We are now doing a much larger trial which will give us a much better understanding if supplemental parenteral nutrition really works. If the strategy is shown to be effective, we will make it standard care for all ICU patients.

3 What does it mean for me?

When intensive care clinicians do not know which is the best treatment for a condition, this type of study is done to help find the answer. All patients are 'randomised' (like flipping a coin) to receive one of two treatments – in this case, either standard nutrition or an intensive nutrition strategy

In the Intensive Care Unit

You were randomised (like flipping a coin) to receive one of two treatments:

- Intensive group:
  - Daily assessment of nutritional intake
  - If nutritional needs are not being met using enteral nutrition and/or food, supplemental parenteral nutrition was started.
  - All other care as per standard ICU practice
- Standard nutrition group:
  - Daily assessment of nutritional intake
  - Nutrition delivered according to best practice guidelines

The study will continue for 28 days or until hospital discharge - whichever occurs first. This may mean that may continue the treatment strategy on the ward.

On the ward

- Intensive group:
  - Nutrition assessment 3 times per week
  - If nutritional needs met with a combination of fortified food, nutrition supplement drinks
  - Enteral nutrition if required
  - Parenteral nutrition if required
- Standard nutrition group:
  - Nutrition assessment 3 times per week
  - Nutritional therapy as per usual ward practice

Blood samples are collected at the start of the study and then weekly to monitor liver function and levels of blood fats. These are taken from a line (drip) that is already in place as part of standard care.

Follow-up

At 3 and 6 months after the study started, we would like to contact you by telephone to see how you have recovered. The phone call will be from the hospital ICU research coordinator who you may have already met. The questions relate to your health, well-being, physical activities and mental function and should take approximately 15 minutes. If we are unable to reach you by telephone we will post the follow-up form to you to complete.

There are no additional costs associated with participating in this research project, nor will you be paid. All nutrition care required as part of the research project will be provided free of charge.

4 What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research; however, possible benefits may include: the receipt of greater amounts of nutrition during ICU and hospital admission; smaller amounts of weight loss and general loss of body condition; improved function and/or quality of life at 3 and 6 months following hospital discharge.

5 What are the possible risks and disadvantages of taking part?

Medical treatments often cause side effects. You may have none, some or all of the effects listed below, and they may be mild, moderate or severe. Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. Tell your study doctor immediately about any new or unusual symptoms.

Overfeeding:

Some patients may receive overfeeding on some days, however there are safeguards in the protocol to avoid this.

Metabolic derangements:

High blood sugar levels and abnormal liver tests are common but unlikely to lead to harm. High blood fats are uncommon but also unlikely to cause harm. ICU patients may experience these symptoms even if they are not taking part in the study. We will monitor your bloods for any abnormalities in these levels.

Infections:

Infections are common in ICU patients. The risk of infection directly related to parenteral nutrition is low. We will monitor if you develop any signs of infection.

Insertion of a drip to deliver parenteral nutrition:

Parenteral nutrition will be delivered in ICU using a drip that is already in place as part of standard ICU care. If you need parenteral nutrition of the ward (rare), we will discuss this with you at the time.

6 What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. If you withdraw during the research project, the study doctor and relevant study staff will not collect additional personal information about you, although information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected up to the time you withdraw will form part of the research project results. If you do not want the researchers to do this, you must tell them.

7 What happens when the research project ends?

We plan to publish the results from this trial in peer-reviewed journals, present the findings at conferences and in a public lay press release. In any publication, information will be provided in such a way that you cannot be identified.

If you would like a lay summary of the results of the research at the completion of the study, please contact the researcher Dr Emma Ridley, via e-mail, Emma.Ridley@monash.edu or telephone 03 9903 0350. It is expected that this project will be completed and the results will be available by July 2022.

Part 2 How is the research project being conducted?

8 What will happen to information about me?

Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, or in compliance with the law. Your information will be stored in coded form using a unique study number to maintain your confidentiality. Study data will be stored in a locked cabinet with access restricted to staff involved in the research project. Data will be entered into a secure username and password protected database with access restricted to project staff, authorities and authorised representatives as described below. All information will be stored indefinitely.

Information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities, the institution relevant to this Participant Information Sheet, ANZIC-RC, or as required by law.
In accordance with relevant Australian and/or [Name of state/territory] privacy and other relevant laws, you have the right to request access to information collected about you and stored by the study team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

9 What happens if an injury occurs as a result of participating in the research project?
If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

10 Who has reviewed the research project?
All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of the Alfred Hospital and Monash University.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

11 Further information and who to contact
The person you may need to contact will depend on the nature of your query. If you want any further information concerning this project or if you have any medical problems which may be related to their involvement in the project (for example, any side effects), you can contact the principal study doctor on 03 9903 0350 or any of the following people:

Clinical contact person

Name	*[Name]*
Position	*[Position]*
Telephone	*[Phone number]*
Email	*[Email address]*

For matters relating to research at the site at which the participant is participating, the details of the local site complaints person are:

Site complaints contact person

Name	*[Name]*
Position	*[Position]*
Telephone	*[Phone number]*
Email	*[Email address]*

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:
Reviewing HREC/Complaints contact person

Position	Complaints Officer, Office of Ethics & Research Governance, Alfred Health
Telephone	(03) 907 6 3619
Email	research@alfred.org.au

Please quote the following HREC reference Number: 294/18

Ridley EJ, *et al. BMJ Open* 2022; 12:e050153. doi: 10.1136/bmjopen-2021-050153

Consent Form – Continuing Consent

Title	INTENT
Short title	Intensive nutrition therapy compared to usual care in critically ill adults: a randomised pilot trial
Protocol Number	ANZIC-RC/ER001
Site Principal Investigator	

Consent Agreement

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to continue participation in this research project as described within this document and understand that I am free to withdraw participation at any time during the research project without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Declaration by Participant

Name of Participant (please print) _____

Signature of Participant _____Date _____

Time (please specify in 24-hour time e.g. 5pm is 17:00) _____

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project

Ridley EJ, *et al. BMJ Open* 2022; 12:e050153. doi: 10.1136/bmjopen-2021-050153