MONASH University

Clinical and functional consequences of energy provided by nutrition in critically ill adults

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A thesis submitted for the degree of *Doctor of Philosophy* at

Monash University in 2018

School of Public Health and Preventive Medicine

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Table of contents

List of tables and figures

Tables:

Figures:

Figures and tables in published papers are not listed here.

Abstract

Provision of nutrition therapy in critical illness is an internationally accepted standard of care, with the delivery of energy one of the main focuses. Many international best practice guidelines recommend that 80–100% of a patient's predicted energy requirement be provided during critical illness, but this is based primarily on expert opinion, and is supported by only a few randomised controlled trials (RCTs). Thus, despite the recommendation to deliver energy in quantities close to predicted requirements, the precise amounts of energy needed to optimise clinical and functional outcomes are unclear. The reasons for this are inability to deliver the amount of energy that critically ill patients are predicted to require, due to patient and environmental factors, with the international average being only 50–60% of the predicted energy requirement; the most common methods used to estimate energy requirements in critical illness are varied and inaccurate; a lack of high-quality definitive RCTs; and finally, all the adequately powered RCTs of energy interventions focused on the early period of critical illness, and provided nutritional interventions of short duration. Critically ill patients often spend more time on the hospital ward than in the intensive care unit (ICU), but little is known about nutrition intake late in the ICU stay and on the hospital ward, and the impact of this on recovery and clinical outcomes.

The aims of the research presented in this thesis were to; (1) understand and document current nutrition therapy practices in Australia, New Zealand and internationally, with a particular focus on energy prescription and delivery; (2) determine if an individually titrated supplemental PN strategy commenced 48–72 hours following ICU admission, and continued for up to 7 days, would increase energy delivery to critically ill adults compared to usual care EN delivery in an Australian and New Zealand population and;

(3) measure energy requirements using indirect calorimetry and nutrition intake in the post-ICU hospitalisation period in critically ill adults.

To address these aims, a program of research was undertaken that included first, a systematic review and meta-analysis of international literature to determine what was known about the impact of energy delivery during critical illness on clinical outcomes. This review found that the literature in this domain predominantly describes small trials, which are usually inconsistently and poorly reported, and no statistically significant differences in clinical outcomes were observed. Second, a practice survey of nutrition provision in ICUs identified that overall, nutrition practices in Australia and New Zealand are largely similar to international practices, but with a few modest differences. Third, a prospective pilot feasibility RCT determined that an individually titrated supplemental PN strategy delivered energy close to recommended levels, without signs of overfeeding, when compared to usual care enteral nutrition delivery. Finally, an observational study indicated that nutrition intake in the post-ICU hospitalisation period is predominately provided by oral nutrition and remains inadequate when compared to predicted and measured energy requirements.

The program of research that contributed to this thesis has established the feasibility of a novel method to improve energy and protein delivery in critical illness, which will be evaluated during postdoctoral work in a larger multi-centre RCT. This program also identified that adequately powered trials, with standardised study processes and outcomes that are intuitive to the mechanisms of a nutrition intervention, are required to better inform clinical practice decisions for nutrition delivery for critically ill patients.

Thesis including published works declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes 5 original papers published in peer-reviewed journals and 2 submitted publications. The core theme of the thesis is delivery of energy in critical illness. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the student, working within the School of Public Health and Preventive Medicine under the supervision of Professor D Jamie Cooper. The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In Chapters 3, 4, 5 and 6, my contribution to the work involved the following:

Thesis Chapter	Publication title	Status (published, in press, accepted or returned for revision, submitted)	Nature and % of student contribution	Co-author name(s) nature and % of co-author's contribution*	Co-author(s), Monash student Y/N*
3	Full-feeding with enteral nutrition is not always "full-feeding" in research and clinical practice	Published	80%. Concept and writing of letter	AR Davies (10%) DJ Copper (10%)	No
3	Full predicted energy from nutrition and the effect on mortality and infectious complications in critically ill adults: a protocol for a systematic review and meta-analysis of parallel randomised controlled trials	Published	65%. Concept, development of search process, writing of the protocol and drafting and critical revision of the manuscript	AR Davies (10%) C Hodgson (5%) A Deane (5%) M Bailey (5%) DJ Cooper (10%)	No
3	Delivery of full predicted energy from nutrition and the effect on mortality in critically ill adults: a systematic review and meta-analysis of randomised controlled trials	Published (In Press)	60%. Concept, screening, data extraction and analysis, drafting and critical revision of the manuscript	AR Davies (15%) C Hodgson (5%) A Deane (5%) M Bailey (5%) DJ Cooper (10%)	No
4	Nutrition therapy in Australia and New Zealand Intensive Care Units: An international comparison study	Submitted	55%. Concept, interpretation of data, drafting and critical revision of the manuscript	SL Peake (5%) M Jarvis (5%) AM Deane (5%) K Lange (10%) AR Davies (5%) M Chapman (10%) DK Heyland (5%)	No
5	Supplemental parenteral nutrition in critically ill patients: a study protocol for a phase II randomised controlled trial	Published	50%. Concept, development of study protocol, drafting and critical revision of the manuscript	AR Davies (10%) Parke R (10%) Bailey M (5%) McArthur C (5%) Gillanders L (5%) DJ Cooper (5%) S McGuinness (10%)	No
5	Supplemental parenteral nutrition versus usual care in critically ill adults: a pilot randomized controlled study	Published	50%. Concept, development of study protocol, drafting and critical revision of the manuscript	AR Davies (10%) Parke R (10%) Bailey M (5%) McArthur C (5%) Gillanders L (5%) DJ Cooper (5%) S McGuinness (10%)	No
6	What happens to nutrition intake in the post-ICU hospitalisation period? An observational cohort study in critically ill adults	Submitted	50%. Concept, development of study protocol, drafting and critical revision of the manuscript	AR Davies (10%) Parke R (10%) Bailey M (5%) C Hodgson (5%) A Deane (5%) DJ Cooper (5%) S McGuinness (10%)	No

I have not renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Student signature: [redacted] **Date:** 8th February 2018

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors.

Main Supervisor signature: [redacted] **Date:** 8th February 2018

Acknowledgements

As a student dietitian at The Alfred, Melbourne, Australia, I knew intensive care was a place I needed to be. So, I would like to begin by thanking Professor Ibolya Nyulasi for giving me a new graduate dietitian position at The Alfred, and for trusting me with so many amazing clinical and leadership opportunities within Alfred Health. These experiences have and will continue to shape my career and I am forever grateful.

Thank you to my supervisors, mentors and colleagues at the Australian and New Zealand Intensive Care Research Centre (ANZIC-RC). In 2008 I decided that I had more questions than answers and took a leap which led me to the ANZIC-RC, and what a decision that was. I am privileged to learn from and work with some of the most talented and inspiring academic clinicians in the world. Specifically, my primary supervisor and ANZIC-RC director Professor D Jamie Cooper – thank you for your guidance and direction and for giving me the feedback that I needed (even if I didn't want it!). To my co-supervisors, A/Professor Carol Hodgson and A/Professor Adam Deane, thank you for your invaluable advice, support, encouragement and patient editing during this process. To Professor Michael Bailey, there would be no PhD without your statistical advice! Thank you for being patient with my basic statistical questions and lack of understanding. And lastly, to one of the best mentors I have ever had, A/Prof Andrew Davies, thank you for giving me a job in 2008 and for all of the advice, guidance and opportunities you have given me, particularly in the early years, it will never be forgotten.

I would also like to acknowledge the co-contributors to the work within this thesis. Many of them are colleagues and friends with whom I have worked for many years. I

have been blessed to work and collaborate with some of the best critical care researchers in the world and this has provided me with unprecedented learning and collaboration opportunities. Specifically, thank you to the management committee of the randomised trial included in this thesis, particularly Dr Shay McGuinness and Dr Rachael Parke, who took me under their wings and recruited a substantial proportion of the participants. A special thank you to the sites (both staff and patients' families who consented to participate), because without you, there would be no research.

To the National Health and Medical Research Council, thank you to those who assessed my PhD application and deemed it worthy of three years of support.

And finally, thank you to my family. To my Mum, Jenny, your support is greatly appreciated and I couldn't have completed this thesis without it. And to my Dad, Alan and brothers, Tom and Dan, thank you for keeping it light and reminding me to have fun. And finally, to my husband Tay, and daughter, Ruby, this family has done this PhD, it is not just mine; without your complete support and understanding I could not have completed it, so thank you. I am grateful to be in a partnership in which I am encouraged and supported to achieve whatever I want. I'm sorry to say that this is just the beginning, not the end ☺!

Never, never, never give up

\- *Winston Churchill*

Dr Campbell Aitken of Express Editing Writing and Research provided professional editing services in accordance with the Institute of Professional Editors' *Guidelines for editing research theses*.

Research outcomes during candidature

Publications directly arising from this thesis:

1. **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. Jan 23 2018;22(1):12.
2. **Ridley EJ**, Davies AR, Hodgson CL, Deane A, Bailey M, Cooper DJ. Delivery of full predicted energy from nutrition and the effect on mortality in critically ill adults: A systematic review and meta-analysis of randomised controlled trials. Clin Nutr. Oct 9 2017. Available http://www.clinicalnutritionjournal.com/article/S0261-5614(17)31358-4/pdf. Epub ahead of print.
3. **Ridley EJ**, Davies AR, Parke R, Bailey M, McArthur C, Gillanders L, et al. Supplemental parenteral nutrition in critically ill patients: a study protocol for a phase II randomised controlled trial. Trials. 2015;16(1):587.
4. **Ridley EJ**, Davies AR, Hodgson C, Deane A, Bailey M, Cooper DJ. Full predicted energy from nutrition and the effect on mortality and infectious complications in critically ill adults: a protocol for a systematic review and meta-analysis of parallel randomised controlled trials. Syst Rev. 2015;4(1):179.
5. **Ridley E**, Davies A, Cooper DJ. Full-feeding with enteral nutrition is not always "full-feeding" in research and clinical practice. JPEN J Parenter Enteral Nutr. 2015;39(4):383.
6. **Ridley EJ**, Peake SL, Jarvis M, Deane AM, Lange K, Davies AR, Chapman M, Heyland D. Nutrition therapy in Australia and New Zealand Intensive Care Units: an international comparison study. JPEN J Parenter Enteral Nutr. 2018.

Research outcomes during candidature (continued)

7. **Ridley EJ**, Parke R, Davies AR, Bailey M, Hodgson CL, Deane A et al. What happens to nutrition intake in the post-ICU hospitalisation period? An observational cohort study in critically ill adults. Accepted, JPEN J Parenter Enteral Nutr. 2018

Other publications during candidature:

8. Litton E, **Ridley EJ**, Delaney A. Cardiac surgery and the low hanging fruit of perioperative nutritional interventions. Journal of Cardiothoracic and Vascular Anesthesia. 05/01/2018. Available https://www.sciencedirect.com/science/article/pii/S1053077017310376. Epub ahead of print.
9. The target investigators on behalf of the ANZICS clinical trials group. Study protocol for The Augmented versus Routine Approach to Giving Energy Trial (TARGET). Crit Care Resusc. Crit Care & Resus. March 2018;20(1): 6-15.
10. The target investigators on behalf of the ANZICS clinical trials group. Statistical analysis plan for The Augmented versus Routine Approach to Giving Energy Trial (TARGET). Crit Care & Resus. March 2018;20(1): 15-22.
11. Charrière M*, **Ridley E*,** Hastings J, Bianchet O, Scheinkestel C, Berger MM. Propofol sedation substantially increases the caloric and lipid intake in critically ill patients. Nutrition. 2017;42:64-8. **Joint 1st authors*.
12. Hastings J, **Ridley EJ**, Bianchet O, Roodenburg O, Levkovich B, Scheinkestel C, et al. Does propofol sedation contribute to overall energy provision in mechanically ventilated critically ill adults? A retrospective observational study. JPEN. 2017:148607117721917.

Research outcomes during candidature (continued)

13. Lambell K, King S, **Ridley E.** Identification of malnutrition in critically ill patients via the Subjective Global Assessment Tool: more consideration needed? J Intensive Care Med. 2017;32(1):95.
14. Reid DB, Chapple LS, O'Connor SN, Bellomo R, Buhr H, Chapman MJ, Davies AR, Eastwood GM, Ferrie S, Lange K, McIntyre J, Needham DM, Peake SL, Rai S, **Ridley EJ**, Rodgers H, Deane AM. The effect of augmenting early nutritional energy delivery on quality of life and employment status one year after ICU admission. Anaesth Intensive Care 2016;44(3):406-12.
15. **Ridley E**, Gantner D, Pellegrino V. Reply Letter to the Editor – Nutrition therapy in critically ill patients – A review of current evidence for clinicians. Clin Nutr. 2016;35(1):244.
16. Tatucu-Babet OA, **Ridley EJ**, Tierney AC. Prevalence of underprescription or overprescription of energy needs in critically ill mechanically ventilated adults as determined by indirect calorimetry: a systematic literature review. JPEN J Parenter Enteral Nutr. 2016;40(2):212-25.
17. Price J, Hoy J, **Ridley E**, Nyulasi I, Paul E, Woolley I. Changes in the prevalence of lipodystrophy, metabolic syndrome and cardiovascular disease risk in HIV-infected men. Sex Health. 2015;12(3):240-8.
18. **Ridley E**, Gantner D, Pellegrino V. Nutrition therapy in critically ill patients – a review of current evidence for clinicians. Clin Nutr. 2015;34(4):565-71.

Research outcomes during candidature (continued)

19. **Ridley EJ**, Davies AR, Robins EJ, Lukas G, Bailey MJ, Fraser JF, et al. Nutrition therapy in adult patients receiving extracorporeal membrane oxygenation: a prospective, multicentre, observational study. Crit Care Resusc. 2015;17(3):183-9. 1.
20. Peake SL, Davies AR, Deane AM, Lange K, Moran JL, O'Connor SN, **Ridley EJ**, Williams PJ, Chapman MJ, investigators T, the A, New Zealand Intensive Care Society Clinical Trials G. Use of a concentrated enteral nutrition solution to increase calorie delivery to critically ill patients: a randomized, double-blind, clinical trial. Am J Clin Nutr 2014;100(2):616-25.

Prizes and awards during candidature:

2017

1. Travel scholarship to attend the American Society of Parenteral and Enteral Nutrition Clinical Nutrition Week, Orlando, USA; Monash University; $2,000
2. Best new project presentation – honourable mention; Australian and New Zealand Intensive Care Society Clinical Trials Group Winter Meeting, Queenstown, New Zealand

2014

3. National Health and Medical Research Council Postgraduate Scholarship; National Health and Medical Research Council, Australia; $102,578

Research outcomes during candidature (continued)

Grants during candidature:

2017

Ridley EJ, Chapple L, Deane A, Hodgson C, Cooper C, Bailey M. Intensive nutrition in critically ill adults: A pilot randomised controlled study; Baxter Healthcare Corporation (United States); $2,381,895

Keynote and invited presentations during candidature:

1. **Ridley E (Keynote).** "*Role of dietitians in critical illness – changing the status quo*". Presented at the 23rd Malaysian Dietitians National Conference, Kuala Lumpur, Malaysia, 2017 July
2. **Ridley E (Invited).** "*Indirect calorimetry and predictive equations in determining the nutrition requirement for critically ill patients*". Presented at the 23rd Malaysian Dietitians National Conference, Kuala Lumpur, Malaysia, July 2017
3. **Ridley E (Invited).** *"Nutrition and metabolic carts"*. Presented at the 11th Alfred ICU Advanced Mechanical Ventilation Conference, Melbourne, July 2017
4. **Ridley E (Invited).** *"Feeding for frailty (and other considerations)"*. Presented at The ICU Physiotherapy & Multidisciplinary Symposium 2017-ICU and The Road to Recovery, Melbourne, 2017 July
5. **Ridley E (Invited).** "*ANZ Supplemental Parenteral Nutrition Study"*. Presented at Collaborative Clinical Trials in Intensive Care Medicine, Prato, Italy, June 2017

Research outcomes during candidature (continued)

6. **Ridley E (Invited within plenary session)**. "*ANZ Supplemental Parenteral Nutrition Study*". Presented at the American Society of Parenteral and Enteral Nutrition Clinical Nutrition Week (CNW) Orlando, USA, January 2017
7. **Ridley E (Invited)**. *"How indirect calorimetry can benefit patients in ICU"*. Presented at the 10th Alfred ICU Advanced Mechanical Ventilation Conference, Melbourne, Australia, July 2016
8. **Ridley E (Invited)**. *"Nutrition requirements for the compromised patient including overfeeding"*. Presented at the Australian Society of Parenteral and Enteral Nutrition *(*AuSPEN) Advanced Clinical Nutrition Course, Sydney, Australia, May 2016
9. **Ridley E (Invited)**. *"Critical appraisal in nutrition support"*. Presented at the Australian Society of Parenteral and Enteral Nutrition *(*AuSPEN) Advanced Clinical Nutrition Course, Sydney, Australia, May 2016
10. **Ridley E (Invited)**. *"Indirect calorimetry in ICU"*. Presented at the Baxter Healthcare ICU Nutrition Symposium, Sydney, Australia, May 2016
11. **Ridley E (Invited)**. "*Early rehabilitation to improve recovery"*. Presented at The ICU Multidisciplinary Symposium: Early Rehabilitation to Improve Recovery, Melbourne, Australia, July 2015
12. **Ridley E (Keynote)**. *"Using technology to enhance clinical practice"*. Presented at the 32nd Dietitian's Association of Australia ASM, Perth, Australia, May 2015.
13. **Ridley E (Invited)**. *"Practice based research – workshop"*. Presented at the 32nd Dietitian's Association of Australia ASM, Perth, Australia, May 2015.

Research outcomes during candidature (continued)

Other presentations during candidature:

14. **Ridley E**. *"Intensive nutrition therapy in critically ill adults: a pilot randomized controlled trial"*. Presented at the Australian and New Zealand Intensive Care Society Clinical Trials Group Winter Meeting, Queenstown, New Zealand, August 2017

Accepted oral abstracts during candidature:

1. King S, Leung J, Eldho P, Ihle J, **Ridley EJ,** Cleland H. "*Measured energy expenditure in critically ill burn patients correlates with time post-injury but not burn size"*. Presented at 43rd AuSPEN ASM, Gold Coast, Australia, November 2017. (Presented by S King)
2. **Ridley EJ,** Davies AR, Hodgson, C, Deane A, Bailey M, DJ Cooper. *"Full predicted energy from nutrition and the effect on mortality in critically ill adults: A systematic review and meta-analysis of parallel randomised controlled trials"*. Presented at 42nd AuSPEN ASM, Melbourne, Australia, November 2017. (Presented by AR Davies due to illness).

Accepted poster presentations during candidature:

1. **Ridley E**, Robins E, Lukas G, Nyulasi I, Davies A, Bailey M, Fraser J. "*Nutrition provision to patients requiring ECMO"*. Presented at Alfred Research Week, The Alfred Hospital, October 2015

Research outcomes during candidature (continued)

2. **Ridley E,** Robins E, Lukas G, Nyulasi I, Davies A, Bailey M, Fraser J. "*Nutrition provision to patients requiring ECMO"*. Presented at American Thoracic Society International Conference, San Diego, USA, May 2014
3. Charriere M, **Ridley E,** Hastings J, Bianchet O, Schienkestel O, Berger M. "*Contribution of propofol sedation to energy and lipid intake in critically ill patients in two university hospitals"*. Presented at the European Society of Enteral and Parenteral Nutrition Congress, Geneva, Switzerland, September 2014 (by M Charriere)

Abbreviations and acronyms

BMR	Basal metabolic rate
EN	Enteral nutrition
Ht	Height
ICU	Intensive care unit
MJ	Megajoule
HBE	Harris-Benedict equation
PN	parenteral nutrition
RCT	Randomised controlled trial
kcal	Kilocalorie
Wt	Weight

Abbreviations in published papers and/or appendices are not listed here

Chapter 1: Introduction

1.1 Chapter summary

This chapter provides an introduction to the research and an update on current literature regarding practice of artificial nutrition delivery during critical illness, with a specific focus on energy metabolism, the estimation of energy requirements and delivery of energy in the intensive care environment.

1.2 Nutrition in the critically ill patient

Each year over 130,000 Australians are admitted to an intensive care unit (ICU) in Australia. These patients are, by definition, some of the sickest in the hospital and consume significant health care resources, costing billions of dollars each year [1]. The provision of artificial nutrition to critically ill patients when they are mechanically ventilated is an accepted international standard of care, as normal intake by mouth is impossible. The primary aims of nutrition in this setting are to:

- minimise negative energy balance, avoid starvation and preserve lean muscle mass;
- maintain tissue function (primarily the liver, immune system, skeletal and respiratory muscles;
- support recovery in the post-ICU period; and
- modify metabolic changes and function using substrates that have been shown to be beneficial [2].

While there is evidence for many aspects of care provided in critical illness, some areas lack robust evidence. The provision of artificial nutrition in critical illness is an example of an element of care which is routinely provided but which lacks robust evidence regarding application and effect on clinical and functional outcomes.

1.3 Components of energy expenditure: health and disease

In healthy people, total daily energy expenditure consists of three main components: resting energy expenditure (also commonly referred to as basal metabolic rate (BMR), approximately 60–80% of total expenditure); the thermic effect of food (10–20% of total expenditure); and activity-related expenditure (also 10–20% of total expenditure) [2]. For critically ill people in care, the thermic effect of food is minimal as artificial nutrition is generally provided in a constant infusion (rather than in bolus form as with normal eating), and the effect of activity on metabolism is removed or minimised with sedation. Thus, resting energy expenditure approximates total daily energy expenditure in critical illness. The amount of lean body mass is the strongest driver of metabolic rate in health and illness, but age, sex, temperature, inflammation and disease course and process also influence it [3].

1.4 Energy metabolism and the metabolic response to injury and illness

The process of metabolism results in the combustion of carbohydrate, protein, fat and alcohol to produce energy for body functions [2]. After critical injury and/or illness occurs, metabolic changes result as an evolutionary response to energy delivery ceasing during the immediate post-illness and/or injury period [2, 4]. In 1942, Cuthbertson described the metabolic changes resulting from critical injury and illness as consisting of three phases [5]:

- the ebb or early phase of decreased metabolism;
- the flow or catabolic phase; and
- the anabolic phase of recovery.

In the early ebb phase, in order to provide the body with energy while food is unavailable, catabolic hormone secretion increases, endogenous glucose production is stimulated, and metabolic rate and insulin sensitivity are decreased [2, 4]. These responses are vital in the short term for survival and to provide glucose to the brain and other essential tissues, but when continued for long periods, result in loss of lean body mass, organ dysfunction and ultimately death if the body does not recover [2, 4]. In a modern-day ICU setting these changes can be moderated and the patient supported to facilitate recovery, but it can mean that the changes persist for long periods of time, with the potential for deleterious consequences [4]. Following the initial ebb phase, the patient's metabolic rate usually increases and a high turnover of substrate follows [4]. In addition to the physiological response, there are many factors which can either increase or decrease the metabolic response to critical illness, often occurring in unison (detailed in Table 1).

Table 1: Parameters that influence energy expenditure in the ICU setting (reproduced with permission [2]):

Metabolic rate is increased by:	
Fever	13% per 1°C
Shivering	100%
Visit of relatives	40%
Work of breathing	25%
Nutrition	9%
Catecolaimes	30%
Metabolic rate is decreased by:	
Hypothermia	13% per 1°C
Muscle relaxants	40%
Analgesia	50%
Adapted ventilation	20%
Starvation	10–20%
Beta blockers	25%

1.5 Determining energy requirements in critical illness

The gold standard method for measuring resting energy expenditure in critical illness is indirect calorimetry [6]. By connecting to the patient's mechanical ventilator, oxygen utilisation and carbon dioxide production are measured for a representative period of time, which – using a standard equation – is then used to determine resting energy expenditure [6]. Although regarded as a gold standard and recommended by many experts, the technology is expensive and definitive evidence about its benefit in

measuring energy expenditure and thus direct energy delivery in critical illness is lacking. Thus, while the technique improves precision regarding energy expenditure, it has not been readily implemented into clinical practice. Similarly, simple bedside methods exist for calculating an approximate energy requirement to guide artificial nutrition delivery, but there are many concerns about their accuracy (discussed in Chapter 2) [7, 8].

1.6 An overview of artificial nutrition therapy in critical illness

The provision of artificial nutrition to critically ill patients when normal oral intake cannot occur plays a vital role in supporting patients through multiple metabolic changes [2, 4]. Best practice guidelines exist to guide the provision of artificial nutrition in critical illness, but are largely based on small trials, observational data or expert opinion and some have not been updated recently [9-13]. It is generally recommended that enteral nutrition (EN), delivered via a gastric tube, be provided within 24–48 hours of ICU admission to patients who are unable to eat [9-12]. EN is preferred as it mimics normal intake, acts to preserve gastrointestinal function and is inexpensive [2]. Furthermore, delivery of EN within 24 hours of admission to the ICU in critical illness has been associated with reduced infective complications and mortality when compared to providing EN after this period [12, 14]. As a specially formulated liquid solution, the recommended dietary intake for all macro and micronutrients is provided in an approximate volume of 1.5–2 L per day depending on weight and metabolic rate. However, the delivery of EN in critically ill patients is not straightforward, with observational data consistently reporting a mean delivery of just 50–60% of the intended energy supply [15, 16]. Patient factors such as gastrointestinal intolerance as a consequence of critical illness, treatments provided (e.g., opioid and

sedation medications) and system factors (e.g., the requirement to fast before procedures) contribute to this problem [17, 18]. Despite these difficulties, it is unknown whether delivery of energy above the 50–60% provided in standard care improves clinical and functional outcomes.

Sometimes EN cannot be provided due to functional issues of the gastrointestinal tract resulting from the patient's underlying illness or condition, or an intolerance that develops due to illness [2, 10]. Parenteral nutrition (PN) is an alternative form of nutrition which provides macro and micronutrients in a ready-to-absorb form into the patient's vein via a central line. PN has been used less than EN in critical illness, because the solutions are more expensive, there have been concerns about increased infective complications, and in the absence of enteral nutrient, atrophy of gastrointestinal enterocytes occurs [19]. PN is usually reserved for situations when the patient has an absolute contraindication to using the gastrointestinal tract or attempts at EN have failed [10]. However, recent well-designed and conducted trials have challenged the perceived higher risk of infective complications with the use of PN than with usual care nutrition delivery in critical illness by reporting no differences in infective complications when provided in a modern ICU setting with stringent line control procedures [20, 21].

1.7 Energy delivery in critical illness

Optimal energy delivery is one of the main functions of artificial nutrition provision in critical illness [2]. Despite the known problems with estimation of energy requirements using predictive equations and with delivery of energy using EN in critical illness, some best practice recommendations continue to suggest that energy requirements be

met in critical illness [9-12]. Observational data suggests that energy delivery close to a predicted requirement is associated with better clinical outcomes, but this has not been replicated in prospective randomised trials [22-25]. Recently, researchers analysed energy delivery according to a measured energy requirement using indirect calorimetry over the whole ICU stay in a predominantly surgical population; a U-shaped relationship was observed with the delivery of energy, suggesting that 70% is the optimal delivery proportion [26]. This relationship remained significant when the analysis was adjusted for other important covariates such as age, gender and illness severity. This is the largest study to investigate the relationship of energy delivery guided by a measured requirement to important clinical outcomes and thus provides valuable information, but the risk of mortality being confounded by factors not accounted for in the cohort study design must be considered in its interpretation. Only a few small prospective trials have specifically investigated the role of a measured requirement in direct nutrition, or included a measured requirement as part of study methodology to answer an alternate question. These trials lack the power needed to show any impact on important clinical benefit and thus do not provide any definitive answers [27-29]. The role of energy in critical illness is therefore uncertain due to the problems associated with meeting energy requirements, the inaccuracy of predicted energy estimations and the lack of definitive evidence about using a measured energy requirement to guide energy delivery. However, due to the current recommendations in many best practice guidelines to meet energy requirements in critical illness, many strategies to improve energy delivery have been proposed and tested in multiple trials [30-35]. Strategies which have been tested to increase energy delivery include use of evidence-based feeding protocols, small bowel feeding tubes, use of prokinetic drugs and manipulation of the acceptable gastric residual volume, which is commonly used to

measure tolerance of EN in critical illness. Many trials of such interventions have not observed increases in energy delivery and the others only modest increases, and none has demonstrated a beneficial effect on clinical outcomes [30-35]. A small pilot trial (on which the author collaborated but which is not included in this thesis) tested a blinded intervention which delivered a 1.5 cal/ml solution at a rate equivalent to a 1 cal/ml solution (standard care), with the purpose of providing additional energy [36]. The strategy was successful in achieving the primary outcome of increased energy delivery in the intervention arm and 90-day mortality was decreased in the intervention group (a secondary outcome of the feasibility trial) [36]. This is the only available EN strategy which has successfully increased energy delivery in critical illness (and has been tested in a large phase III trial (ClinicalTrials.gov, NCT02306746)) in which the author was also involved, to be published in 2018). The only other successful strategy to increase energy delivery close to a predicted or measured energy requirement is the combination of PN with EN. One large trial and several feasibility-sized trials have tested this hypothesis and found that this strategy was able to deliver additional energy in critical illness, but the effect on clinical outcomes was conflicting (Chapter 2, Tables 5 and 6) [27-29, 37, 38].

1.8 Gaps in the literature on energy delivery in critical illness

There are several plausible reasons for the lack of definitive evidence for the role of energy in critical illness. Of particular importance is that trials to date have not considered dynamic metabolic requirements in relation to energy utilisation during the phases of critical illness and recovery, and therefore tailoring energy delivery over time accordingly has not occurred. Due to the problems with the current methods available to predict energy needs, a constant requirement is often assumed from the beginning to

the end of a critically ill patient's stay in ICU; this may be inadequate when the time-variable metabolic response to illness is considered (Figure 1).

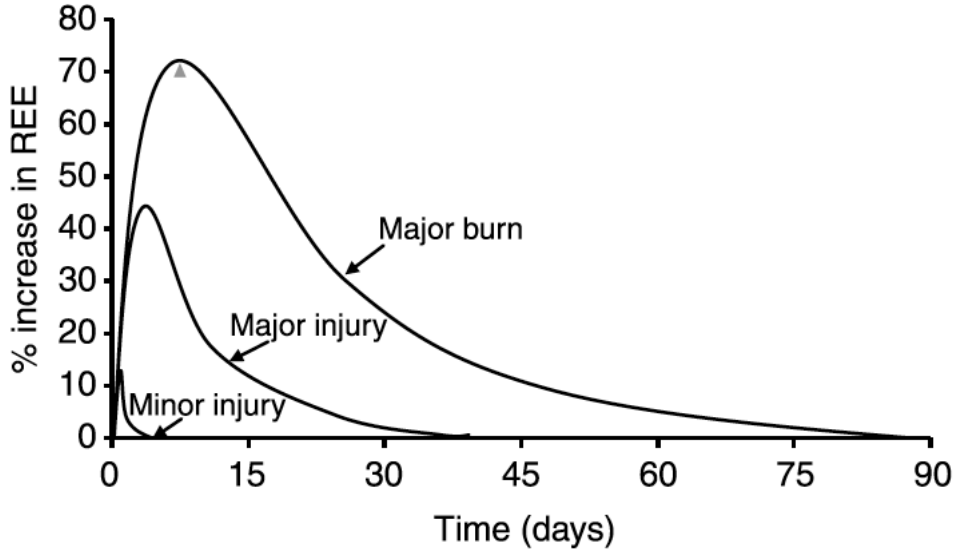

Figure 1: Approximate change in resting metabolic rate over the time course of injury and/or illness (reproduced with permission [39]).

Due to the dynamic nature of energy utilisation in critical illness, the importance of exogenous nutrition in the form of artificial nutrition is likely to differ during metabolic phases, as is the response to exogenous energy supply, but evidence on this is scarce. Early in critical illness, the metabolic and hormone changes which mobilise endogenous glucose supply provide a substantial proportion of energy needs [40]. This may indicate that provision of exogenous energy via artificial nutrition during this period does not need to be as substantial as once thought. This may also explain why several trials of short-term hypocaloric energy delivery have not shown its superiority to standard care; the energy deficit assumed in hypocaloric interventions, when applied early in illness, may not have been as great due to endogenous energy supply [41, 42]. Moreover, all of the currently published major clinical trials in critical care nutrition

which investigated an energy-related topic have provided early interventions for short durations (usually 5–7 days, with the longest 14 days), and none has considered what happens to nutrition intake in the post-ICU period (often longer than critically ill patients' time in the ICU) [43]. The question thus becomes: when do these endogenous energy stores decrease and exogenous provision of nutrition become important? Later in the ICU stay, when endogenous glucose supplies are depleted, the metabolic requirements change to that of an anabolic phase, in which exogenous energy sources may be more important [40]. There is however, very little information about nutrition intake in critically ill survivors late in the ICU stay and when the patient is transferred to the ward. The little information that is available indicates that nutrition intake in this period remains below estimated requirements and that there are multiple complex patient, organisational culture and system reasons for this [44-46].

1.9 Aims and hypotheses of this thesis

There are three key hypotheses in relation to this thesis:

1. **The majority of evidence available in the field of critical care nutrition is of low quality;**
2. **Energy delivery in critical illness remains below recommended and prescribed amounts in critically ill adults throughout hospitalisation; and**
3. **A supplemental parenteral nutrition strategy will provide additional energy to critically ill adults compared to standard care nutrition delivery**

The aims of the research presented in this thesis were to; (1) Assess the effect of near-target energy delivery (80-100% of energy requirements) on mortality and other clinically important outcomes (Chapter 3, hypothesis 1); (2) understand and document

current nutrition therapy practices in Australia, New Zealand and internationally, with a particular focus on energy prescription and delivery (Chapter 4, hypothesis 2); (3) determine if an individually titrated supplemental PN strategy commenced 48–72 hours following ICU admission, and continued for up to 7 days, would increase energy delivery to critically ill adults compared to usual care EN delivery in an Australian and New Zealand population (Chapter 5, hypothesis 2 and 3) and; (3) measure energy requirements using indirect calorimetry and nutrition intake in the post-ICU hospitalisation period in critically ill adults (Chapter 6, hypothesis 2).

Chapter 2: Methodology of energy estimation and supplemental parenteral nutrition to provide additional energy in critical illness

2.1 Chapter summary

This chapter provides detailed methodology for two key aspects of the research: commonly used methods to assess energy requirements in critical illness, and supplemental PN as an intervention to provide additional energy in critical illness.

2.2 Estimation of energy requirements in critical illness

Indirect calorimetry is rarely used in the intensive care setting, particularly outside trial settings [47]. As such, mathematical equations have been developed to predict energy requirements [3]. Most of these equations were developed based on small numbers of participants, and often in healthy populations. In healthy people the equations provide an estimate of resting metabolic rate, but in ill people they fail to account for the effect of injury and/or illness on metabolism. To account for this, 'injury' or 'stress' factors are applied according to clinical condition, with the aim being to extrapolate the healthy estimate to the hospital setting (including in intensive care) [3, 7]. The extrapolation of these equations from a healthy state to disease states, like critical illness, usually results in inaccuracy when compared to energy expenditure measured by indirect calorimetry [7, 8]. The inaccuracies exist for several reasons:

individual patient heterogeneity in the metabolic response to critical illness;

differing body compositions of lean body and fat mass;

the population in which the equation was originally developed (including their age, body composition and disease state);

the characteristics of the population in which the equation is being used;

the addition of commonly used ‘injury’ or ‘stress’ factors; and

adjustments of body weight when using the equations, so to avoid overfeeding in obese individuals.

Importantly, these inaccuracies are often greater as populations become more unwell, more obese, more malnourished and older – the very populations most likely to require accurate energy assessment and delivery [7, 48]. Despite these issues, however, predictive energy estimations are easy to implement and because of their practicality, they remain the most common methods of energy estimation in clinical practice [3].

2.3 Injury and illness factors used to adjust predictive equations in hospital settings

As noted earlier, injury or stress factors have been developed to extrapolate predictive energy estimates developed in healthy individuals to the hospital setting (Figure 2) [3, 39, 49].

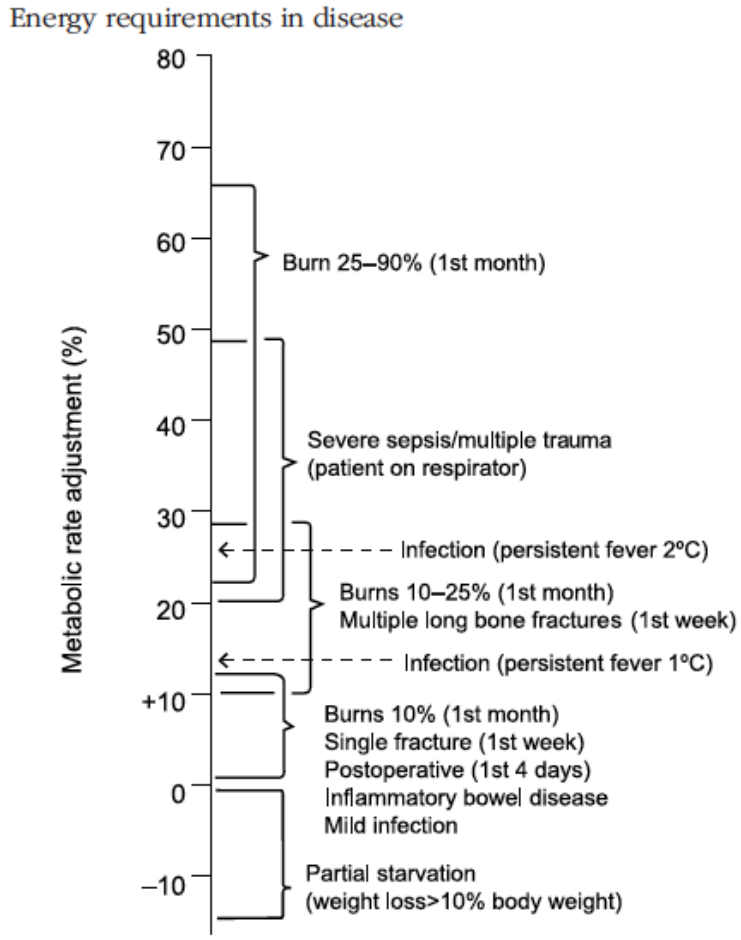

Figure 2: Suggested increases in basal metabolic rate due to common illnesses and/or injuries (reproduced with permission [39]).

In critical illness, the resting energy expenditure obtained from a predictive equation estimate is multiplied by the factor corresponding to the clinical condition to provide an overall energy estimate. The multiplication of an already inaccurate estimate by another estimated factor further contributes to the inaccuracy of predictive energy estimates compared to measured estimates [3]. Furthermore, the most commonly used factors

were developed many years ago (1979 [49] and 1994 respectively [50] and were based on small sample sizes [3, 39, 49]. Advances in components of medical management which affect metabolism in critically ill patients (such as surgery and sedation practices, pain and ventilation management) have modified the metabolic response to illness and thus the injury factors are very likely to have changed over time. Furthermore, considerable variation can exist between patients with the same clinical condition, and may affect metabolic rate, making one adjustment factor unsuitable. Despite these failings the factors continue to be used in clinical practice, and clinicians receive little guidance about how to use and choose the relevant factor.

2.4 Predictive methods of estimating energy expenditure

2.4.1 Harris–Benedict equation

The Harris–Benedict equation (HBE) (Table 2) is the most popular predictive equation for energy expenditure, used worldwide in all hospital settings [40, 51]. First published in 1918, it was based on 239 healthy subjects, including 93 newborns. An adjustment for illness was later published to account for the unwell hospitalised patient; a stress factor of 1.2–1.6 was recommended depending on the clinical condition [3]. Comparison of the original and the adjusted equation to a measured estimate found the equations to be inaccurate in critical illness, and consequently neither equation is recommended for use in that setting [3].

Table 2: The Harris–Benedict equation [51]

Male	**Female**
13.75(Wt) + 5(Ht)- 6.8(age) + 66	9.6(Wt) + 1.8(Ht) – 4.7(age) + 655

NB: In illness the result should be multiplied by 1.2–1.6 depending on the clinical condition: Ht: Height; Wt: Weight

2.4.2 Schofield equation

Developed in 1985 from a meta-analysis of 100 studies including 7173 healthy participants, the Schofield equation is the predictive estimate equation most commonly used in hospitals in the United Kingdom and Australia (Table 3) [48, 52]. The studies included in the meta-analysis were published between 1914 and 1988; 2200 subjects were Italian soldiers and there were very few people over the age of 60 in the cohort [48]. A study of 27 mechanically ventilated patients compared the outcomes of multiple commonly used predictive equations to the results of continuous indirect calorimetry monitoring for a minimum of five days. The use of the Schofield equation with actual weight to guide energy delivery would have resulted in underfeeding (<80% of measured energy expenditure) in 15% of patients and overfeeding (>110% of measured energy expenditure) in 19% of patients [53].

Table 3: The Schofield equation [52]

Males	**BMR**	**Females**	**BMR**
Age (years)	MJ/day	Age (years)	MJ/day
10–17	0.074 x Wt + 2.754	10–18	0.056 x Wt + 2.898
18–29	0.063 x Wt + 2.896	18–30	0.062 x Wt + 2.036
30–59	0.048 x Wt + 3.653	30–60	0.034 x Wt + 3.538
60–74	0.0499 x Wt + 2.930	60–74	0.0386 x Wt + 2.875
Over 75	0.0350 x Wt +3.434	Over 75	0.041 x Wt + 2.610

BMR: Basal metabolic rate; MJ: Megajoule; Wt: Weight

2.4.3 Equations specifically developed for critically ill populations

Due to the inaccuracy of the original predictive equations when applied to critically ill populations, several equations specific to critical care have been proposed [3]. The American College of Chest Physicians fixed prescription estimate of 25kcal/kg/day is the most popular weight-based fixed equation, determined via a consensus procedure and published in 1997 [54]. It is also one of the most popular overall methods for assessment of energy requirements with both medical staff and dietitians working in critical illness, probably because of its ease of application [3]. The patient's weight is multiplied by the 25 kcal/kg requirement to obtain an overall daily energy estimate [54]. The chosen amount of 25 kcal/kg/day was not referenced in the original statement, but does lie within the range of energy requirements in critical illness (confirmed by indirect calorimetry, 20–35 kcal/kg/day) [3, 7]. Whilst this method is straightforward to implement at the bedside, several issues contribute to the inaccuracy of the estimation: which weight to use (particularly in obesity – the patient's current or 'adjusted' weight), and use of a blanket prescription of 25 kcal/kg/day for all critically ill patients regardless of clinical condition, body composition and length of time in ICU [3]. This method's accuracy (defined as estimating within 10% of a requirement measured by indirect calorimetry) has been reported to be 35% when actual body weight is used in the estimate and 46% when an adjusted weight is used, and the proportion of estimates with large errors (>15% of the measured estimate) as 43–51% [7].

The Ireton-Jones, Penn State and Swinamer Equations are all predictive equations developed specifically with data from critically ill populations (Table 4). The studies conducted to develop them contained small numbers, and few validation studies have

occurred [3, 55-58]. These equations are not widely adopted by clinicians as they are often more complex than earlier equations, thus taking more time, and there is a lack of definitive evidence as to their relative benefit [3]. Of all of the available equations, the Penn State has been reported to the most accurate across multiple patient sub-groups [7]. Originally derived in 1998 from data on 169 ventilated critically ill patients, the equation used the HBE as a basis to estimate resting energy expenditure and applied factors which modify metabolism in critical illness [55]. It was modified in 2003, with the Mifflin St Joer equation substituted for the HBE to improve accuracy [55, 59]. In a comparison of multiple general and ICU-specific predictive equations to indirect calorimetry measurements in 202 ventilated adult ICU patients, the Penn-State equation was reported to be 67% accurate in the overall population, and 77% accurate in sub-group analysis of elderly non-obese patients [7]. This accuracy does vary, however, depending on the study methodology utilised, with other reports being less favourable [3]. Two comprehensive reviews of the accuracy of predictive estimates compared to measured requirements recommend the use of Penn-State equation in the absence of indirect calorimetry, but best practice guidelines commonly recommend 20-25 kcal/kg day, despite the known accuracy issues, in the absence of indirect calorimetry [3, 10, 11, 60]. This discrepancy reflects the lack of definitive evidence in this area.

Table 4: Predictive equations developed in critically ill populations

Equation name	Equations
Ireton-Jones 1992 [57]	1925 -(5)Wt- Age(10) + (281 if male) + (292 if Trauma present) + (851 if burns present)
Ireton-Jones 2002 [56]	1784 - Age (11) + (5)Wt+ (244 if male) + (239 if trauma present) + (804 if burns present)
Penn State (PSU) [55]	
PSU (HBE)	HBE(0.85) + Tmax(175)* + Ve(32)^{1} - 6344
PSU (HBE adjusted weight)	HBE adjusted(1.1) + Tmax(140)* + Ve(32)^{1} - 5340
PSU (Mifflin)	Mifflin(0.96) + Tmax(167)* + Ve(31)^{1} - 6212
Swinamer [58]	BSA(941) - Age(6.3) + T(104) + RR(24) + Vt(804) - 4243

*Tmax is the maximum body temperature in the previous 24 hours; ^{1}Ve is minute ventilation recorded on the ventilator at the time of assessment

BSA: Body surface area; HBE: Harris–Benedict Equation; Ht: height; T: body temperature in degrees centigrade; Ve: expired minute ventilation; Vt: tidal volume in L/breath; Wt: Weight

2.5 Supplemental parenteral nutrition as an intervention to increase energy provision in critical illness

With the risks which were previously a concern with PN appearing to be similar to those associated with EN use, the combination of PN with EN (termed supplemental PN) has been proposed to meet the energy deficit associated with EN (Figure 3) [20, 21, 61].

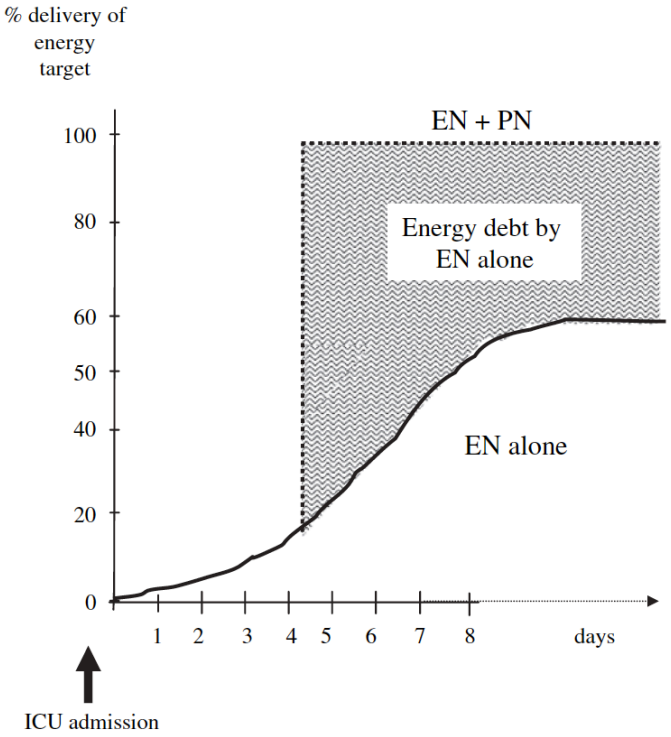

Figure 3: Supplemental parenteral nutrition to meet energy needs with insufficient enteral nutrition delivery (reproduced with permission [61]).

When applying this intervention in clinical practice or research, PN is provided in addition to EN in patients in whom continued artificial nutrition is thought to be beneficial and in whom delivery of EN close to predicted targets is impossible [60]. When using the intervention, it is important that it is not commenced immediately on ICU admission, but rather, 3–5 days after admission so that the need for ongoing

artificial nutrition is established, the risk of overfeeding is reduced and adequate delivery of EN has been attempted [61]. Close monitoring is also required, so that the provision of total energy from EN and PN achieves between 80–100% of the estimated requirement [61]. Table 1 in the Appendix to this Chapter summarises the key randomised trials of supplemental PN intervention in ICU.

2.6 Conclusion

The gold standard method for energy estimation (indirect calorimetry) is largely unavailable in routine practice; instead, several bedside predictive equations are used to estimate energy requirements in critical illness. These methods were mostly developed in healthy populations and are extrapolated to critical illness with injury factors, resulting in poor accuracy compared to measured estimates. Those methods developed specifically in critically ill populations still pose accuracy concerns, largely due to the inability of any equation to account for the individual variation in patient and clinical factors which drives metabolism. Best practice guidelines usually recommend that nutrition delivery should provide close to predicted energy needs in critical illness, but there are many delivery problems with the use of EN alone. Supplemental PN is a strategy which has been proven to deliver additional energy in critical illness.

Chapter appendices:

2.7 Table 5: Description of RCTs that have investigated a supplemental PN intervention

Author, year, country (ref)	No. of centres	Study objective	Intervention (I)	Control (C)	No. randomized in each group		Age (years ± SD)		BMI (kg/m²± SD)		Sex (n, % male)		Main population admission category (%)		APACHE II (score ± SD)	
					I	C	I	C	I	C	I	C	I	C	I	C
Bauer, 2000, France [62]	2	To determine whether nutrient intake by early EN with PN improves levels of retinol-binding protein and prealbumin (primary endpoint) and reduces morbidity and mortality (secondary endpoint)	EN plus PN	EN plus placebo	60	60	53±18	55±18	n/a	n/a	40, 66%	42, 70%	Medical (58%)	Surgical (57%)	n/a	n/a
Casaer, 2011, Belgium [38]	7	To investigate whether prevention of a energy deficit during critical illness by providing SPN early in the disease course would reduce the rate of complications or whether withholding PN for 1 week would be clinically superior	Late initiation SPN	Early initiation SPN	2328	2312	64±15	64±14	n/a	n/a	1486, 64%	1486, 64%	Cardiac (61%)	Cardiac (61%)	23±11	23±10
Heidegger, 2013, Switzerland [28]	2	To determine if individually optimised energy provision by SPN for 5 days after day 3 of ICU admission could improve clinical outcome in severely ill patients in the ICU for whom EN alone was insufficient	SPN	Usual care EN	153	152	61±16	60±16	25±4	26±5	110, 72%	105, 69%	Neurological (15%)	Neurological (15%	22±7	23±7
Wischmeyer, 2017, USA, Candad, Belgium and France [37]	1	To ensure a clinically significant difference in energy/protein intake (approximately 30% difference; or 600-1000 kcal/day and 20-30g of protein/day) with the intervention.	SPN + EN	Usual care EN delivery	52	73	56±20	55±16	34±15	33 ±15	21, 40%	39, 53%	Sepsis (15%)	Respiratory (33%)	21±6	21±7

APACHE: Acute Physiology And Chronic Health Evaluation; BMI: Body mass index; EN: Enteral nutrition; ICU: Intensive care unit; PN: Parenteral nutrition; SD: Standard deviation; SPN: Supplemental parenteral nutrition

2.8 Table 6: Intervention details, outcomes and methodological considerations in RCTs that have investigated a supplemental PN intervention

Author, year, country (ref)	Energy estimation method	Intervention description	Duration of intervention	Energy delivered control (kcal or kcal/kg/day ± SD), % target)	Energy delivered intervention (kcal ± SD), % target)	Protein delivery control (g/day±SD or % requirements ± % SD)	Protein delivery (g/day±SD or % requirements ± % SD))	Primary outcome	Primary result	Methodological considerations
Bauer, 2000, [62]	25 kcal/kg	3-in-1 PN solution with vitamins, administered at 1cal/ml through central line (not dedicated to nutrition). EN was BOLUS 4/24 with a standard polymeric formula. Using the total amount of calories, EN was adjusted daily such that the target rate 25 kcal/kg was achieved early.	7 days	14.2 ± 6.5, 57%	24.6 ± 4.9, 98%	n/a	n/a	Rate of correction of RBP and prealbumin after 4 and/or 7 days	RBP and prealbumin increased significantly from day 0 to 7 (in favour of intervention)	– Small study, likely underpowered for clinical outcomes – EN was provided in bolus form
Casaer, 2011, [38]	kcal/kg x corrected IBW + Age > 60 years: – 24 kcal/kg (F); – 30 kcal/kg (M) Age ≤ 60 years: – 30 kcal/kg (F); – 36 kcal/kg (M)	5% glucose provided in a volume equal to that of the PN provided in the early group, accounting for EN that was received. If EN was insufficient after 7 days, PN was initiated on day 8 to meet the energy aim.	ICU stay	750 [63]	1850 [63]	n/a	n/a	Duration of ICU stay & time to D/C alive from ICU	6.3% likelihood of being D/C alive an earlier from the ICU; HR 1.06; 95% CI 1.00-1.13; p=0.04) (in favour of intervention)	– IIT used – Glucose used in both groups – Most well population – Short length of ICU stay – Cardiac populations
Heidegger, 2013, [28]	25kcal/kg (F) or 30 kcal/kg (M) to commence, then indirect calorimetry	SPN provided from day 4 for 5 days with the aim to provide 100% of energy and protein needs (checked twice daily).	5 days	20±7, 77%	28±5, 103%	0.8 ± 0.3	1.2 ± 0.2	Nosocomial infections after day 8 until day 28	Lower occurrence of nosocomial infections; HR 0.65, 95% CI 0.43-0.97; p=0.0338 (in favour of intervention)	– Change of primary outcome after trial commencement – Small study, likely underpowered for clinical outcomes – Used IC to direct energy
Wischmeyer, 2017 [37]	BMI<25: 25 kcal/kg actual wt BMI>35: 20 kcal/kg adjusted weight*	SPN was commenced as soon as possible post inclusion via a central line. PN was adjusted daily to ensure patients received 100% of the energy prescription.	Up to 7 days	Proportion (%(SD)): 69 ± 28	Proportion (%(SD)): 95 ± 13	Proportion (%(SD)): 64 ± 26	Proportion (%(SD)): 86 ± 16	30% increase in energy and protein delivery	26% and 22% increase in energy and protein delivery in intervention	– Pilot trial – Small study, likely underpowered for clinical outcomes

BMI: Body mass index; CI: Confidence interval; D/C: Discharge; EN: Enteral nutrition; F: Female; HR: Hazard ratio; ICU: Intensive care unit; IIT: Intensive insulin therapy; M: Male; PN: Parenteral nutrition; RPB: Retinol binding protein; SD: Standard deviation; SPN: Supplemental parenteral nutrition

*Adjusted weight details [37]:

ABW= IBW+ [actual weight-IBW]*0.25 (IBW is based on a BMI of 25 kg/m^2 for patients height)

$^+$Calculation of energy target [38]:

Caloric target = Caloric need x Corrected Ideal Body Weight

Formula for calculating Ideal Body Weight (IBW)

- Female patient 45.5 + [0.91 x (height in cm – 152.4)]
- Male patient 50 + [0.91 x (height in cm – 152.4)]

Corrected Ideal body weight

- If BMI < 18.5 (IBW + Actual Body Weight) / 2
- If 27 ≥ BMI ≥ 18.5 IBW
- If BMI > 27 IBW x 1.2

Chapter 3: Energy provision in critical illness

3.1 Chapter summary

This chapter describes observational research into the provision of optimal energy in critical illness. It begins with a letter to the editor in which the limitations of previously published systematic reviews and meta-analyses on this topic are discussed. Next, a systematic review and meta-analysis are presented; this work specifically identifies studies that compared near-target energy delivery (80–100% of energy requirements) to critically ill adults and energy delivery provided in standard care. The aim of this article was to assess the effect of near-target energy delivery on mortality and other clinically important patient outcomes. The work in this Chapter relates to thesis aim and hypothesis 1.

3.1 Letter to the editor: "Full Feeding with enteral nutrition is not always full-feeding in research and clinical practice (reproduced with permission) [64]"

Letters to the Editor

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American Society for Parenteral and Enteral Nutrition

Full-Feeding With Enteral Nutrition Is Not Always "Full-Feeding" in Research and Clinical Practice

DOI: 10.1177/0148607114556841

Journal of Parenteral and Enteral Nutrition
Volume 39 Number 4
May 2015 383–384

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Dr Choi and colleagues[1] recently published a meta-analysis to compare the effect of initial underfeeding with full feeding from enteral nutrition (EN) alone on mortality and other clinical outcomes in critically ill adults. The investigators concluded that "none of the analyzed clinical outcomes were significantly influenced . . . by the calorie intake of the initial EN." We believe this conclusion to be flawed due to the study selection criteria used for the "full-feeding" group and due to the nature of the few available randomized trials on this topic. In our opinion, the fundamental difficulty in comparing studies of calorie intake relates to the inability to provide sufficient EN to meet calorie goals, even in research settings, and problems with accurate determination of calorie goals in this population.

The authors attempted to identify a full-feeding group in their analysis by finding trials that sought to reach 90%–100% of predicted caloric requirements. However, the proportion of predicted caloric requirements actually delivered in the included studies ranged from 71.4% to 95%. Aside from the study that achieved 95% of requirements, we consider this still to be underfeeding. Hence the majority of the full-feeding patient group was still underfed, which may explain the lack of clinical outcome difference. Inability to meet calorie goals when using EN is a common clinical practice issue, with literature suggesting that on average only 45% of caloric goals are met.[2]

The other issue impacting this meta-analysis is the accurate prediction of calorie requirements. Three of the 4 trials included in the full-feeding group used a fixed prescription estimate method, and 1 trial used the Harris Benedict equation with adjusted stress factors to estimate calorie goals.[1] These calorie estimation methods have been shown to be considerably inaccurate, either overestimating or underestimating compared with measured calorie goals.[3] In our experience with indirect calorimetry, in practice and in research, we believe underfeeding to be more common than overfeeding when predictive equation estimates are used, meaning that the percentage of actual requirements provided to patients in these reported trials is highly likely to be less than reported. This would mean that the full-feeding group in the included trials may even be more underfed than reported.

We have also noted that Figure 2 appears to be incorrectly labeled; the top part of this figure appears to pertain to the studies belonging to the "one-third to two-thirds of the standard caloric requirement" analysis and the middle pertains to the "lower one-third," rather than how it was labeled in the publication.

We commend the authors for attempting to answer this question with what appears to be a methodologically robust meta-analysis; however, we don't believe the study selection criteria for the full-feeding group allow this question to be answered satisfactorily. Clinicians' inability to either determine or meet calorie goals for critically ill adults in both research and clinical practice requires further study.

Emma Ridley, BNutriDiet, MPH
Andrew Davies, FRACP
David (Jamie) Cooper, BMBS, MD, FRACP, FCICM
ANZIC Research Centre, Monash University, Melbourne, Australia

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Response to Ridley et al

DOI:10.1177/0148607114556842

We appreciate Ridley and colleagues' interest in our article "Calorie Intake of Enteral Nutrition and Clinical Outcomes in Acutely Critically Ill Patients: A Meta-Analysis of Randomized Controlled Trials."[1]

Your question might have originated from a matter of word choice. However, we do not believe that a term such as "full feeding" is incorrect. Your concept of full feeding is extremely ideal. As you know, there is no absolute standard of "full feeding" in adults.

All 4 studies in our meta-analysis used different names for the full-feeding group: the immediate optimal-flow group, target feeding, full-energy feeding group, and full-feeding group, respectively. The term "full feeding" indicates the intention to reach the predicted caloric requirements as soon as possible,

and we thus elected to use this term. In randomized controlled trials, we encounter a great variety of unexpected situations, especially in the intensive care unit (ICU). We believe that the 4 studies in our meta-analysis adhered to the prespecified feeding protocol with consideration of patient safety, although the full-feeding group in our analysis did not reach 90%–100% of the predicted caloric requirements. Also, each trial in our analysis used a different feeding protocol and measured the residual gastric volume (RGV), to which the feeding rate was adjusted. Thus, a full-feeding group was not actually achieved in all of the studies. A recent multicenter, randomized, controlled, noninferiority trial showed that absence of RGV monitoring in patients undergoing invasive mechanical ventilation and early enteral nutrition is not inferior to RGV monitoring in terms of VAP prevention.[2] Despite the higher vomiting rate without RGV monitoring, the rate of prokinetic drug use was lower and the proportion of patients achieving the caloric targets was higher in this group. The absence of RGV monitoring was not inferior to the performance of RGV monitoring with respect to new infections, lengths of ICU and hospital stays, organ failure scores, or mortality rates. Elimination of RGV monitoring from the feeding protocol may have improved enteral nutrition delivery and could have allowed the patients to reach predicted caloric requirements. The use of indirect calorimetry could be helpful for predicting accurate calorie requirements. Future studies should consider the following questions: "How can we determine accurate calorie requirements in critically ill adults?" and "How can we achieve sufficient enteral nutrition?"

As you know, our meta-analysis reached a conservative conclusion regarding feeding in the ICU after several rounds of strict peer review. We assume that the 4 primary research studies in our meta-analysis also passed strict peer review before being published. If you intend to pose the same question to each author and reviewer of the primary research studies included in our meta-analysis, we will be glad to consider their conclusions as well.

As you noted, Figure 2 was labeled incorrectly. The labels "1/3 to 2/3 of the standard caloric requirement" and "lower 1/3" have been exchanged.

Thank you for your comments and interest.

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3.2 Manuscript: "Delivery of full predicted energy from nutrition and the effect on mortality in critically ill adults: A systematic review and meta-analysis of randomised controlled trials (reproduced with permission) [65]"

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Clinical Nutrition xxx (2017) 1–13

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Meta-analyses

Delivery of full predicted energy from nutrition and the effect on mortality in critically ill adults: A systematic review and meta-analysis of randomised controlled trials☆

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ARTICLE INFO

Article history:
Received 23 March 2017
Accepted 29 September 2017

Keywords:
Enteral nutrition
Parenteral nutrition
Energy
Critically ill
Systematic review
Meta-analysis

SUMMARY

Background: The amount of energy required to improve clinical outcomes in critically ill adults is unknown.
Objective: The aim of this systematic review and meta-analysis was to evaluate the impact of near target energy delivery to critically ill adults on mortality and other clinically relevant outcomes.
Design: Following PRISMA guidelines, MEDLINE, EMBASE, CINHAL and the Cochrane Library were searched for randomised controlled trials evaluating nutrition interventions in adult critical care populations. Included studies compared delivery of ≥80% of predicted energy requirements (near target) from enteral and/or parenteral nutrition to <80% (standard care) and reported mortality. The quality of individual studies was assessed using the Cochrane 'Risk of Bias' tool, and the overall body of evidence using the GRADE approach. Fixed or random effect meta-analyses were used pending the presence of heterogeneity ($I^2 > 50\%$) when 3 or more studies reported the same outcome. Outcomes are presented as risk ratio (RR), 95% confidence interval (CI).
Results: Ten trials with 3155 participants were included. Mortality was unaffected by the intervention (RR 1.02, 95% CI 0.81, 1.27, p = 0.89, $I^2 = 25\%$). Evaluation of studies of higher quality and low risk of bias did not alter the mortality inference (3 trials, 352 participants, RR 0.83, 95% CI 0.49, 1.40, p = 0.19, $I^2 = 39\%$). The quality of evidence across outcomes was very low.
Conclusions: The delivery of near target energy when compared to standard care in adult critically ill patients was not associated with an effect on mortality. Because the quality of the evidence across outcomes was very low there is considerable uncertainty surrounding this estimate. This has implications for clinical utility of the evidence within the included reviews.

1. Introduction

Nutrition therapy is a widely provided intervention to critically ill patients internationally but there is uncertainty as to the amount of energy that should be provided to optimise outcomes. Several randomised controlled trials (RCTs) have compared the delivery of less than predicted energy requirements in both arms (60–70%) or to even lesser amounts (20–30%) [2–4]. It can be argued that failing to compare delivery of energy close to targeted requirements risks

☆ Registry information: PROSPERO (CRD42015027512) and the protocol is pre-published[1].

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https://doi.org/10.1016/j.clnu.2017.09.026
0261-5614/

Please cite this article in press as: Ridley EJ, et al., Delivery of full predicted energy from nutrition and the effect on mortality in critically ill adults: A systematic review and meta-analysis of randomised controlled trials, Clinical Nutrition (2017), https://doi.org/10.1016/j.clnu.2017.09.026

Abbreviations

CENTRAL	Cochrane Central Register of Controlled Trials
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CI	Confidence interval
EN	Enteral nutrition
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
ICU	Intensive care unit
LOS	Length of stay
MD	Mean difference
MV	Mechanical ventilation
PN	Parenteral nutrition
OR	Odds ratio
RCT	Randomised controlled trial
RR	Risk ratio
SD	Standard deviation

flawed interpretation and does not reflect current best practice recommendations [5–8].

The results of the aforementioned trials have been mixed and confusing for clinicians. Methodologies such as systematic reviews and meta-analyses have been utilised to try and combine trial results and obtain guidance. Five published meta-analyses have investigated the role of energy delivery at varying amounts to critically ill adults and the association with clinical outcomes [9–13]. None have however specifically focused on studies which aim to deliver near target energy levels recommended in best practice guidelines, or completed a quality assessment across outcomes, significantly limiting confidence and clinical utility of the findings [14].

The aim of this systematic review and meta-analysis was to assess the effect of near target energy provision from nutrition (defined as provision of ≥80% of the predicted energy determined by any method) on mortality and other important clinical outcomes in critically ill adults including detailed assessments of evidence quality.

2. Methods

Methodologies detailed by expert groups and best practice guidelines were utilised in this review [15–17].

The question posed was "In critically ill adults (population), does delivery of full predicted energy from nutrition (intervention) influence mortality or other important clinical outcomes (outcome) compared to delivery of less than full predicted energy from nutrition (comparator)?" Full details can be viewed on PROSPERO (CRD42015027512) or in the pre-published protocol [1]. In summary, all processes were conducted independently by 2 authors (AD and ER), piloted on 10 papers, discussed to assess agreement, refine processes and ensure consistency in methodology. The agreed methodology was used for the full set of articles at each stage and a third review author was consulted if required. A conservative approach was favoured if relevant information could not be obtained clearly from the abstract and title and the full-text article was reviewed. The EndNote reference manager software program (version X7.7, New York City: Thomas Reuters, 2011), Covidence 2013 (www.covidence.org), Review Manager (version 5.3) and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) portal (https://gradepro.org/) were used to coordinate the review and track processes.

2.1. Data sources and eligibility

Current issues of the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (Ovid SP, from 1948 to date), EMBASE (Ovid SP, from 1948 to date) and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCOhost, from 1948 to date) were searched for the first time on the 21st of November 2014 and last updated on the 17th of November 2016. Sensitivity-maximizing strategies and publication restrictions were applied for each database as described in the Cochrane Handbook for Systematic Reviews of Interventions and after advice from a senior librarian with expertise in medical systematic reviews [16]. All searches were restricted to adult participants, the English language and human studies. Supplementary file 1 demonstrates the final MEDLINE search strategy which was adopted for other search engines. Reference lists of relevant systematic reviews and included articles were also checked.

2.2. Participants

Published parallel RCTs were considered for inclusion if they enrolled adult patients (≥16 years) who were critically ill, irrespective of admission diagnosis and provided enteral (EN) and/or parenteral nutrition (PN) for any duration. To determine if a study included 'critically ill participants' established definitions were adapted [18]. The full inclusion and exclusion criteria and definition of critically ill participants can be viewed at supplementary file 2.

2.3. Interventions

The intervention was defined as a mean energy delivery of ≥80% of estimated or measured energy requirements by EN and/or PN during the study period. This aim was chosen because it was significantly higher than the reported international mean energy delivery of 50–60% and approximated energy delivery amounts recommended by clinical practice guidelines (whilst allowing for additional energy from non-nutrition sources) [6,8,19]. Secondly, observational evidence at the time of protocol development was suggesting an association with improved clinical outcomes with energy delivery at this level [6,8,19,20]. The comparator was defined as mean energy delivery of <80% of full predicted energy requirements.

2.4. Outcome measures

The outcome measures in this study were divided into primary and secondary outcomes. Some changes were made to the review compared to the original published protocol following data extraction but prior to analysis [1]. Hospital mortality was originally a primary outcome, few studies reported this consistently so the primary outcome was amended to 'mortality' at any time point, and analysed using a random effects model. Hospital mortality thus became a secondary outcome. Studies did not provide data to enable survivor versus non-survivor comparisons for primary or secondary outcomes. To avoid the complexity of analysis of co-primary outcomes it was decided that 'mortality at any time point' would be the sole primary outcome, with other outcomes being moved to secondary outcomes.

The primary and secondary outcomes for the final analysis were:

2.5. Primary

1. Mortality at any time point

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2.6. Secondary

1. ICU, hospital and 90-day mortality
2. ICU and hospital LOS in days
3. Infectious complications, defined as any confirmed infectious complication event after randomization. Events must have been reported or able to be calculated as the total number of events for each arm of the RCT.
4. Duration of MV

2.7. Data extraction and risk of bias within studies

Information was collected from each individual trial on; participants, inclusion and exclusion criteria, characteristics of energy assessment, mode, method and duration of nutrition therapy delivery and outcome measures (see Supplementary File 3). Data were not extracted if they were provided in a format which could not be easily entered into a meta-analysis or transposed. Authors were not contacted where data were unavailable in the primary publication. Risk of bias in individual studies was assessed using the Cochrane Risk of Bias Tool.

2.8. Summary measures

Mortality outcomes are presented as risk ratio (RR) with 95% confidence intervals (CIs) and the other binomial outcome (infectious complications) is presented as odds ratio (OR) with 95% CIs. For continuous outcomes the treatment effect is mean difference (MD) with 95% CIs. Non-normally distributed variables were unable to be transposed for the analysis due to the data reported in the included studies

2.9. Synthesis of results

The Chi-square statistic was used to test statistical heterogeneity between studies, with a P value $\leq$ 0.10 indicating significant statistical heterogeneity and an I^2 statistic >50% was considered to indicate problematic heterogeneity between studies [16]. In this instance both fixed and random effects meta-analyses were conducted and the results of the random effects analysis reported if the two were not consistent.

2.10. Risk of bias within outcomes

Risk of bias within outcomes was assessed using the GRADE approach. The GRADE approach defines the quality of each individual outcome within a systematic review to determine the confidence which can be held in an estimate of effect or association [16]. The components of the GRADE assessment are risk of bias, inconsistency (referring to unexplained heterogeneity of results), indirectness (assessing if the population recruited is similar to which the intervention would be applied), imprecision (confidence in the effect size observed) and finally, other risks of bias including the risk of publication bias. Each of the primary and secondary outcomes were assessed, paying particular attention to the elements of the GRADE assessment in context of the evidence included in the review.

2.11. Additional analysis

Subgroup analyses were defined *a priori*, however not all those defined originally were possible with the included studies and available data. Those conducted were:

- Studies using only EN in the intervention group
- Studies assessed as high quality and low risk of bias

Time to event analysis for mortality was pre-planned, however the data was not provided in a format for us to conduct this analysis.

3. Results

There were 9335 papers identified and after duplicates and irrelevant papers were excluded on abstracts alone, 509 underwent full text review. Ten papers were eligible including 3155 participants (Fig. 1) [3,21–29].

The included trials were conducted in a variety of locations and over a wide range of years (4 in Europe, 2 in the United Kingdom and 1 each in Israel, Australia, Asia and the United States of America between 1997 and 2015). Six studies used EN alone as the intervention, 2 compared EN to PN, and 1 each used PN alone and EN in combination with PN. The methods used to estimate energy requirements and provide nutrition therapy were highly variable. The average amount of energy provided in the standard care and intervention arms was 70.3% and 88.7% of predicted requirements, respectively. Detailed information on included studies can be seen in Table 1: Characteristics of included studies table, Table 2: Nutrition characteristics of included studies table and Table 3: Outcomes reported in included studies.

3.1. Risk of bias in ten included studies

The risk of bias assessment of included studies can be seen in Fig. 2a and b. Three studies were considered of high quality and of low risk of bias (Bauer 2000, Kagan 2014, Peake 2014); a separate mortality analysis was conducted with these studies as specified *a priori*.

1. Incomplete outcome data (attrition bias)

Complete follow up was observed for the majority of primary outcomes stated within the included studies, with the exception of two papers. Reynolds (1997) did not clearly state the outcomes of interest in their study and Huang (2012) reported mortality outcome data in fewer patients than were originally randomised in both arms of the study.

2. Allocation concealment (selection bias)

Five trials (Desachy 2008, Huang 2012, Huschak 2005, Reynolds 1997, Schneider 2011) had a high or unclear risk of selection bias due to inadequate reporting of methods used to conceal allocation. The remaining 5 had a low risk of bias.

3. Blinding of participants, personnel and outcome assessors (performance bias)

One trial (Peake 2014) blinded participants, personnel and outcome assessors. In 2 trials it was unclear if blinding occurred (Kagan 2015 and Bauer 2000) and in all remaining trials (7) there was no blinding.

4. Selective outcome reporting (reporting bias)

One trial (Harvey 2014) had a protocol that was easily accessible and allowed comparisons between outcomes reported in the primary publication and the pre-published study protocol. Two studies (Braunschweig 2015 and Huang 2012) had a high risk of

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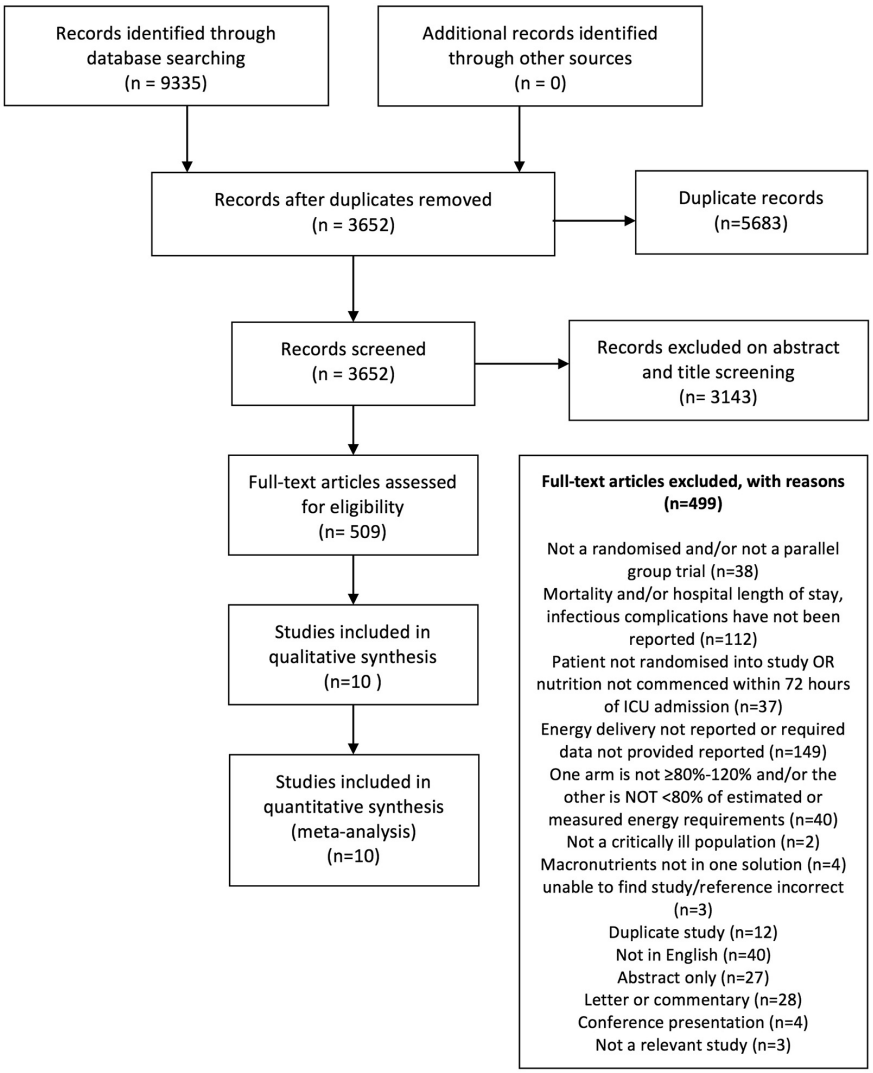

Fig. 1. Flow diagram of review processes.

bias. Braunschweig reported data that could not be readily transformed or imputed into a meta-analysis. ICU mortality and length of ventilation were not reported in the primary paper by Huang 2012. Due to the other outcomes reported in the study it was deemed likely these variables were collected but not published. All other trials were marked as unclear if the protocol was not available publically.

5. Other sources of bias

One trial (Braunschweig 2015) was marked as a high risk of 'other bias' as it was stopped early at an interim analysis. Two other trials (Huschak 2005 and Reynolds 1997) were unclear due to methodological concerns, which were not clearly reported. All other papers were marked as low risk. Publication bias was strongly suspected for the primary outcome, as indicated by the asymmetric funnel plot (Supplementary file 4). A Funnel plot was only constructed for the mortality outcome due to the low number of studies available for other outcomes.

6. Sequence generation (selection bias)

In 5 trials (Braunschweig 2015, Harvey 2014, Huang 2012, Kagan 2015, Peake 2014), sequence generation was adequately described (low risk of bias), and in the remaining 5 trials it was unclear.

3.2. Meta-analysis of the primary outcome

1. Mortality at any time point

Provision of ≥80% predicted energy to critically ill adults was not associated with overall mortality (Fig. 3a, 10 trials, 3155

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Table 1
Characteristics of included studies.

Author, year, country (ref)	No. of centres	Study objective	Study arm <80% energy	Study arm ≥80% energy	No. randomized in each group		Age (years ± SD)		BMI (kg/m^2 ± SD)		Sex (n, % male)		Main population admission category (%)		APACHE (score ± SD)	
					<80%	≥80%	<80%	≥80%	<80%	≥80%	<80%	≥80%	<80%	≥80%	<80%	≥80%
Bauer, 2000, France [21]	2	To determine whether nutrient intake by early EN with PN improves levels of retinol-binding protein and prealbumin (primary endpoint) and reduces morbidity and mortality (secondary endpoint)	EN plus placebo	EN plus PN (intervention)	60	60	55 ± 18	53 ± 18	n/a	n/a	42, 70%	40, 66%	Surgical (57%)	Medical (58%)	n/a	n/a
Brauns-chweig, 2015, USA [22]	1	To determine if a comprehensive nutrition program from ALI diagnosis to hospital D/C could improve morbidity and influence mortality in normal and malnourished ICU patients.	Standard care	Quickly commenced EN	38	40	58.6 ± 16.2	52.5 ± 17.1	30.1 ± 8.9	29.8 ± 9.3	21, 55%	19, 47.5%	ALI (100%)	ALI (100%)	27 ± 7.9	23.4 ± 9.3
Desachy, 2008, France [23]	2	To compare, in intubated and MV patients, the initial (D7) efficacy in terms of calorie intake and tolerability of early EN with immediate vs. gradual introduction of optimal flow rate.	Gradual EN	Immediate EN (intervention)	50	50	64 ± 13	58 ± 19	27 ± 5	25 ± 3	31, 62%	38, 76%	Medical (70%)	Medical (66%)	n/a	n/a
Harvey, 2014, UK [3]	33	To test the hypothesis that the PN route is superior to the EN route for the delivery of early nutritional support in adults who had an unplanned admission to an ICU and who could be fed through either route.	EN	PN (intervention)	1197	1191	62.9 ± 15.4	63.3 ± 15.1	26.8 ± n/a	26.2 ± n/a	725, 60.5%	689, 58%	n/a	n/a	19.6 ± 7.0	19.6 ± 6.9
Huang, 2012, Taiwan [24]	1	To test whether illness severity influences the efficacy of enteral feeding route on clinical outcomes in patients with critical illness.	NG	ND (intervention)	51	50	68.3 ± 6.2	70.9 ± 13.2	23.4 ± 4.1	24.0 ± 6.1	35, 69%	37, 74%	Medical (n/a)	Medical (n/a)	19.6 ± 6.2	21.0 ± 6.8

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Table 1 (*continued*)

Author, year, country (ref)	No. of centres	Study objective	Study arm <80% energy	Study arm ≥80% energy	No. randomized in each group		Age (years ± SD)		BMI (kg/m^2 ± SD)		Sex (n, % male)		Main population admission category (%)		APACHE (score ± SD)	
					<80%	≥80%	<80%	≥80%	<80%	≥80%	<80%	≥80%	<80%	≥80%	<80%	≥80%
Huschak, 2005, Germany [25]	1	To test the safety of an olive oil lipid-based vs. a conventional glucose-based PN/EN regimen and its effect on blood glucose, duration of MV, and LOS in ICU.	Lipid (intervention)	Glucose	18	15	36.7 ± 18.9	39.7 ± 16.2	26.2 ± 4.5	28.1 ± 5.3	13, 72%	14, 93%	Multiple trauma (100%)	Multiple trauma (100%)	21.6 ± 4.6	22.1 ± 3.7
Author, year, country (ref)	No. of centres	Study objective	Study arm <80% energy	Study arm ≥80% energy	No. randomized in each group		Age (years ± SD), if reported		BMI (kg/m^2 ± SD)		Sex (n, % male)		Main population admission category (%)		APACHE	
					<80%	≥80%	<80%	≥80%	<80%	≥80%	<80%	≥80%	<80%	≥80%	<80%	≥80%
Kagan, 2015, Israel[26]	1	To assess the effects of an EN formula enriched with EPA, GLA and antioxidants, started upon admission of the patient to the ICU, on respiratory parameters in patients with multiple trauma requiring MV.	Immune EN (intervention)	Standard EN	58	62	38.4 ± 16.8	42.9 ± 18.6	n/a	n/a	47, 81%	49, 79%	Trauma/ neurological (100%)	Trauma/ neurological (100%)	n/a	n/a
Peake, 2014, Australia [27]	5	To determine whether the substitution of a 1.5-kcal/mL EN solution for a 1.0-kcal/mL solution resulted in greater calorie delivery to critically ill patients	1.0 cal/ml EN	1.5 cal/ml EN (intervention)	55	57	56.5 ± 16.1	56.4 ± 16.8	26.2 ± 6.4	27.8 ± 7.9	41, 75%	42, 74%	Respiratory (n/a)	Cardio-vascular (n/a)	22 ± 8.9	23 ± 9.1
Reynolds, 1997, UK [28]	1	To compare EN with PN in a RCT and to measure directly the effect of these nutrition approaches on gut barrier integrity and the sequelae of altered barrier function.	EN	PN (intervention)	33	34	69	67	n/a	n/a	26, 79%	27, 79%	Surgical (100%)	Surgical (100%)	n/a	n/a
Schneider, 2011, Germany [29]	1	To compare early supplementation with antioxidants and glutamine using a low volume EN supplement to an energy adjusted standard elementary diet and to investigate its effect on clinical efficacy and tolerability in critically ill patients with sepsis/SIRS.	Standard EN	Supplemented EN (intervention)	29	29	46.7 ± 15.8	46.6 ± 14.3	27.9 ± 6.5	25.5 ± 6.3	18, 62%	15, 52%	Sepsis (58%)	Sepsis (55%)	21.1 ± 6.8	22.0 ± 6.7

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Table 2
Nutrition characteristics of included studies.

Author, year, country (ref)	Energy estimation method	Study arm <80% energy	Study arm ≥80% energy	Intervention description	Duration of intervention	Energy delivered control (kcal or kcal/kg/day ± SD), (% target)	Energy delivered intervention (kcal ± SD), (% target)	Protein delivery control (g/day ± SD or % requirements ± % SD)	Protein delivery intervention (g/day ± SD or (% requirements ± % SD))
Bauer, 2000, France [21]	25 kcal/kg	EN plus placebo	EN plus PN (intervention)	3-in-1 TPN solution with vitamins, administered at 1 cal/ml through central line (not dedicated to nutrition). EN was BOLUS 4/24 with a standard polymeric formula. Using the total amount of calories, EN was adjusted daily such that the target rate 25 kcal/kg was achieved early.	7 days	14.2 ± 6.5 kcal/kg/day, 57%	24.6 ± 4.9 kcal/kg/day, 98%	n/a	n/a
Brauns-chweig, 2015, USA [22]	30 kcal/kg	Standard care	Quickly commenced EN	EN tubes placed and commenced more rapidly, EN rates adjusted to account for fasting, fast commencement of oral diet post extubation, enhanced strategies to encourage oral intake.	Appeared to be ICU admission	1221 ± 423, 55%	1798 (509), 85%	60.4 ± 24	82 ± 23
Desachy, 2008, France [23]	25 kcal/kg	Gradual EN	Immediate EN (intervention)	EN started within 24 h of admission to ICU, using the same protocol in both groups. In the immediate EN group, EN was started at target rate.	Appeared to be ICU admission	1297 ± 331, 72%	1715 ± 331, 93%	n/a	n/a
Harvey, 2014, UK [3]	25 kcal/kg	EN	PN (intervention)	Nutritional support was initiated as soon as possible after randomization (within 36 h after admission). Patients in the PN group received nutrition through a CVC with a dedicated lumen.	5 days or until exclusive oral feeding, D/C from the ICU, or death	18.5 ± 7.7 kcal/kg/day, 74%	21.3 ± 7.7 kcal/kg/day, 85%	0.6 ± 0.3 g/kg/day	0.7 ± 0.3 g/kg/day
Huang, 2012, Taiwan [24]	25-30 kcal/kg	NG	ND (intervention)	EN feeding tube was placed into a patient's stomach or duodenum (target position of the ND tube was at or beyond the second portion of the duodenum, confirmed via x-ray). If duodenal placement failed, reposition of the tube was attempted or the gastroenterologist would place the feeding tube via the gastro-endoscopic method in the ICU. EN was commenced at 20 ml/h and advanced by 20 ml/h 4/24 until the target was reached.	Up to 21 days	76.2% ± 24.9%	90.4% ± 20.5%	78.6% ± 28.5%	93.2% ± 26.9%
Huschak, 2005, Germany [25]	IC	Lipid (intervention)	Glucose	Intervention patients received a lipid-based PN with a lipid/glucose ratio (percentage kcal/percentage kcal of non-protein energy) of 75/25. No other sources of glucose were given. Both groups received 20% of their parenteral energy supply as amino acids. To avoid a high intake of n-6-fatty acids intervention patients received a fat emulsion based on olive oil. The PN was given continuously over 24 h. EN was started on day 1 with a daily maximum of 5 kcal/kg during the first 6 days. The lipid group also received an EN containing high fat based on olive oil and the glucose group received an standard EN diet. After day 6 the parenteral energy supply was reduced while the EN energy was increased dependent on tolerability.	Not stated	75% ± 17%	86% ± 26%	n/a	n/a
Kagan, 2015, Israel [26]	IC measurement or Fagon formula [42]	Immune EN (intervention)	Standard EN	EN, based on randomization, was delivered within 48 h of admission via a nasogastric or orogastric tube whose position was confirmed by X-ray. The amount of EN prescribed daily was meant to provide at least 80% of all energy requirements as determined by measurement of REE. All other procedures followed a standard EN feeding protocol reflecting best practice recommendations.	EN was continued until ICU discharge, death or completion of 28 days of the study	1786.6 ± 565.1, 79%	1744.3 ± 783.9, 84%	n/a	n/a

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Table 2 (*continued*)

Author, year, country (ref)	Energy estimation method	Study arm <80% energy	Study arm ≥80% energy	Intervention description	Duration of intervention	Energy delivered control (kcal or kcal/kg/day ± SD), (% target)	Energy delivered intervention (kcal ± SD), (% target)	Protein delivery control (g/day ± SD or % requirements ± % SD)	Protein delivery (g/day ± SD or (% requirements ± % SD))
Peake, 2014, Australia [27]	1 cal/ml/kg	1.0 cal/ml EN	1.5 cal/ml EN (intervention)	Delivered at a goal rate of 1 ml/kg IBW in both groups. All other management of feeding was as per the treating clinicians at the participating sites.	10 days unless EN ceased earlier	1291 ± 623, 70%	1617 ± 740, 87.5%	74 ± 30	70 ± 20
Reynolds, 1997, UK [28]	Blanket prescription (2035 kcal intervention, 2000 kcal control)	EN	PN (intervention)	Via CVC. Started at 9 am the day after surgery	7 days	1300 ± 300 (SE), 68%	1800 ± 100 (SE), 88%	50 ± 3	65 ± 1
Schneider, 2011, Germany [29]	Harris-benedict	Standard EN	Supplemented EN (intervention)	Immune supplemented EN solution with a standard EN solution. Supplemental PN given if less than 60% or REE was received.	Not clearly described	76.6% ± 26.6%	90.2% ± 25.8%	n/a	n/a

participants, random effects analysis, RR 1.02, 95% CI 0.81, 1.27, $p = 0.89$, $I^2 = 25\%$) [3,21–29]. Studies of high quality and low risk of bias were evaluated separately and the result did not change (Fig. 3b, 3 trials, 352 participants, RR 0.83, 95% CI 0.49, 1.40, $p = 0.19$, $I^2 = 39\%$) [3,21,26,27]. In both cases, wide confidence intervals provide uncertainty for the point estimates.

3.3. Meta analysis of secondary outcomes

1. ICU, Hospital and 90-day mortality

ICU mortality was not associated with the intervention (supplementary file 5, 3 studies, 2599 participants, RR 0.90, 95% CI 0.79, 1.02, $p = 0.74$, $I^2 = 0\%$), neither were hospital nor 90-day mortality, (4 studies, 2679 participants, RR 0.97, 95% CI 0.87, 1.07, $p = 0.56$, $I^2 = 0\%$, and 3 studies, 2604 participants, RR 0.94, 95% CI 0.85, 1.04, $p = 0.20$, $I^2 = 38\%$, supplementary file 6 and 7, respectively) [3,21,23,24,27].

2. ICU and hospital LOS

There was no association between the intervention or the control groups on length of ICU or hospital stay (supplementary file 8, 6 studies, 487 patients, MD 1.43 days, 95% CI −0.69, 3.54, $p = 0.19$, I2 = 0%) [22–26,29] and (supplementary file 9, 5 studies, 389 participants, MD 4.71 days, 95% CI -0.33, 9.75 days, $p = 0.07$, $I^2 = 0\%$) [22,23,25,26,29], respectively.

3. Infectious complications

There was no association between the intervention or the control groups and infectious complications (supplementary file 10, 3 studies, 195 participants, OR 1.33 95% CI 0.59–3.01, $p = 0.50$, $I^2 = 39\%$) [21,28,29].

4. Duration of MV

Duration of MV was a secondary outcome, however, there were insufficient studies which reported this to allow meta analysis.

3.4. Additional analysis

Subgroup analysis was conducted on studies which investigated EN in both the intervention and control arms. No association was found in the intervention or control groups for mortality (supplementary file 11, 6 studies [22–24,26,27,29], 564 participants, OR 1.15, 95% CI 0.76, 1.76, $p = 0.09$, $I^2 = 48\%$), ICU LOS (supplementary file 12, 5 studies [22–24,26,29], 454 participants, MD 0.78 days, 95% CI −1.46, 3.01, $p = 0.50$, $I^2 = 0\%$), or hospital LOS (supplementary file 13, 4 studies [22,23,26,29], 356 participants, MD 4.72 days, 95% CI -0.35, 9.78, $p = 0.07$, $I^2 = 0\%$). Studies which were considered high quality and low risk of bias did not report any of the same outcomes (except overall mortality), and so could not be combined for any other analyses (Fig. 3b).

3.5. Risk of bias within outcomes

As all studies were RCTs, the outcomes analysed started with a high quality rating. After GRADE assessment, the quality of evidence for all outcomes was ranked as 'very low'. All mortality outcomes were ranked as 'critical' in importance to the patient, with the remaining outcomes ranked as 'important'.

For the primary outcome of mortality, risk of bias and inconsistency in the included studies was ranked as 'not serious' due to the objective nature of mortality as an outcome. The population

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Table 3
Outcomes reported in included studies.

Author, year, country (ref)	Primary outcomes reported and included in primary analysis: 1. Mortality 2. Hospital LOS 3. Infectious complications	Secondary outcomes reported and included in analysis: 1. ICU mortality 2. Hospital mortality 3. 90-day mortality 4. ICU LOS in days	Sub-group analysis
Bauer, 2000, France [19]	1. Yes, 90 D mortality 2. No 3. Yes	1. No 2. No 3. Yes 4. Yes	Low risk of bias
Braunschweig, 2015, USA [20]	1. Yes, mortality during study period 2. Yes 3. No	1. No 2. No 3. No 4. Yes	EN only study: Mortality, ICU and hospital LOS
Desachy, 2008, France [21]	1. Yes, hospital mortality 2. Yes 3. No	1. Yes 2. Yes 3. No 4. Yes	EN only study: Mortality, ICU and hospital LOS
Harvey, 2014, UK [22]	1. Yes, death in 30 days 2. No 3. No	1. Yes 2. Yes 3. Yes 4. No	
Huang, 2012, Taiwan [23]	1. Yes, hospital mortality 2. Yes 3. Yes	1. No 2. Yes 3. No 4. Yes	EN only study: Mortality, ICU LOS
Huschak, 2005, Germany [3]	1. Yes, 6 months 2. Yes 3. No	1. No 2. No 3. No 4. Yes	
Kagan, 2015, Israel [24]	1. Yes, 28 days 2. Yes 3. No	1. No 2. No 3. No 4. Yes	Low risk of bias, EN only study: Mortality, ICU and hospital LOS
Peake, 2014, ANZ [25]	1. Yes, 90D mortality 2. No 3. No	1. Yes 2. Yes 3. Yes 4. No	Low risk of bias, EN only study: Mortality, ICU LOS
Reynolds, 1997, UK [26]	1. Yes, within 30 days 2. No 3. Yes	1. No 2. No 3. No 4. No	
Schneider, 2011, Germany [27]	1. Yes, study period 2. Yes 3. Yes	1. No 2. No 3. No 4. Yes	

Abbreviations used in tables: ALI: Acute lung injury; Cal: calories; CVC: Central venous catheter; EN: Enteral nutrition; EPA: Eicosapentaenoic acid; GLA: Gamma-linolenic acid; IC: Indirect calorimetry; ICU: Intensive care unit; LOS: Length of stay; MV: Mechanical ventilation; n/a: not available; ND: Naso-duodenal; PN: Parenteral nutrition; REE: Resting energy expenditure: SD: Standard deviation; SE: Standard error; TPN: Total parenteral nutrition.

included in the studies in this review were heterogenic, reflecting that of a true ICU population, however the way in which interventions and standard care are applied in nutrition trials are often heterogenic, so indirectness was ranked as 'serious'. Imprecision was marked as 'serious' as the majority of studies randomised a small number of participants, resulting in wide CIs around the estimates of effect and point estimates were therefore uncertain. Finally, publication bias was strongly suspected due to the asymmetric funnel plot (supplementary file 3). A full GRADE evidence profile with ratings for each element assessed for the primary outcome is provided at Table 4 and for all secondary outcomes at supplementary file 14.

4. Discussion

4.1. Key findings

This systematic review and meta-analysis did not find any associations with delivery of energy at near target (≥80% of predicted amounts), compared to standard care (<80% of predicted amounts) and important clinical outcomes in critically ill adults. However, the quality of evidence for all primary and secondary outcomes was rated 'very low' using the GRADE assessment, indicating low confidence in this result. The novelty of this systematic review and meta-analysis is that randomised trials were only included where one of the groups of patients received energy at near target levels. Further, a detailed assessment of trial quality across outcomes for this topic has not been previously reported. This assessment provides clinicians with vital information about the quality of current evidence which guides clinical practice.

4.2. Issues of quality at the study and outcome level

The reporting of elements to assess trial quality was inconsistent and not always explicitly stated. The extent to which this alters the risk of bias greatly depends on the subjectiveness of the outcomes used in the study. An 'unclear' rating was chosen when information was not available. Future RCTs in nutrition should consistently

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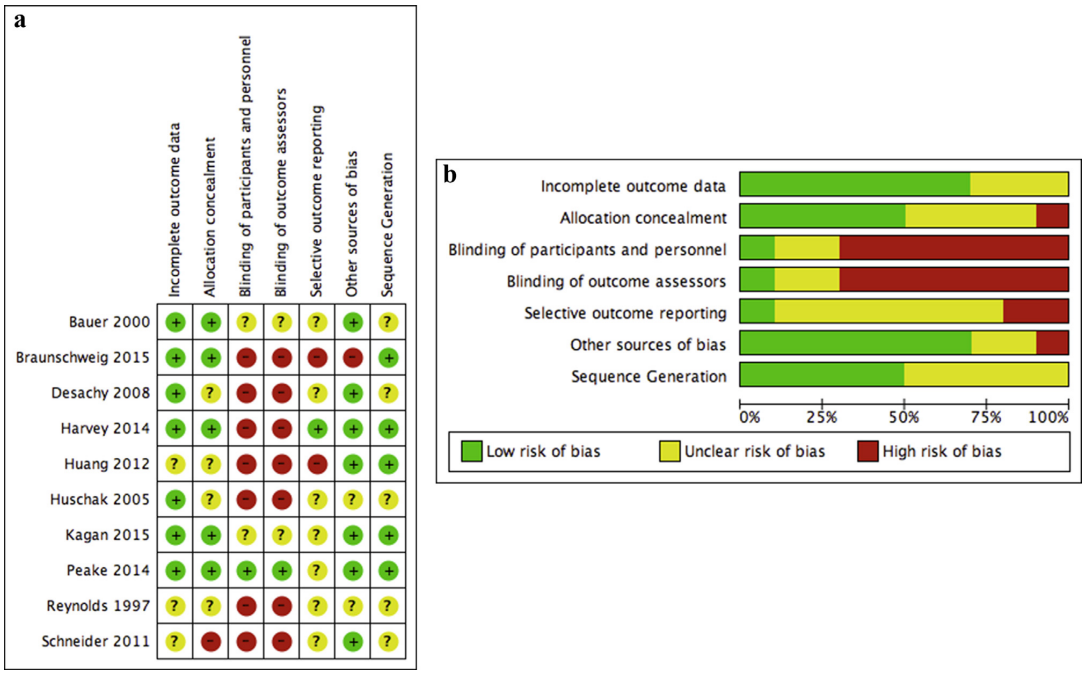

Fig. 2. a) Risk of bias summary graph- Review authors' judgements about each risk of bias item for each included study. b) Risk of bias graph- Review authors' judgements about each risk of bias item presented as percentages across all included studies.

report all quality elements, as recommended in best practice recommendations [30].

The quality issues at the study level led to quality issues in the outcomes using the GRADE assessment. This important (but often neglected) assessment allows an understanding of the strength of findings in a systematic review within the context of evidence quality across outcomes [14].

4.3. Comparison to current literature

There are no large prospective RCTs which have delivered near target energy amounts in critically ill patients. Thus, the question really asked in published studies has usually been whether one less than target intervention is different to another (standard care). Studies investigating energy delivery at standard care amounts have usually not found any clinical differences, but interestingly, some have found that delivery of energy amounts far less than recommendations have also not been associated with clinical differences [2,4]. This literature provides little guidance for clinicians.

Five meta-analyses addressing the role of energy delivery on clinical outcomes in the critically ill exist [9–13]. Three investigated the provision of energy as 'trophic' or 'permissive underfeeding' when compared to standard care, and two compared standard to less than standard energy delivery. No reviews assessed the quality of evidence within each outcome. Two meta-analyses found minimal associations with clinical outcomes, two found associations with mortality and one with blood stream infections and incident renal replacement therapy [9–13]. One reported a point estimate of lesser mortality with permissive underfeeding (average energy 49% compared to 72% standard care) when 4 trials which only provided EN and included 1317 patients were combined (OR 0.80, 95% CI 0.62, 1.02, $p = 0.07$, $I^2 = 0\%$), however the confidence intervals did include the risk of greater mortality [10]. The second (4 trials, including 2 of the same trials as the previous review) reported a similar result, with lesser mortality in patients who received 33–66% energy during the initial part of ICU stay, compared to 72% of requirements, (risk ratio (RR) 0.68, 0.51, 0.92, $p = 0.01$, $I^2 = 0\%$) [12]. The third systematic review found a lower RR of blood stream infections in patients who received caloric restriction compared to non-caloric restriction with a mean energy difference of 445 kcal (12 studies investigating EN only), (RR 0.72; 95% CI 0.51, 0.99 $p = 0.046$, $I^2 = 26.7\%$) [13]. The same paper also observed an association between the risk of incident renal replacement therapy and calorie intake with the risk being lower in the caloric restriction group. The conclusions made in all of the reviews differed considerably with some acknowledging the risk of bias in the literature at the study level and others making practice recommendations based on the findings. Assessment of evidence quality within outcomes is lacking in all previous reviews and despite the point estimates being consistent between meta-analyses, a failure to assess the quality of evidence within the reported outcomes risks misleading conclusions [14].

4.4. Strengths and weaknesses of this review

This is the first systematic review and meta-analysis to compare energy delivery recommended in best practice guidelines to amounts commonly received in standard practice and to include an assessment of trial quality across outcomes. The assessment of trial quality across outcomes highlights a vital issue with the available evidence on energy delivery in critical illness; due to the poor quality of evidence, current clinical practice is based on evidence in which we have very low confidence in the estimates of effect. This highlights the need for large high quality RCTs to determine the

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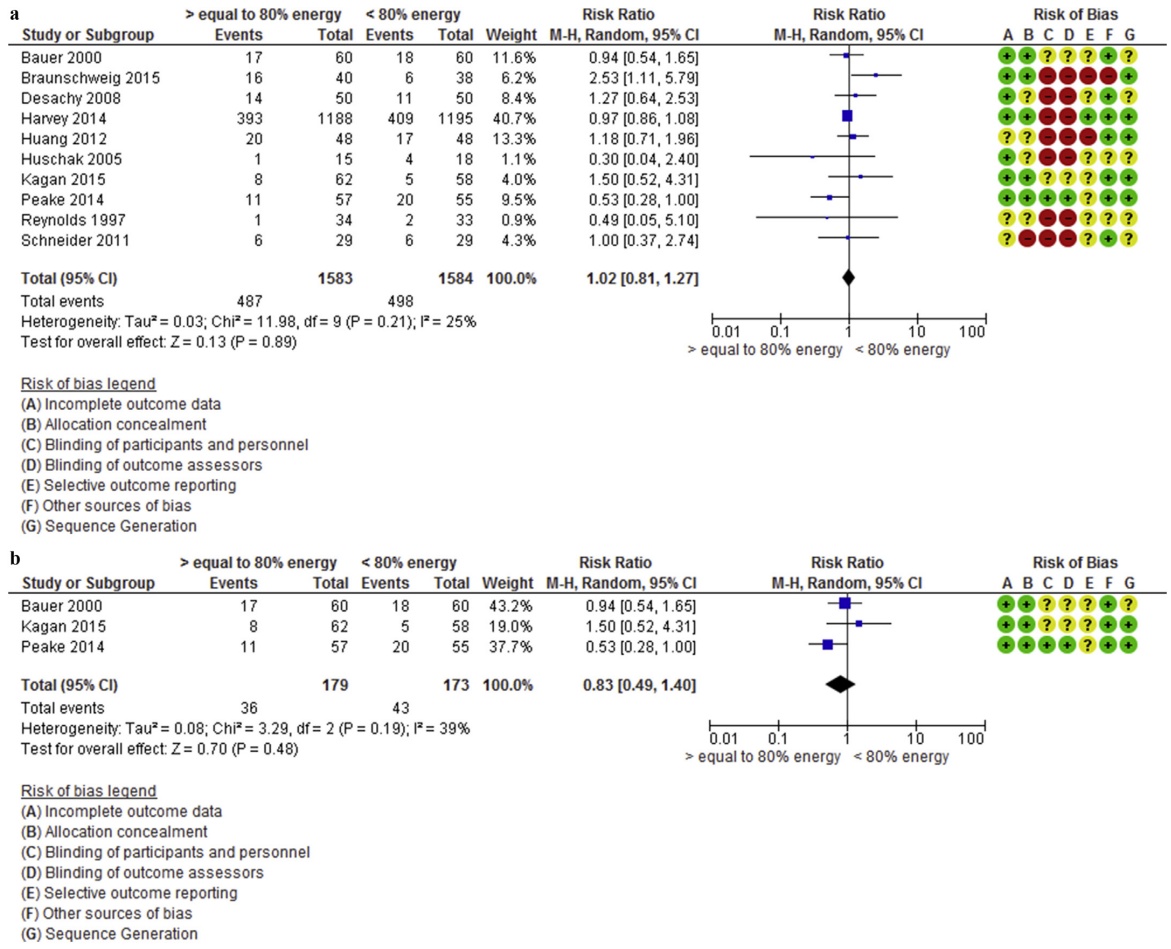

Fig. 3. a) Comparison of ≥ to 80% vs < 80% of full predicted energy, primary outcome: Mortality. b) Comparison of ≥ to 80% vs < 80% of full predicted energy, primary outcome: Mortality, low risk of bias studies.

effectiveness of energy delivery in critical illness. A large number of articles were reviewed for inclusion into this review (more than any other reviews on similar topics), giving the best possible chance of obtaining all relevant articles for screening and thus reducing potential bias [9–13].

There are several weaknesses to this review which reflects the issues with the available evidence in this field. There were a modest total number of patients included in the review of the primary outcome (3167 participants from 10 trials) and the quality of most trials was low. Inclusion of low quality trials was justified for completeness. It is highly unlikely that continuous duration variables such as LOS and length of MV were normally distributed, and subject to bias in survivors and non-survivor analysis. Reported data in the trials prevented reliable survivor versus non-survivor analyses. Further, there was a wide SD observed in energy delivery, likely reflecting a lack of normality in this outcome, this is also a limitation.

There are significant variations in the application of nutrition therapy in clinical practice and research and this may be influencing the findings in this review. The possible impact of protein delivery on the outcomes of patients may also be important and is a topic for further research. It is thus plausible that the protein intake achieved in the studies investigated has influenced clinical outcomes in the studies contained in this review.

Next, while studies in our control group provided less than 80% of full predicted energy requirements, there was a large range within this. It is possible that the observed 18% difference in energy delivery in the intervention arm was not large enough to influence patient outcomes. Evidence also suggests that the use of indirect calorimetry to predict energy requirements and target energy provision may lead to improved clinical outcomes compared to predictive equations [31–33]. These elements remain to be explored in prospective RCTs. Further, studies were included that delivered both EN, PN or a combination. This is not perceived to be an issue due to recent RCTs, demonstrating that the risks of PN administered in a modern day ICU are minimal and similar to the risks of EN administration [3,34].

Several observational studies support the use of near target feeding with associations of improved patient outcomes, however this has not been replicated in prospective trials [35–38].

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Table 4
Grade evidence profile and summary of findings table for the primary outcome.

Quality assessment								No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		> equal to 80%	<80% of full predicted energy	Relative (95% CI)	Absolute (95% CI)		
Mortality													
10	randomised trials	not serious	not serious[a]	serious[b]	serious[a]	publication bias strongly suspected[c]		487/1583 (30.8%)	498/1584 (31.4%)	**RR 1.01** (0.81–1.25)	**3 more per 1000** (from 60 fewer to 79 more)	⊕○○○ VERY LOW	CRITICAL
Mortality (low risk bias)													
3	randomised trials	not serious	not serious	serious[d]	serious[a]	publication bias strongly suspected[c]		36/179 (20.1%)	43/173 (24.9%)	**RR 0.83** (0.46–1.40)	**42 fewer per 1000** (from 99 more to 134 fewer)	⊕○○○ VERY LOW	CRITICAL

GRADE Working Group grades of evidence: High quality: We are very confident that the true effect lies close to that of the estimate of the effect. **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
CI: Confidence interval; RR: Risk ratio; MD: Mean difference; OR: Odds ratio.
a) The CI around the estimate is not sufficiently narrow. Further, the number of patients in estimate probably means the outcome is underpowered.
b) Significant heterogeneity in the application of interventions within studies.
c) Funnel plot asymmetrical, trials to bottom right missing. Also, nutrition literature is dominated by smaller trials, therefore much greater likelihood of publication bias.
d) Trials are unblinded, (outcome assessors and/or study personal, participants), outcome is subjective.

Heterogeneity in the patients whom nutrition is provided is a possible explanation for why these associations have not been replicated in prospective nutrition studies to date. Nutrition risk may be an important influencer on a patients response to nutrition therapy in critical illness, however definitive data is still required [20,36,39]. Heterogeneity in application of nutrition therapy and patient populations will remain a significant challenge in the interpretation of nutrition literature until a consensus is reached about the role of nutrition therapy via prospective trials.

There was a change to the primary outcomes during the data extraction process but prior to any analysis as few studies reported outcomes as we had anticipated. Articles published in languages other than English and conference abstracts which were never published in full format were excluded from the review. It is thus possible that some studies were missed however it is not anticipated that this would have impacted significantly on the findings. Further, there are known issues with the accuracy of data which is presented in abstract form and never fully published and this was the basis for our decision to exclude them [40]. Publication bias was strongly suspected for the primary outcome. Usually studies with larger effect sizes are more likely to be published, resulting in an inflation of the observed result. Publication bias may thus weaken the findings from this review further [41].

Several authors of this review are investigators on a current large RCT investigating the effect of energy on clinical outcomes [27]. We included an independent third reviewer during the assessment processes to ensure transparency.

5. Conclusions

The delivery of near target energy at ≥ 80% of predicted requirements, when compared to standard care energy delivery, did not influence mortality or any other relevant clinical outcomes in adult critically ill patients. However, the quality of most randomised trials was low, suggesting that the true estimate of effect may be different. Robust large prospective RCTs with consistent reporting are required to determine the optimal amount of energy provision in critical illness, and to provide reliable guidance to clinicians.

Author contribution to the manuscript

EJR and ARD had responsibility for the research design, performed the literature review, collected and analysed the data. EJR, ARD, CH, AD, MB and DJC provided crucial intellectual input to the analysis and interpretation of the results and drafting of the manuscript. All authors read and approved the final manuscript.

Conflict of interest

The authors have no relevant financial or personal disclosures in relation to this work.

Funding

This review was conducted as part of a PhD with funding from the National Health and Medical Research Council (APP1075288).

Disclaimer

ARD, AD and EJR are involved in the TARGET study which investigates the role of energy delivery in critically ill adults (NCT02306746).

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Acknowledgements

Thank you to Lorena Romero, Senior Medical Librarian, The Ian Potter Library, Alfred Health for advice during the review.

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3.3 Online supplementary material from manuscript "Delivery of full predicted energy from nutrition and the effect on mortality in critically ill adults: A systematic review and meta-analysis of parallel randomised controlled trials"

Supplementary file 1: Sample search strategy for MEDLINE

#	**Searches**
1	(((intensive or critica*) adj3 (care or unit* or illness*)) or ICU or (critical* adj ill) or (mechanical* adj4 ventilat*)).tw.
2	(artificial* adj2 (respirat* or ventilat*)).tw.
3	exp critical illness/ or exp critical care/ or exp intensive care/ or exp respiration, artificial/ or exp ventilation, mechanical/ or exp critical care nursing/ or exp intensive care units/
4	exp Multiple Organ Failure/ or exp Systemic Inflammatory Response Syndrome/
5	(multiple organ dysfunction* or multiple organ failure* or multi-organ failure* or Systemic Inflammatory Response or septic shock or sepsis syndrome*).tw.
6	Respiratory Distress Syndrome, Adult/
7	Respiratory Distress Syndrome*.tw.
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	((calorie* or energy) and (nutrient* or nutrition* or diet*)).tw.
10	(calori* or energy or underfe* or overfe* or hypercaloric or undernutrition or underprescription).tw.
11	exp intubation, gastrointestinal/
12	exp energy intake/ or exp caloric restriction/ or exp nutrition assessment/ or exp nutritional requirements/ or exp nutritional support/ or exp nutritional status/ or exp parenteral nutrition/ or energy metabolism/ or basal metabolism/ or nutrition therapy/ or exp enteral nutrition/
13	((parenteral* or intravenous*) adj2 (feed or feeding or feeds or fed or nutrition)).tw.
14	((enteral* or enteric or nasogastric) adj2 (feed or feeding or feeds or fed or nutrition)).tw.
15	(nutrition assessment* or nutrition* requirement* or nutrition* support* or nutrition* status or basal metabolism or nutrition* therap*).tw.

16	exp dietary supplements/
17	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18	8 and 17
19	(randomized controlled trial or controlled clinical trial).pt. or (random* or trial or placebo).tw. or clinical trial*.pt.
20	18 and 19
21	exp animals/ not humans.sh.
22	(child* or infan* or pediatr* or paediatr* or neonat* or preterm or newborn* or NICU).mp.
23	20 not (21 or 22)
24	limit 23 to english language

Supplementary file 2: Inclusion criteria and definition of critically ill patients

Inclusion criteria

Trials were screened based on the following inclusion criteria:

1. Parallel group randomized controlled trials
2. Mortality and/or hospital length of stay and/or infectious complications have been reported.
3. Patients were randomized into the study within 72 hours of admission and nutrition therapy was commenced to both arms within 72 hours of admission or appears to have been if it is not precisely reported
4. Energy delivery from EN, PN or any combination was reported as a proportion of estimated requirements (by any method) or the required data to calculate this was provided
5. One arm of the trial reported mean energy delivery of ≥ 80%-120% of estimated or measured energy requirements and the other reported mean energy delivery of <80% of estimated or measured energy requirements
6. Conducted in adult (≥ 16 years) critically ill patients
7. Both study arms received carbohydrate, lipid and protein as part of nutrition therapy
8. The primary intervention in the research study was delivered as a component of nutrition therapy

Abstracts alone, where the subsequent primary publication could not be located were excluded, as were cluster-randomised , non-randomised or quasi-randomised trials. Cross-over trials were also excluded because this methodology did not allow us to investigate the outcomes chosen.

Definition of critically ill participants:

This definition of critically ill participants was adapted from Simpson and Doig 2005 [66]:

A study was deemed to be conducted in a critically ill population if the participants were; Patients recruited in an ICU.

1. The inclusion criteria specified in the study deemed that the patients would be required to be cared for in an ICU i.e. invasive organ support.
2. The patients had an average ICU length of stay of greater than or equal to 2 days.

Supplementary file 3: Data points collected during data extraction

Study Identification

- Sponsorship source
- Country
- Setting
- Authors name
- Institution
- Email
- Address

Methods:

- Design

Population:

- Inclusion criteria
- Exclusion criteria
- Group differences
- No. of participants
- Type of ICU (General, medical, surgical, cardiothoracic, neurological, trauma, burn or multi-centre/mixed)
- Number of centers included in the trial
- Age
- Gender (male)
- Country where the study was conducted
- Number of population: medical
- Proportion of population: surgical

- Proportion of population: other (multiple trauma)
- Overall energy estimation method
- Overall energy prescription amount
- Overall protein prescription amount

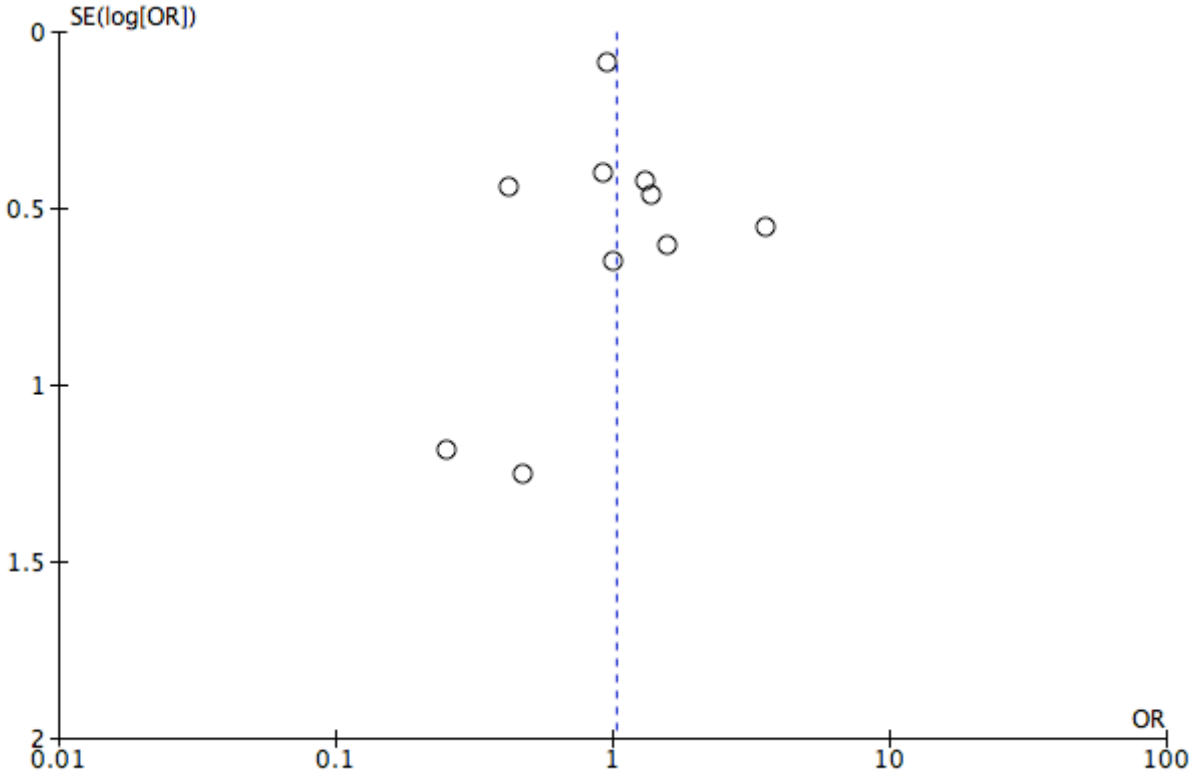
Interventions:

- Type (EN only/ PN only/ EN and PN/ Immunonutrition)
- Method of delivery (details)
- Actual amount of energy delivered to each group
- Actual amount of protein delivered in each group
- Duration of the intervention

Outcomes:

- Mortality
- ICU LOS
- Length of MV (days)
- Infectious complications
- Hospital LOS
- Infectious complications- count/rate

Supplementary File 4: Funnel plot for primary outcome- Mortality

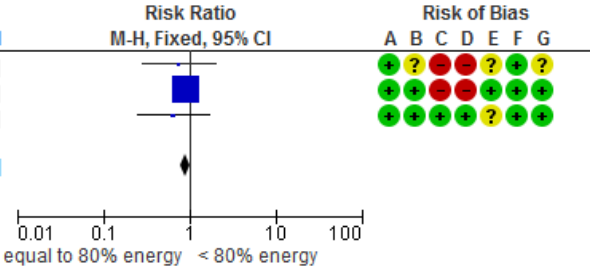


Supplementary Files: Forest Plots for Secondary Outcomes and sub-group analysis

Supplementary file 5: Comparison of ≥ to 80% vs < 80% of full predicted energy, secondary outcome: ICU mortality

Study or Subgroup	> equal to 80% energy Events	Total	< 80% energy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Desachy 2008	6	50	8	50	2.2%	0.75 [0.28, 2.00]
Harvey 2014	317	1190	352	1197	95.3%	0.91 [0.80, 1.03]
Peake 2014	6	57	9	55	2.5%	0.64 [0.25, 1.69]
Total (95% CI)		**1297**		**1302**	**100.0%**	**0.90 [0.79, 1.02]**
Total events	329		369			

Heterogeneity: Chi² = 0.61, df = 2 (P = 0.74); I² = 0%
Test for overall effect: Z = 1.70 (P = 0.09)

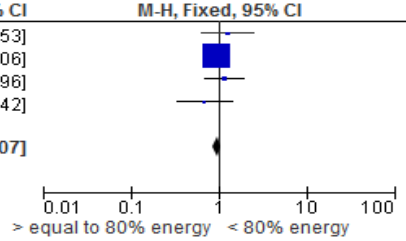


Risk of bias legend
(A) Incomplete outcome data
(B) Allocation concealment
(C) Blinding of participants and personnel
(D) Blinding of outcome assessors
(E) Selective outcome reporting
(F) Other sources of bias
(G) Sequence Generation

Supplementary file 6: Comparison of ≥ to 80% vs < 80% of full predicted energy, secondary outcome: Hospital Mortality

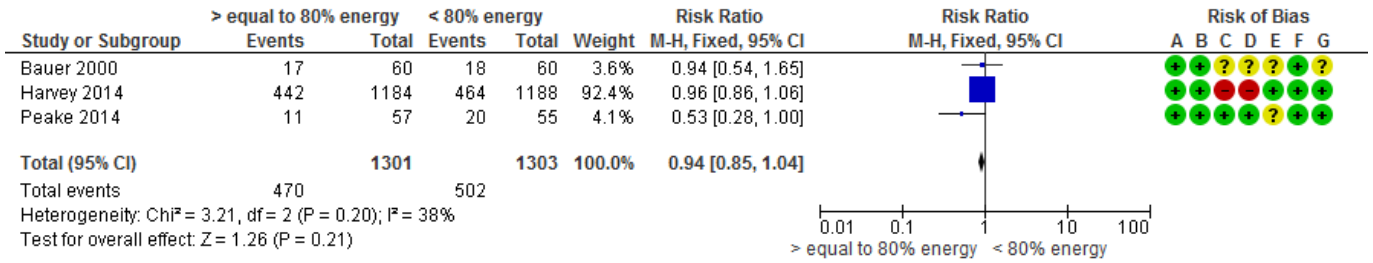
Study or Subgroup	> equal to 80% energy Events	Total	< 80% energy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Desachy 2008	14	50	11	50	2.2%	1.27 [0.64, 2.53]
Harvey 2014	431	1185	450	1186	91.4%	0.96 [0.86, 1.06]
Huang 2012	20	48	17	48	3.5%	1.18 [0.71, 1.96]
Peake 2014	10	57	14	55	2.9%	0.69 [0.33, 1.42]
Total (95% CI)		**1340**		**1339**	**100.0%**	**0.97 [0.87, 1.07]**
Total events	475		492			

Heterogeneity: Chi² = 2.06, df = 3 (P = 0.56); I² = 0%
Test for overall effect: Z = 0.69 (P = 0.49)



Risk of bias legend
(A) Incomplete outcome data
(B) Allocation concealment
(C) Blinding of participants and personnel
(D) Blinding of outcome assessors
(E) Selective outcome reporting
(F) Other sources of bias
(G) Sequence Generation

Supplementary file 7: Comparison of ≥ to 80% vs < 80% of full predicted energy, secondary outcome: 90D Mortality



Risk of bias legend
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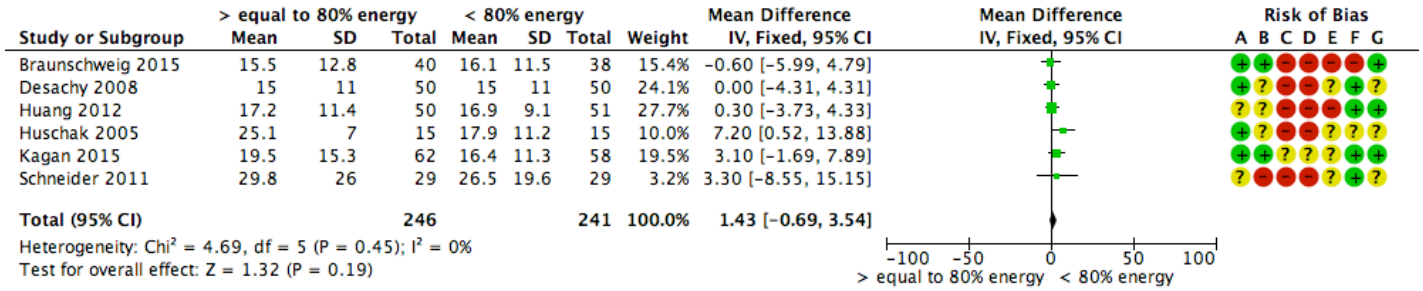
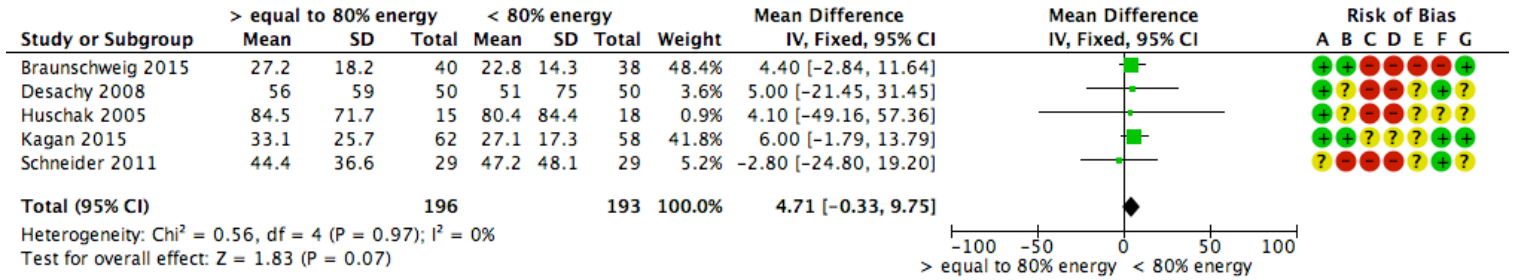
(B) Allocation concealment
(C) Blinding of participants and personnel
(D) Blinding of outcome assessors
(E) Selective outcome reporting
(F) Other sources of bias
(G) Sequence Generation

Supplementary file 8: Comparison of ≥ to 80% vs < 80% of full predicted energy, secondary outcome: ICU LOS



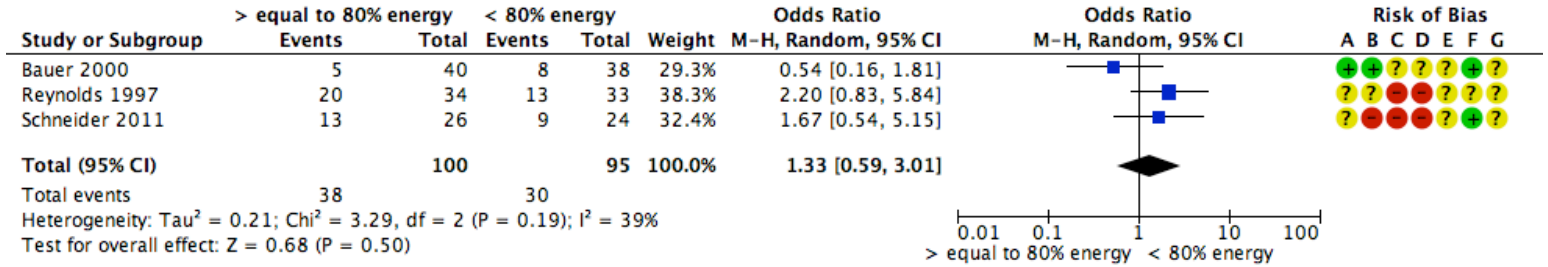
Risk of bias legend
(A) Incomplete outcome data
(B) Allocation concealment
(C) Blinding of participants and personnel
(D) Blinding of outcome assessors
(E) Selective outcome reporting
(F) Other sources of bias
(G) Sequence Generation

Supplementary file 9: Comparison of ≥ to 80% vs < 80% of full predicted energy, secondary outcome: Hospital LOS



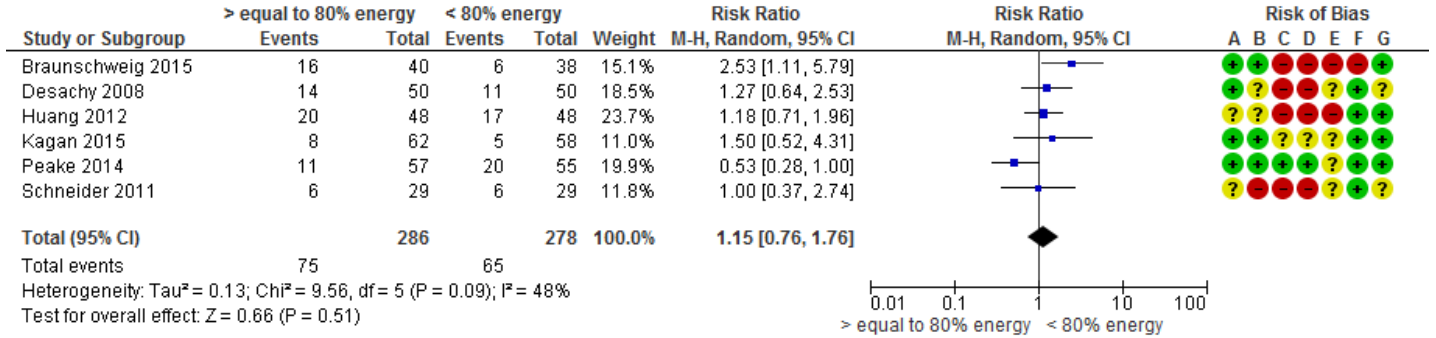
Risk of bias legend
(A) Incomplete outcome data
(B) Allocation concealment
(C) Blinding of participants and personnel
(D) Blinding of outcome assessors
(E) Selective outcome reporting
(F) Other sources of bias
(G) Sequence Generation

Supplementary file 10: Comparison of ≥ to 80% vs < 80% of full predicted energy, secondary outcome: Infectious complications



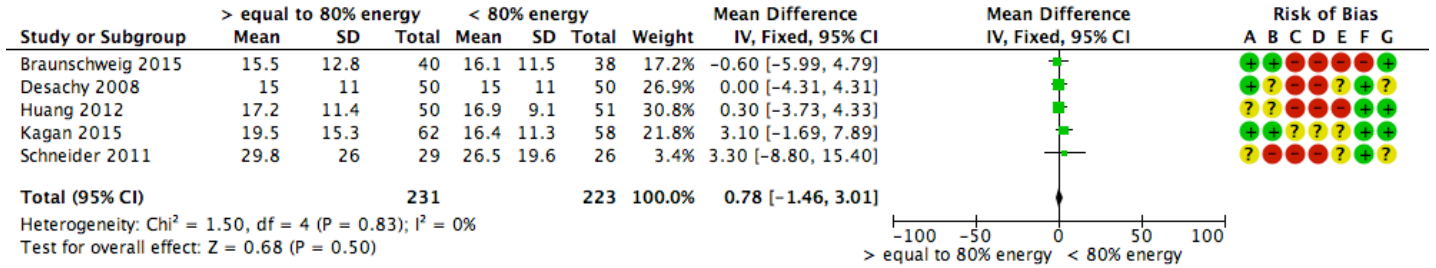
Risk of bias legend
(A) Incomplete outcome data
(B) Allocation concealment
(C) Blinding of participants and personnel
(D) Blinding of outcome assessors
(E) Selective outcome reporting
(F) Other sources of bias
(G) Sequence Generation

Supplementary file 11: Comparison of ≥ to 80% vs < 80% of full predicted energy, secondary outcome: Mortality- EN only



Risk of bias legend
(A) Incomplete outcome data
(B) Allocation concealment
(C) Blinding of participants and personnel
(D) Blinding of outcome assessors
(E) Selective outcome reporting
(F) Other sources of bias
(G) Sequence Generation

Supplementary file 12: Comparison of ≥ to 80% vs < 80% of full predicted energy, secondary outcome: ICU LOS- EN only

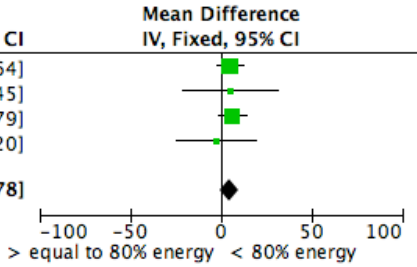


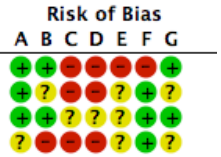
Risk of bias legend
(A) Incomplete outcome data
(B) Allocation concealment
(C) Blinding of participants and personnel
(D) Blinding of outcome assessors
(E) Selective outcome reporting
(F) Other sources of bias
(G) Sequence Generation

Supplementary file 13: Comparison of ≥ to 80% vs < 80% of full predicted energy, secondary outcome: Hospital LOS- EN only

Study or Subgroup	> equal to 80% energy Mean	SD	Total	< 80% energy Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Braunschweig 2015	27.2	18.2	40	22.8	14.3	38	48.8%	4.40 [-2.84, 11.64]
Desachy 2008	56	59	50	51	75	50	3.7%	5.00 [-21.45, 31.45]
Kagan 2015	33.1	25.7	62	27.1	17.3	58	42.2%	6.00 [-1.79, 13.79]
Schneider 2011	44.4	36.6	29	47.2	48.1	29	5.3%	-2.80 [-24.80, 19.20]
Total (95% CI)			**181**			**175**	**100.0%**	**4.72 [-0.35, 9.78]**

Heterogeneity: Chi² = 0.56, df = 3 (P = 0.91); I² = 0%
Test for overall effect: Z = 1.83 (P = 0.07)





Risk of bias legend
(A) Incomplete outcome data
(B) Allocation concealment
(C) Blinding of participants and personnel
(D) Blinding of outcome assessors
(E) Selective outcome reporting
(F) Other sources of bias
(G) Sequence Generation

Supplementary file 14: GRADE Evidence profile summary for secondary outcomes and sub-groups

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	> equal to 80%	< 80% of full predicted energy	Relative (95% CI)	Absolute (95% CI)		
ICU mortality												
3	randomised trials	not serious	not serious [a]	serious [b]	serious [a]	publication bias strongly suspected [c]	329/1297 (25.4%)	369/1302 (28.3%)	**RR 0.90** (0.78 to 1.01)	**28 fewer per 1,000** (from 3 more to 62 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Hospital mortality												
4	randomised trials	not serious	not serious [a]	serious [b]	serious [a]	publication bias strongly suspected [c]	475/1340 (35.4%)	492/1339 (36.7%)	**RR 0.97** (0.87 to 1.07)	**11 fewer per 1,000** (from 26 more to 48 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
90D mortality												
3	randomised trials	not serious	not serious [a]	serious [b]	serious [a]	publication bias strongly suspected [c]	470/1301 (36.1%)	502/1303 (38.5%)	**RR 0.94** (0.84 to 1.04)	**23 fewer per 1,000** (from 15 more to 62 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
ICU LOS												
6	randomised trials	serious [d]	not serious	not serious	serious [e]	publication bias strongly suspected [c]	246	241	-	MD **1.43 higher** (0.69 lower to 3.54 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Hospital LOS												
5	randomised trials	serious [d]	not serious	not serious	serious [e]	publication bias strongly suspected [c]	196	193	-	MD **4.71 higher** (0.33 lower to 9.75 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Infectious complications												
3	randomised trials	not serious [f]	not serious	serious [b]	serious [a]	publication bias strongly suspected [c]	38/100 (38.0%)	30/95 (31.6%)	**OR 1.33** (0.59 to 3.01)	**65 more per 1,000** (from 102 fewer to 266 more)	⨁◯◯◯ VERY LOW	NOT IMPORTANT

Mortality (EN only)												
6	randomised trials	not serious	not serious	serious [b]	serious [a]	publication bias strongly suspected [c]	75/286 (26.2%)	65/278 (23.4%)	**RR 1.17** (0.74 to 1.71)	**40 more per 1,000** (from 61 fewer to 166 more)	⨁◯◯◯ VERY LOW	IMPORTANT
ICU LOS (EN only)												
5	randomised trials	serious [d]	not serious	serious [b]	serious [e]	publication bias strongly suspected [c]	231	223	-	MD **0.78 higher** (1.46 lower to 3.01 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Hospital LOS (EN only)												
4	randomised trials	serious [d]	not serious	serious [b,g]	serious [e]	publication bias strongly suspected [c]	181	175	-	MD **4.72 higher** (0.35 lower to 9.78 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **OR:** Odds ratio

a) The CI around the estimate is not sufficiently narrow. Further, the number of patients in estimate probably means the outcome is underpowered
b) Significant heterogenity in the application of interventions within studies
c) Funnel plot asymetrical, trials to bottom right missing. Also, nutrition literature is dominated by smaller trials, therefore much greater likelihood of publication bias
d) Trials are unblinded, (outcome assessors and/or study personal, participants), outcome is subjective
e) Optimal information size calculation: The number of patients included in the review is below that required as part of a conventional sample size calculation for precision in the outcome
f) No explanation was provided

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from t

Chapter appendices

3.4 PROSPERO registration for systematic review

UNIVERSITY of York
Centre for Reviews and Dissemination

NHS
National Institute for Health Research

PROSPERO International prospective register of systematic reviews

Delivery of full predicted energy from nutrition and the effect on mortality in critically ill adults: a systematic review and meta-analysis of parallel randomised controlled trials

Emma Ridley, Andrew Davies, Carol Hodgson, Adam Deane, Michael Bailey, David Cooper

Citation
Emma Ridley, Andrew Davies, Carol Hodgson, Adam Deane, Michael Bailey, David Cooper. Delivery of full predicted energy from nutrition and the effect on mortality in critically ill adults: a systematic review and meta-analysis of parallel randomised controlled trials. PROSPERO 2015:CRD42015027512 Available from http://www.crd.york.ac.uk/PROSPERO_REBRANDING/display_record.asp?ID=CRD42015027512

Review question(s)
The clinical question posed in this review is "Does delivery of full predicted energy from nutrition influence mortality or other important clinical outcomes in critically ill adults compared to delivery of less than full predicted energy from nutrition?"

Searches
The current issues of the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (Ovid SP, from 1948 to date), EMBASE (Ovid SP, from 1948 to date) and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCOhost, from 1948 to date) will be searched.

Publication restrictions for English language and studies containing adults and humans will be used.

Types of study to be included
Parallel randomised controlled trials.

Condition or domain being studied
Critically ill adult patients (>= 16 years) irrespective of admission diagnosis that receive enteral and/or parenteral nutrition.

Participants/ population
Critically ill adult patients (>= 16 years) irrespective of admission diagnosis that receive enteral and/or parenteral nutrition.

Intervention(s), exposure(s)
The intervention group (delivery of full predicted energy from nutrition) will comprise study arms which report that patients received a mean energy delivery of = 80% of estimated or measured energy requirements by enteral and/or parenteral nutrition (PN) during the study period.

Comparator(s)/ control
The other arm will be the control (comparator) group (mean energy delivery <80% of full predicted energy requirements).

Outcome(s)
Primary outcomes
Mortality at any time point.

Secondary outcomes
1. Hospital, ICU and 90-day mortality;

2. Infectious complications;

3. ICU and hospital length of stay, measured in days;

4. Duration of mechanical ventilation, measured in days.

Data extraction, (selection and coding)
Two review authors will independently extract data using the 'Covidence' systematic review program. A third will be used to resolve any discrepancies.

Risk of bias (quality) assessment
The Cochrane Risk of Bias tool will be used. Where studies of high quality and at low risk of bias exist, we will consider doing a separate analysis with these studies alone to further investigate any clinical effect.

Strategy for data synthesis
Data will be synthesised aggregately with both a quantitative and narrative synthesis pending studies found. If a quantitative synthesis is not possible then a narrative synthesis will be performed.

Analysis of subgroups or subsets
A priori, and pending study numbers, we would like to conduct sub group analysis of:

• Studies using only EN in the intervention group;

• Studies using only PN in the intervention group;

• Studies using EN and PN in the intervention group;

• Trials investigating immunonutrition as the primary intervention;

• Studies assessed as high quality and low risk of bias.

Dissemination plans
Publication of the full protocol and final review.

Contact details for further information
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http://www.anzicrc.monash.org/

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Professor Michael Bailey, Australian and New Zealand Intensive Care Research Centre, Department of Epidemiology and Preventive Medicine, Monash University
Professor David Cooper, Australian and New Zealand Intensive Care Research Centre, Department of Epidemiology and Preventive Medicine, Monash University; 5Department of Intensive Care Medicine, The Alfred, Commercial Road, Melbourne 3004, Australia; Department of Intensive Care Medicine

Anticipated or actual start date
21 November 2014

Anticipated completion date
31 January 2016

Funding sources/sponsors
None

Conflicts of interest
ER, AD, CH, ADe, MB and DJC are involved in two currently recruiting RCTs investigating optimisation of energy in critically ill patients. ER, AD and ADe have been involved in one completed and published RCT investigating optimisation of energy in critically ill patients and which may be considered for inclusion in the systematic review following the outlined processes.

Language
English

Country
Australia

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Adult; Critical Illness; Energy Intake; Energy Metabolism; Enteral Nutrition; Humans; Infectious Diseases; Mortality; Nutritional Status

Stage of review
Ongoing

Date of registration in PROSPERO
26 October 2015

Date of publication of this revision
10 April 2017

DOI
10.15124/CRD42015027512

Stage of review at time of this submission	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

3.5 Manuscript: "Full predicted energy from nutrition and the effect on mortality and infectious complications in critically ill adults: a protocol for a systematic review and meta-analysis of parallel randomised controlled trials [67]"

Ridley *et al. Systematic Reviews* (2015) 4:179
DOI 10.1186/s13643-015-0165-5

Systematic Reviews

PROTOCOL Open Access

Full predicted energy from nutrition and the effect on mortality and infectious complications in critically ill adults: a protocol for a systematic review and meta-analysis of parallel randomised controlled trials

Emma J. Ridley[1,2*], Andrew R. Davies[1], Carol Hodgson[1], Adam Deane[1,3,4], Michael Bailey[1] and D. James Cooper[1,5]

Abstract

Background: Whilst nutrition is vital to survival in health, the precise role of nutrition during critical illness is controversial. More specifically, the exact amount of energy that is required during critical illness to optimally influence clinical outcomes remains unknown. The aim of this systematic literature review and meta-analysis is to evaluate the clinical effects of optimising nutrition to critically ill adult patients, such that the entire predicted amount of energy that the patient requires is delivered, on mortality and other important outcomes.

Methods: A systematic literature review and meta-analysis will be conducted by searching for studies indexed in Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica Database (EMBASE), Cumulative Index to Nursing and Allied Health Literature (CINAHL) and the Cochrane Library. Searches will be restricted to English. Studies will be considered for inclusion if they are a parallel randomised controlled trial investigating a nutrition intervention in an adult critical care population, where one arm delivers 'full predicted energy from nutrition' (defined as provision of ≥80 % of the predicted energy required) and the other arm delivers energy less than 80 % of the predicted requirement. Two authors will independently perform title screening, full-text screening, data extraction and quality assessment for this review. The quality of individual studies will be assessed using the 'Risk of Bias' tool, and to assess the overall body of evidence, a 'Summary of Findings' table and the Grades of Recommendation, Assessment, Development and Evaluation system will be used, all recommended by the Cochrane Library. Pending the study heterogeneity that is determined, a fixed-effect meta-analysis with pre-defined subgroup analyses will be performed.

Discussion: Currently, it is controversial whether optimal energy delivery is beneficial for outcomes in critically ill patients. This systematic review and meta-analysis will evaluate whether delivering optimal energy to critically ill adult patients improves outcomes when compared to delivery of lesser amounts.

Systematic review registration: PROSPERO CRD42015027512

Keywords: Enteral nutrition, Parenteral nutrition, Nutrition, Energy, Critically ill, Systematic review, Meta-analysis

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Full list of author information is available at the end of the article

Background

Nutrition is vital to survival in health. In critical illness, however, the role of nutrition is less defined. More specifically, the exact amount of energy that is required during critical illness to optimally influence clinical outcomes remains unknown. Prolonged provision of nutrition below a patient's individual nutrition requirements (including under provision of energy, specifically) can result in malnutrition. Whist the prevalence of malnutrition in critically ill patients is generally poorly documented, poorly defined, and varies depending on the criteria used, reports indicate that worldwide prevalence in hospitalised patients is between 20 and 50 % internationally [1]. Malnutrition is thus likely to be commonplace in critically ill patients. In the acute hospitalised population, malnutrition has been associated with many undesirable clinical consequences such as reduced immune function, increased length of hospital stay, impaired wound healing, muscle wasting and ultimately increased health care costs [1]. Conversely, it is known that excessive nutrition can lead to over provision of energy and result in adverse patient effects including increased metabolic stress, hyperglycaemia and deranged liver function [2].

Despite the known consequences of significant under- or overfeeding in critically ill patients, there is considerable uncertainty regarding the ideal amount of energy to provide to optimise outcomes. One of the most significant issues in studies of critical illness nutrition is that delivery of the full (or even near-full) predicted energy amounts (where the full amount of energy a patient is predicted to require is administered) has been uncommon. This often leads to all patient groups in nutrition studies receiving less than their full predicted energy requirements [3–7]. This occurs in clinical practice too, with a large international multicentre observational study including 158 intensive care units (ICUs) and 2946 patients indicating that only 45 % of predicted energy was provided by standard enteral nutrition (EN) alone, probably due to delays in commencement, intestinal dysfunction, and withholding of EN for medical procedures [8–10]. Several small studies have suggested improved clinical outcomes when energy delivery approximates full predicted energy requirements from nutrition; however, this evidence has not been translated into clinical practice [11–13].

Given the lack of clear evidence to make recommendations regarding the optimum amount of energy to provide to critically ill patients, we sought to conduct a systematic review to aggregate and summarise the evidence from the trials in this field to inform future research and clinical practice.

Objectives

The aim of this systematic literature review and meta-analysis is to assess the effect of delivery of full predicted energy from nutrition on mortality and other important clinical outcomes in critically ill adults. 'Full predicted energy from nutrition' is defined as provision of ≥80 % of the predicted energy determined by any method, and the comparator will be the delivery of energy less than 80 % of the predicted requirement determined by any method.

The clinical question posed in this review is 'Does the delivery of full predicted energy from nutrition influence mortality or other important clinical outcomes in critically ill adults compared to the delivery of less than full predicted energy from nutrition?'

Methods/design

A rigorous systematic review and meta-analysis of randomised controlled trials (RCTs) will be conducted using the methodology detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* [14] and the Centre for Research and Dissemination (CRD)'s *Guidance for Undertaking Reviews in Health Care* [15].

Population

We will include studies in critically ill adult patients (≥16 years) irrespective of admission diagnosis that receive enteral and/or parenteral nutrition (PN).

Study participants will be defined as 'critically ill' if they meet one of the following criteria (adapted from Simpson and Doig 2005 [16]):

1. The patients were recruited in an ICU.
2. The inclusion criteria specified in the study deemed that the patients would be required to be cared for in an ICU, i.e. invasive organ support.
3. The patients had an average ICU length of stay of greater than or equal to 2 days.

Interventions and comparators

The intervention group (delivery of full predicted energy from nutrition) will comprise study arms which report that patients received a mean energy delivery of ≥80 % of estimated or measured energy requirements. Energy delivery must be provided by EN and/or PN but may also include some non-nutritional calorie sources such as propofol and dextrose. The alternate arm will be the control (comparator) group (mean energy delivery <80 % of full predicted energy requirements).

The metric of ≥80 % of estimated or measured energy requirements was chosen by the authors as it is above the international mean for energy delivery, it approximates energy requirements and observational evidence is emerging that receipt of ≥80 % of estimated energy requirements may improve clinical outcomes in certain patient groups [8, 17].

Outcome measures

Primary

1. Hospital mortality
2. Hospital length of stay
3. Infectious complications

Infectious complications will be defined as any confirmed infectious event after randomisation, reported as the total number of events for each arm of the RCT, if an objective measure is described (i.e. positive blood culture).

Secondary

1. ICU and 90-day mortality
2. Duration of mechanical ventilation in survivors and non-survivors, measured in days
3. ICU and hospital length of stay in survivors and non-survivors, measured in days

Inclusion criteria

Trials will be screened based on the following inclusion criteria:

1. Parallel group randomised controlled trials.
2. Mortality, hospital length of stay and/or infectious complications have been reported.
3. Patients were randomised into the study within 72 h of admission and nutrition therapy was commenced to both arms within 72 h of admission or appears to have been if it is not precisely reported.
4. Energy delivery from EN, PN or any combination is reported as a proportion of estimated requirements (by any method) or the required data to calculate this is provided.
5. One arm of the trial reports mean energy delivery of ≥80–120 % of the estimated or measured energy requirements, and the other reports mean energy delivery of <80 % of the estimated or measured energy requirements.
6. Conducted in adult (≥16 years) critically ill patients.
7. Both study arms received carbohydrate, lipid and protein as part of nutrition therapy.
8. The primary intervention in the research study was delivered as a component of nutrition therapy.

Abstracts alone, where the subsequent primary publication cannot be located, will be excluded.

We will not include cluster-randomised trials, non-randomised or quasi-randomised trials. We will also exclude cross-over trials because this methodology will not allow us to investigate the outcomes we have chosen.

Search strategy

The current issues of the Cochrane Central Register of Controlled Trials (CENTRAL), Medical Literature Analysis and Retrieval System Online (MEDLINE) (Ovid SP, from 1948 to date), Excerpta Medica Database (EMBASE) (Ovid SP, from 1948 to date) and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCOhost, from 1948 to date) will be searched. Sensitivity-maximising strategies will be applied for each database as described in the Cochrane Handbook for Systematic Reviews of Interventions [14], and advice from a senior librarian with extensive knowledge in the area of medical systematic review will be sought. Publication restrictions for English language and studies containing adults and humans will be used pending the accuracy of the indexing for each search engine and at the advice of the senior librarian. Appendix demonstrates the MEDLINE search strategy which will be adopted for other search engines. Once included studies are identified, the reference lists, other systematic reviews on similar topics and clinical practice guidelines will be hand-searched to identify any other potential articles.

Study selection and management of review processes

The EndNote reference manager software program (version X7.3, New York City: Thomas Reuters, 2011) and online systematic review management program, Covidence 2013 (www.covidence.org) will be used to coordinate the screening and data collection process. Covidence allows multiple authors to independently conduct the processes associated with a systematic review and then resolve any conflicts whilst tracking processes.

At each stage of study screening, selection for inclusion and exclusion criteria and data extraction processes, two authors will independently pilot suggested processes on 10 papers and then discuss to assess agreement, refine processes and ensure there is consistency in methodology. Once a final methodology has been agreed upon, it will be imputed into Covidence and used for the full set of articles as a final version at each stage.

Study selection

Results of the searches described above will be merged in the reference manager software. Selection of relevant articles will be conducted in stages.

Stage 1: Remove duplicates
Using the reference manager software, one author will remove obvious duplicate articles from the initial search.

Stage 2: Remove irrelevant articles
Using the reference manager software one author will remove obviously irrelevant articles and those which

are not RCTs (editorials, letters, abstracts, reviews, meta-analysis). This will be checked by the second author and over inclusion for screening will be preferred to exclusion at this stage.
The final list after removal of duplicates and irrelevant articles will be uploaded into Covidence systematic review software for screening by two authors independently.

Stage 3: Determine a final list of potentially relevant articles
Two authors will then independently screen titles and abstracts using the Covidence software to determine a final list of potentially relevant studies for full-text review. After this screening process, the results will be compared and any conflicts resolved by discussion. Where eligibility cannot be determined using the abstract alone, the article will remain in consideration and the full text will be obtained. In the case of inability to reach consensus, a third review author will be consulted. Once a list of potentially relevant articles has been produced, the full text will be retrieved.

Stage 4: Retrieve full-text reports for compliance of studies and determine eligibility criteria
The same two authors will independently assess the full-text articles using a hierarchy of inclusion criteria previously outlined. The reasons for exclusion and any conflicts will be independently noted.

Conflicts will be resolved by discussion, with the two authors using the hierarchy of inclusion criteria to re-assess the articles together in an attempt to obtain a consensus for inclusion or exclusion. In cases of inability to reach a consensus, a third review author will be asked to independently assess the article. A final list will be compiled of all eligible studies along with a list of excluded studies based on the review of the authors. The reference lists of the included studies and systematic reviews of similar topics (with and without meta-analysis) will also be checked to ensure there are no missing relevant articles. The final list of included and excluded studies will be discussed with the whole authorship group and any articles that may have been excluded but would have been expected to be included prior to assessment will be presented to ensure we have consensus and a 'characteristics of excluded studies' table will be developed. Any eligible studies will also be reviewed and compared at this stage to ensure there are no duplicate reports of studies.

Data extraction
Study data extraction points will be developed based on the Cochrane Collaboration Study Selection and Data Extraction form [14]. These study characteristics will be pre-specified prior to data extraction and relate to patient and setting characteristics, study methodology, detailed data on nutrition therapy (including mode delivered, energy requirements (estimated or measured), energy delivered and duration of nutrition therapy) and detailed data on outcome variables such as how they were defined, how they were reported, the sample sizes in each group, missing data and any other relevant comments on each paper.

Assessment of bias in included studies
Two review authors will independently assess the risk of bias in included articles using the Cochrane risk of bias tool, with a particular focus on sequence generation, allocation concealment, blinding, incomplete or selective reporting of outcome data and other sources of bias as recommended in the Cochrane Handbook for assessment of parallel trials [14]. To ensure consistency in assessment between authors, we will use the exact instructions provided by Cochrane for each domain, as set out in the Cochrane Handbook [14]. Where there is disagreement between author assessments, a conservative approach will be favoured, where article quality will be downgraded in the first instance. If consensus cannot be reached, a third author will be required to assess the article(s).

Assessment of reporting biases
If 10 or more studies are identified, funnel plot, as recommended by Egger [18], will be created using the statistical software of The Cochrane Collaboration, Review Manager (RevMan) 5.3 [19]. We will conduct sensitivity analyses to explore the robustness of the meta-analysis in terms of conclusions related to the causes of funnel plot asymmetry.

Data synthesis
Only available data will be synthesised; no missing date will be imputed. The included data will be quantitatively reviewed and combined by energy delivery for each specified primary and secondary outcome using RevMan 5.3 [19]. We will synthesise these data only in the absence of important clinical or statistical heterogeneity (see definition of important heterogeneity under 'Assessment of statistical heterogeneity' below).

Unit of analysis issues
We will include in our review only RCTs with a parallel-group design. The issue of repeated measures is not relevant for the outcomes under investigation.

Where different scales are used to measure the same outcome, we will present the treatment effect as the standardised mean difference (SMD) with 95 % confidence intervals (CIs). Measurements in different units will not be combined.

Assessment of statistical heterogeneity

We will consider the χ^2 statistic to test statistical heterogeneity between studies and will consider a P value ≤0.10 as indicating significant statistical heterogeneity; we will use the I^2 statistic to assess the magnitude of heterogeneity [14]. We will consider $I^2 > 50$ % to indicate problematic heterogeneity between studies and will carefully consider the value of any pooled analysis. If I^2 is greater than 50 %, we will use a random-effects model analysis to determine the best estimate of the intervention effect; otherwise, a fixed-effect model of analysis will be used. If the two do not coincide, we will not consider the random-effects estimate as the actual intervention effect in the population under study. We will construct forest plots to summarise findings from the included studies.

Statistical analysis and measures of treatment effect

The analysis will be undertaken using RevMan 5.3 software [19].

One of the primary outcomes (mortality) and one of the secondary outcomes (infectious outcomes) is binomial, whilst all other outcomes are continuous.

For binomial outcomes, we will present the treatment effect as an odds ratio (OR) with 95 % CIs.

For continuous outcomes, we will present the treatment effect as a mean difference (MD) or SMD with 95 % CIs. If variables are found to be non-normally distributed, appropriate statistical methods will be utilised for analysis where possible.

In addition to analysing the primary outcome variable (mortality) as a binomial variable, should sufficient data exist, we will also conduct time to event analysis for survival with results reported as hazard ratio (HR) with 95 % CIs in accordance with Tierney at al. and as specified in the Cochrane Handbook [14, 20]. Analysis using this data will be conducted using the generic inverse-variance method and the fixed and random effect analyses compared.

Subgroup analyses have been defined a priori. If obvious unexplained heterogeneity is observed ($I^2 > 50$ %) between studies, we will consider other subgroup analysis and report these separately. Further, where studies of high quality and at low risk of bias exist, we will consider doing a separate analysis with these studies alone to further investigate any clinical effect. All analyses will be presented in the final paper. Where subgroup analyses are performed, the method described by Deeks and recommended by Cochrane will be used [14, 21].

Subgroup analyses

A priori, and pending study numbers, we would like to conduct subgroup analysis of:

- Studies using only EN in the intervention group
- Studies using only PN in the intervention group
- Studies using EN and PN in the intervention group
- Trials investigating immunonutrition as the primary intervention
- Studies assessed as high quality and low risk of bias

These subgroups have been chosen as it is plausible that the mode of nutrition therapy may affect the specified outcomes differently. Immunonutrition has been pre-specified as the literature in this area is conflicting (and may include harm in the critically ill [22]) and so separate analysis is warranted.

Summary of findings and quality of the body of evidence

We will present study findings in a standard 'Summary of Findings' (SOF) table, which will include the magnitude of effect, the numbers of participants and studies addressing each outcome and a grade for the overall quality of the body of evidence for each outcome. Space will be provided for comments.

We will use the principles of the Grades of Recommendation, Assessment, Development and Evaluation system [23] to assess the quality of the body of evidence associated with specific outcomes.

Publication

The results of the meta-analysis will be published in a peer reviewed journal with all contributors listed as authors.

Discussion

Inform future studies

This systematic review and meta-analysis will inform the design of future nutrition studies investigating the relationship of energy dose in critical illness. We will also identify the gaps in the literature and trial design in relation to energy dose in nutrition research, which may assist in improving methodological quality of future studies. Nutrition is a universally provided standard of care to the critically ill and is inexpensive compared to other therapies, but the risks and benefits to patient outcomes are remarkably poorly understood.

Expected benefits of this review

This will be the first published systematic review and meta-analysis to our knowledge that will investigate the effect of delivering full predicted energy from nutrition

on clinical outcomes in critically ill adults, compared to delivering less than full predicted energy requirements. The literature available on this topic is conflicting and confusing for clinicians and could potentially lead to misleading conclusions being made regarding the role of nutrition in critical illness. This systematic review and meta-analysis will benefit clinicians by providing a summary of the available literature and provide further guidance.

Appendix

Table 1 Sample search strategy for MEDLINE (other searches will be based on this)

Number	Searches
1	(((intensive or critica*) adj3 (care or unit* or illness*)) or ICU or (critical* adj ill) or (mechanical* adj4 ventilat*)).tw.
2	(artificial* adj2 (respirat* or ventilat*)).tw.
3	exp critical illness/ or exp critical care/ or exp intensive care/ or exp respiration, artificial/ or exp ventilation, mechanical/ or exp critical care nursing/ or exp intensive care units/
4	exp Multiple Organ Failure/ or exp Systemic Inflammatory Response Syndrome/
5	(multiple organ dysfunction* or multiple organ failure* or multi-organ failure* or Systemic Inflammatory Response or septic shock or sepsis syndrome*).tw.
6	Respiratory Distress Syndrome, Adult/
7	Respiratory Distress Syndrome*.tw.
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	((calorie* or energy) and (nutrient* or nutrition* or diet*)).tw.
10	(calori* or energy or underfe* or overfe* or hypercaloric or undernutrition or underprescription).tw.
11	exp intubation, gastrointestinal/
12	exp energy intake/ or exp caloric restriction/ or exp nutrition assessment/ or exp nutritional requirements/ or exp nutritional support/ or exp nutritional status/ or exp parenteral nutrition/ or energy metabolism/ or basal metabolism/ or nutrition therapy/ or exp enteral nutrition/
13	((parenteral* or intravenous*) adj2 (feed or feeding or feeds or fed or nutrition)).tw.
14	((enteral* or enteric or nasogastric) adj2 (feed or feeding or feeds or fed or nutrition)).tw.
15	(nutrition assessment* or nutrition* requirement* or nutrition* support* or nutrition* status or basal metabolism or nutrition* therap*).tw.
16	exp dietary supplements/
17	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18	8 and 17
19	(randomized controlled trial or controlled clinical trial).pt. or (random* or trial or placebo).tw. or clinical trial*.pt.
20	18 and 19
21	exp animals/ not humans.sh.
22	(child* or infan* or pediatr* or paediatr* or neonat* or preterm or newborn* or NICU).mp.
23	20 not (21 or 22)
24	limit 23 to english language

Chapter 4: What is the current practice of nutrition therapy provision in Australia and New Zealand?

4.1 Summary

This chapter describes a retrospective analysis of prospective data collected as part of a large international quality improvement survey of nutrition practice in ICU, conducted over 2007–13. The aim of this work was to compare nutrition practice in ICUs in Australia and New Zealand to practice in international ICUs, with a specific focus on the energy delivery and caloric content of EN solutions. This work in this Chapter relates to thesis aim and hypothesis 2.

4.2 Manuscript “Nutrition therapy in Australia and New Zealand Intensive Care Units: An international comparison study”, under review, JPEN

Nutrition therapy in Australia and New Zealand Intensive Care Units:

An international comparison study

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Clinical relevancy statement:

The **A**ugmented versus **R**outine approach to **G**iving **E**nergy **T**rial (TARGET) is the largest blinded enteral nutrition intervention trial to be conducted in the critically ill. 4000 critically ill patients in Australia and New Zealand (ANZ) have been randomized to energy dense (1.5kcal/ml) enteral nutrition or routine care to evaluate whether increasing energy delivery effects clinical outcomes. To determine the external validity of the TARGET results we have compared ANZ and international nutritional practices. These data are important for critical care clinicians throughout the world to interpret the upcoming TARGET results.

Statement of Authorship:

EJR, SLP, MJ, MJC, DH equally contributed to the conception and design of the research;

ARD, AD, KL contributed to the design of the research; ER, MJ, MJC, DH and KL contributed to the analysis of the data; ER, SP, MJ, AD, ARD, MJC, DH and KL contributed to the interpretation of the data; ER, MJC, AD and KL drafted the manuscript; all authors critically revised the manuscript and agree to be fully accountable

for the integrity and accuracy of the work. All authors have read and approved the final version of the manuscript.

Financial disclosure:

There was no specific funding for this project. This work is part of PhD thesis and EJR has a National Health and Medical Research Council (NHMRC) postgraduate scholarship.

Conflict of interest statement:

The authors have no conflicts to declare.

Disclosure:

ER, SP, AD, ARD, MJC and KL are all investigators on the TARGET trial.

AD is an employee of Baxter Healthcare Corporation, Australia. EJR has received unrestricted research funding for an investigator initiated study from Baxter Healthcare Corporation. AD and MJC are on the management committee for this study.

ABSTRACT:

Background: **T**he **A**ugmented versus **R**outine approach to **G**iving **E**nergy **T**rial (TARGET) is the largest blinded enteral nutrition (EN) intervention trial evaluating energy delivery to be conducted in the critically ill. To determine the external validity of TARGET results, nutrition practices in intensive care units (ICUs) in Australia and New Zealand (ANZ) are described and compared to international practices.

Methods: Retrospective analysis of prospectively collected data for the International Nutrition Surveys, 2007-2013. Data are presented as mean (SD).

Results: 17,154 patients (ANZ: n=2776 vs. international n=14 378) were included from 923 ICUs (146 and 777 respectively). EN was the most common route of feeding (ANZ: 85%, n=2365 patients vs international: 84%, n=12 034, p=0.258) and EN concentration was also similar (<1.25kcal/ml ANZ: 70%, n=12 396 vs international: 65%, n=56 891 administrations, p<0.001). Protein delivery was substantially below the estimated prescriptions but similar between the regions (0.6 (0.4) g/kg/day vs 0.6 (0.4) g/kg/day, p=0.849). Patients in ANZ received slightly more energy (1133 (572) vs 948 (536) kcal/day, p <0.001), possibly because more energy was prescribed (1947 (348) vs 1747 (376) kcal/day, p<0.001), nutrition protocols were more commonly used (98% vs 75%, p<0.001) and included recommendations for therapies such as prokinetic agents (87%, vs 51%, n=399, p<0.001), and small bowel feeding (62% vs 40% p<0.001) compared to international ICUs.

Conclusions:

Key elements of nutrition practice are similar in ANZ and international ICUs. These data can be used to determine the external validity and relevance of the TARGET results.

INTRODUCTION

The provision of nutrition therapy to critically ill patients is a widely accepted international standard of care [11, 12, 60, 68, 69]. Practice guidelines assist clinicians to implement evidence based nutrition therapy and generally recommend that nutrition, delivered via an enteric tube (termed enteral nutrition (EN)), be started within 24-48 hours of admission to the intensive care unit (ICU) in the hemodynamically stable patient [11, 12, 60, 68, 69]. Delivery of nutrition in this way has been associated with reduced infective complications, length of ventilation, time in the ICU and mortality [11, 12, 68, 69]. Beyond these elements however, there exists several areas of uncertainty due to lack of definitive evidence, specifically, the effect of nutrition risk, use of indirect calorimetry vs predictive equations, optimal timing of nutrition, the amount of energy and protein to provide, and how best to optimise nutrition delivery. This uncertainty leaves leaving recommendations contained in best practice guidelines open to significant interpretation and confusion.

One of the largest areas of area of uncertainty is the amount of energy to provide to critically ill patients to elicit optimum clinical outcomes. **T**he **A**ugmented versus **R**outine approach to **G**iving **E**nergy **T**rial (TARGET) is the largest blinded enteral nutrition intervention trial evaluating energy delivery to be conducted [70]. The primary aim of this trial TARGET is to determine if augmentation of energy delivery using energy dense EN (a 1.5 kcal/ml EN solution) improves 90-day survival when compared to routine care. Whilst this trial is only being conducted in Australia and New Zealand (ANZ), the pragmatic nature of the intervention provides the opportunity for these data to be generalizable to international nutrition practice. It is however plausible that the current lack of definitive evidence regarding the role of energy and

other key elements of nutrition practice in critical illness has resulted in significant temporal and geographical heterogeneity in practice. Thus, prior to the publication of TARGET and to establish external validity of the results, it is important to describe nutrition practices in ANZ and compare this to practice in international ICUs, with a focus on choice of EN solution and energy delivery.

METHODOLOGY

This was a retrospective analysis of data collected prospectively as part of the International Nutrition Survey (INS), a quality improvement activity coordinated by The Clinical Research Evaluation Unit (CERU), Ontario, Canada. Data were obtained for the survey annually from years 2007 to 2013 inclusive (with the exception of 2010 and there was no survey in 2012). The methods of this survey have previously been described in detail [22]. In summary, participation in the survey was voluntary, provided ICUs had at least 8 beds and a person with knowledge and ability to collect data. Available survey data included demographics on the hospital, ICU and nutrition service, as well as individual patient nutrition therapy information for a maximum of 12 days. Consecutive patients who had mechanical ventilation initiated in the first 48 hours of ICU stay and remained in ICU for more than 72 hours were eligible for inclusion in the survey. Management of the patient was according to the individual clinicians in the ICUs. Data obtained for this analysis were: (1) hospital and ICU organisation details; (2) detailed nutrition assessment information (which was only collected in survey years 2011 and 2013); (3) daily nutrition provision information; and (4) outcome information.

Mode of nutrition therapy delivered on a study day was defined when a patient received EN, parenteral nutrition (PN) or oral nutrition alone or in any combination and each

patient could contribute a minimum of 0 days and a maximum of 12 days. For each patient, a maximum of 3 unique EN solutions (as defined in the INS methodology) were collected during an EN study day (which have been defined as 'EN administrations' for the purpose of this analysis). Caloric content of EN solutions was confirmed using product information. If information was unavailable, it was unclear how the solution was being delivered or it was specifically designed to be a 'supplemental' product, the solution was excluded. EN solutions were grouped according to calorie content for analysis (kcal/ml): <1.25 (defined as standard EN solution); 1.25 to 1.49; 1.5 to 1.99; ≥2. To simplify the description, methods to determine weight for the purpose of energy and protein estimations, and the choice of predictive equations were described as the most popular choice if ≥ 80% of the patients underwent the same method at the site level and otherwise were defined as 'mixed' if the site did not report the same method for ≥ 80% of the patients included in the analysis. Days where transition to permanent oral nutrition was noted have been excluded, as has day of discharge/death.

ICUs in ANZ were defined as those self-identified as being located in ANZ and international sites were defined as all other sites that did not identify as an ICU in ANZ.

Ethics approval for the larger survey was obtained by the CERU at Queens University, Canada and if required, by individual sites for each participating year of the survey. Further approvals were not required for this secondary analysis of data.

Statistical analysis

Categorical data are reported as numbers and percentages (%). Continuous data are reported as mean (standard deviation (SD)) where normally distributed or as median and

interquartile range [IQR] where not normally distributed. Site characteristics are compared between regions using chi-square tests for categorical variables and 2-sample t-tests or Mann-Whitney tests for continuous data. Patient characteristics are compared using generalized estimating equations (GEE). Logistic and ordinal regression were used for categorical data and linear regression for continuous data, accounting for the clustering of patients within sites. Duration of mechanical ventilation and length of stay were censored at 60 days and log transformed for analysis. Time to discharge alive was censored at 60 days and analyzed via a log-rank test with death treated as a competing event. Analysis of EN administrations was done via a GEE logistic regression with clustering of administrations within patients, and patients within sites. Analysis was performed using SPSS version 22 and a two- sided p-value of 0.05 was considered to be statistically significant. Because sites may have participated in the survey in multiple years, a sensitivity analysis was repeated for energy and protein delivery only including data from the most recent survey from each site. Sensitivity analyses were also conducted to assess potential differences over the five survey years in the use of methods for estimating energy requirements and in the caloric content of EN administrations by including year and year-by-region fixed effects in the analysis models.

RESULTS

Overall site and patient characteristics

Patient characteristics are shown in Table 1 and site characteristics in Table 2. There were 923 ICUs in the data set from all survey years (146 from ANZ and 777 international), from 592 unique sites (70 from ANZ and 177 international) contributing 17 154 patients (2776 from ANZ and 14 378 international). Of sites from ANZ, 48% had

participated once in the survey and 52% had participated multiple times, and for international sites it was 67% and 33% respectively.

Nutrition assessment

Overall, the mean percentage of patients per site in the analysis who received a nutrition assessment was 88% (26%) (n=7228). The mean proportion of patients who had a nutrition assessment was less in ANZ sites compared to international ICUs (80% (28%), n=75 vs 88% (25%), n=340 sites, p=0.001) and sites in ANZ were less likely to primarily use actual weights in energy estimations compared to international ICUs (13%, n=18, vs 30%, n=230 sites, p<0.001). The preferred methods to estimate energy requirements differed between ANZ and international ICUs; in ANZ ICUs, the Schofield equation[52] and 'mixed methods' were the most common choices (both 33%, n=47) whereas in international ICUs the weight based energy estimation[54] was the most common primary method (47%, n=385). There were no significant differences in usage over the 5 survey timepoints, except for the weight based energy estimation (year-by-region, p=0.016). When the weight based method was compared across years within each region the statistical differences did not remain (ANZ 34% in 2007 to 47% in 2013; International 51% in 2007 to 47% in 2013, p>0.95 for both).

The mean calorie and protein prescription differed between ICUs (Energy: 1947 (348) calories in ANZ vs 1747 (376) calories internationally, p<0.001 and protein; 1.12 (0.25) g/kg/day in ANZ vs 1.17 (0.31) g/kg/day internationally, p<0.001. Table 1 and 2 report further nutrition assessment information.

Mode of nutrition and choice of EN solution

EN was the most common mode of nutrition delivery overall (84%, n=14 399 patients) and this was similar across regions (ANZ: 85%, n=2365 patients and international: 84%, n=12 034, p=0.258) however EN was commenced earlier in ANZ; 19.3 [8-38] hours after admission compared to 28 [14-54] hours in international ICUs, p<0.001. The percentage of patients receiving PN was also similar (ANZ: 20%, n=544 and international: 21%, n=3024, p=0.331) but oral nutrition was provided more commonly in ANZ (43%, n=1196 vs 31%, n=4476 patients, p<0.001). Figure 1 demonstrates combinations of nutrition therapy provided during the study period.

Information on caloric content was available in 90% (n=105 515) of the 117 891 EN administrations. Overall, the most commonly used EN solution in both ANZ (70% of administrations, n=12 396) and international ICUs (65% of administrations, n=56 891, <0.001) was a standard solution (<1.25kcal/ml). Figure 2 provides further data on EN solution preference. There was no significant change over time in the use of any caloric density in the sensitivity analysis (year-by-region interaction and year p>0.05), with administrations of standard solution (<1.25kcal/ml) ranging from 71% in 2007 to 67% in 2013 in ANZ, and 68% in 2007 to 63% in 2013 internationally.

Adequacy of nutrition delivery

In ANZ patients, total energy delivery (from EN, PN and propofol) was slightly more than internationally (1133 (572) calories or 15 (8) kcal/kg/day vs 948 (536) calories or 13 (8) kcal/kg/day, p<0.001). However, protein delivery was similar in the two

populations (46 (26) g or 0.6 (0.4) g/kg/day g vs 44 (28) g or 0.6 (0.4) g/kg/day, p=0.85). Figure 3 shows daily energy and protein over the 12 day study period.

When excluding surveys from repeat contributing sites for the sensitivity analysis, the small point estimate differences between ANZ and international community for both energy delivery and protein became less (total energy 1086 (583) kcal/day or 14.0 (7.8) kcal/kg/day vs. 949 (538) or 13.2 (7.9); p=0.064; and total protein 44 (26) g/day or 0.57 (0.35) g/kg/day vs 44 (28) or 0.60 (0.39)) g/kg/day, p=0.131)

Nutrition service

Nutrition therapy protocols were reported in 79% (n=717) of ICUs in the analysis but were more common in ANZ ICUs (98%, n=143 vs 75%, n=564, p<0.001) than those located internationally and the contents recommendations for management of nutrition significantly differed. ANZ ICUs more commonly reported the inclusion of prokinetic agents (87%, n=127 vs 51%, n=399, p<0.001), small bowel feeding tubes (62%, n=90 vs 40%, n=314, p<0.001), withholding of EN for clinical procedures (52%, n=76 vs 35%, n=272, p<0.001).

It was more common to have a dietitian in an ANZ ICU compared to an international ICU (93% vs 81%, p=0.001), however, if a dietitian was present, the mean full time equivalent (FTE) per 10 beds was lower in ANZ sites compared to international sites (0.32 (0.20) vs 0.46 (0.32) FTE), p<0.001). Further nutrition service information can be viewed in Table 2.

Interruptions to EN delivery

EN was interrupted in more ANZ patients than internationally (72%, n=1695 vs 59%, n=7103, p=<0.001), with the most common reason being for a procedure (ANZ: 69%, n=1173 vs 61%, n=4361, p=<0.00) (Table 3).

Clinical outcomes

Clinical outcome data are shown in Table 4.

DISCUSSION

Summary of main findings

This is the first study to compare nutrition practice in ANZ to international practice. Overall, differences were observed in nutrition assessment techniques, nutrition service and delivery details, however many of these were modest. The route of delivery and the type of EN formula used were similar between regions. Energy delivery was slightly higher in ANZ ICUs, but significantly below predicted energy requirements in both regions. This may be because predicted energy requirements were higher and practice within ANZ more frequently utilised a protocol which included elements recommended in best practice guidelines to increase energy delivery, or, there may be population characteristics which are contributing. While differences were observed, they were modest, and such observations are important as in general, they support the external validity of TARGET results and can be used in interpretation and application of the findings.

How does this fit with current literature?

Sites in ANZ prescribed and delivered higher amounts of energy compared to international sites; however, the overall provision of energy and protein in both regions remained substantially less than the estimated requirements. The delivery of less than recommended energy and protein during critical illness is a consistent observation regardless of region investigated and/or different survey data are used [15, 16, 71, 72]. Importantly, this establishes that the group randomised to receive routine care in TARGET, as identified in the pilot trial, represents standard practice within ANZ and internationally [36]. Several practice issues have previously been described as contributing to nutrition inadequacy in critical illness and may be contributing in this analysis; interruptions to EN (which were frequently observed in this study and a feature of nutrition therapy guidelines in ANZ ICUs); delayed initiation of nutrition; and gastrointestinal intolerance [17, 18]. An alternate explanation for the persistent nutrition inadequacy may be that clinicians have decided to stop advocating for meeting nutrition goals beyond that achieved in standard care until definitive evidence is available regarding the optimal energy and protein target in critical illness.

A standard concentration (<1.25kcal/ml) EN solution was the most commonly prescribed solution in both ANZ and international sites. The frequent use of a standard concentration EN solution has previously been documented in observational data from ANZ [73]. Although there was a slightly higher use of standard formulae in the ANZ group, which was statistically significant due to the large numbers analysed, the difference was numerically inconsequential.

Implications for clinical practice and research

This study demonstrates that the use of a standard concentration EN solution (<1.25kcal/ml) is the most commonly used formula and that delivery of energy and protein is substantially below estimated requirements throughout the world. The exact amount of energy and protein to be delivered (and how this relates to an estimated or measured target) is one of the fundamental unanswered questions in critical care nutrition; TARGET will be the largest blinded enteral nutrition trial conducted in the critically ill and will thus provide important evidence as to the role of energy delivery during the acute phase of critical illness. If provision of energy close to recommended goal is beneficial in critical illness, the strategy applied in TARGET (which delivers a 1.5 kcal/ml EN solution at the same goal rate as a 1 kcal/ml solution) has the potential to be widely adopted without a major change in feeding principles [36]. Finally, this study has identified that in ANZ there is a considerable proportion of patients ingesting oral nutrition, with or without supplemental tube liquid enteral nutrient. This poses a new challenge for clinicians in both practice and research. Little is currently understood regarding the management and optimisation of oral intake during critical illness, with several small studies indicating significant difficulties for multifactorial reasons [45, 74]. This remains to be investigated in future work.

There are several plausible explanations for the difference in energy delivery observed between the two regions, which should be considered when interpreting the results. The increased energy delivery in ANZ patients may be due to differences in specific aspects of nutrition management and the patient population. Compared to international ICUs, sites in ANZ reported greater dietitian presence and more use of nutrition protocols. The

protocols more commonly included elements associated with improved nutrition delivery as recommended by best practice feeding guidelines. The differences in protocol content may account for the shorter time to commencing EN and the increased prescribed and delivered energy in the ANZ cohort, however evidence for the role of nutrition protocols in both increasing energy delivery and in improving clinical outcomes is conflicting [31, 32]. This may thus explain the observation of varied existence and content of nutrition therapy protocols. Further, the lack of definite evidence in many areas of critical care nutrition practice makes definitive practice recommendations difficult and may also contribute to the differing contents reported in protocols. Alternatively, the higher proportion of overweight and obese patients in ANZ compared to international ICUs may also account for the higher energy delivery (due to the higher energy aim).

Strengths and limitations

This a large dataset that provide valuable information of international and ANZ specific nutrition delivery and informing the generalizability of future nutrition trials conducted in ANZ such as TARGET. There are however some potential limitations. This study was observational and uses data that were collected for quality improvement activities. As such, the data collection is unlikely to be as robust as that collected as part of a clinical trial and we were limited by the information available. Further, this was a retrospective analysis and is therefore subject to the limitations associated with an analysis of this type. Many ICUs participated over multiple years, and when adjusted for in a sensitivity analysis the moderate difference between ANZ and international energy and protein delivery were even less. Accordingly, ANZ ICUs interested in nutrition may have been more likely to participate in the survey and therefore exacerbate any differences that

exist. It must also be noted that in the analysis, all ICUs from regions outside of ANZ were grouped together to form the international cohort. Regions that are larger may therefore be influencing the results more than smaller regions, and there may also be differences in practice between smaller regions which were not described with this method. Nutrition risk in critically ill patients may influence the prescription and response to artificial nutrition therapy [75, 76]. We were unable to assess any relationship between prescription practices and nutrition risk due to limited survey data on nutrition risk. And importantly, practice may have changed since the last and over the duration of the survey years, with the first survey being performed 10 years ago and the last, 5 years ago. Despite this possibility, the data from the INS is the largest and most comprehensive data available to inform on current nutrition therapy practice. Finally, it is also possible that different practices in medical management and service delivery which were not collected as part of the survey explain some of the differences between the two regions, such as greater energy delivery and proportion of patients receiving oral nutrition.

It must also be acknowledged that due to the size of the database, many variables were statistically significant in their comparisons but were not always clinically important. Specifically, the energy difference observed (187 kcal/day or 2 kcal/kg/day) was relatively minor and it seems intuitively unlikely that such a difference will result in meaningful improvements in patient centered outcomes. This must be considered in the interpretation of the results.

The data also suggest that the cohort in ANZ may be less unwell than the international cohort, supported by more favourable clinical outcomes in the ANZ population, although

many of the differences were modest and probably statistically significant only due to the size of the sample. This may also partially explain better energy delivery in the ANZ cohort; clinicians may have prioritised nutrition delivery earlier and/or EN tolerance may have been greater in a less sick cohort. These slight differences in population should however be considered when applying the results of the TARGET trial to populations outside of ANZ.

CONCLUSION

Differences were observed in nutrition assessment, service and delivery between ANZ and international ICUs; however, such differences were modest and while statistically significant they may not be clinically meaningful. Overall, key elements of nutrition practice in ANZ that relate to design aspects of TARGET appear sufficiently similar to international practice to ensure external validity and relevance of the TARGET results to the international community.

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Table 1: Patient characteristics

Characteristic	Overall n=17 154	ANZ N=2776	International N=14 378	P-value
Proportion of patients by site location, n (%)				
ANZ	2776 (16)			
Canada	3231 (19)			
USA	4906 (29)	n/a	n/a	n/a
Europe & Sth Africa	2403 (14)			
Latin America	1270 (7)			
Asia	2568 (15)			
Age, years, mean (SD)	60 (18)	58 (18)	60 (18)	<0.001
Gender, male, n (%)	10 347 (60)	1737 (63)	8610 (60)	0.011
BMI, kg/m^2, mean (SD)	27 (8)	28 (7)	27 (8)	0.003
Underweight (<18.5 kg/m2), n (%)	863 (5)	109 (4)	754 (5)	<0.001
Normal (18.5-24.9 kg/m2), n (%)	6849 (40)	968 (35)	5881 (41)	
Overweight (25-29.9 kg/m2), n (%)	4965 (29)	901 (33)	4064 (28)	
Obese (30+ kg/m2), n (%)	4393 (26)	775 (28)	3618 (25)	
Admission type, n (%)				
Medical	10866 (63)	1612 (58)	9254 (64)	0.003
Surgical emergency	4140 (24)	720 (26)	3420 (24)	
Surgical elective	2147 (13)	444 (16)	1703 (12)	
Admission Diagnosis, n (%)				
Medical: Respiratory	4151 (24)	526 (19)	3625 (25)	<0.001
Surgical: Gastrointestinal	1896 (11)	364 (13)	1532 (11)	0.009
Medical: Sepsis	1643 (10)	209 (8)	1434 (10)	0.001
APACHE II Score, median (IQR)	22 (16-27)	21 (16-26)	22 (17-27)	0.021
Energy and protein requirements, mean (SD)				
Prescribed energy requirements (kcal/day)	1780 (379)	1947 (348)	1747 (376)	<0.001
Prescribed energy requirements (kcal/kg/day)	24 (6)	25 (5)	24 (6)	<0.001
Prescribed protein requirements (g/day)	88 (25)	87 (21)	88 (26)	0.851
Prescribed protein requirements (g/kg/day)	1.16 (0.30)	1.12 (0.25)	1.17 (0.31)	<0.001

APACHE: Acute Physiology and Chronic Health Evaluation II; BMI: Body mass index; IQR: Interquartile range; kcal: Kilocalorie; SD: Standard deviation

Table 2: Site and nutrition assessment characteristics (data is by site)

Characteristic	Overall n=923	ANZ N=146	International N=777	P-value
Location of international sites, n (%)				
Canada	n/a	n/a	171 (19)	n/a
USA			270 (29)	
Europe & Sth Africa			129 (14)	
Latin America			64 (7)	
Asia			143 (16)	
Hospital size, beds, mean (SD)	595 (407)	525 (225)	608 (432)	0.540
ICU size, beds, mean (SD)	18 (10)	16 (8)	18 (10)	0.390
Contents of feeding protocol, yes, n (%)				
Head of bed elevation	562 (61)	79 (54)	483 (62)	0.067
GRV, ml, mean (SD)	246 (90)	242 (79)	247 (92)	0.364
BGL and insulin protocol, yes, n (%)	795 (86)	113 (77)	682 (88)	<0.001
BGL targets in protocols, mmol/L, mean (SD)				
Upper	8.5 (1.6)	8.9 (1.4)	8.4 (1.7)	0.004
Lower	4.9 (1.2)	5.0 (1.3)	4.9 (1.2)	0.562
Weight used in energy estimation, n (%)				
Actual	248 (27)	18 (13)	230 (30)	<0.001
Estimated	40 (4)	8 (6)	32 (4)	0.472
Ideal based on BMI 20-25kg/m2	46 (5)	9 (6)	37 (5)	0.489
Mixed-use	511 (57)	97 (67)	414 (54)	0.004
Method to estimate energy requirements, n (%)	66 (7)	47 (33)	28 (3)	<0.001
Schofield Equation[7] with adjustment for stress and/or activity	426 (44)	41 (29)	385 (47)	<0.001
Weight based[8]	268 (28)	47 (33)	221 (27)	0.360
Mixed-use				

EN: Enteral nutrition; ICU: Intensive care unit; kcal: Kilocalorie; SD: Standard deviation

Table 3: Nutrition delivery information (data is by patient)

Characteristics	Overall n=17 154	ANZ N=2776	International N=14 378	P-value
Energy and protein delivery from EN during study period, mean (SD)				
Energy from EN (kcal/day)	745 (553)	855 (596)	724 (542)	<0.001
Protein from EN (g/day)	36 (28)	38 (27)	36 (28)	0.075
Percentage of energy and protein requirements provided during the study period, mean (SD)				
Energy requirements met by EN	42 (31)	44 (30)	42 (31)	0.095
Protein requirements met by EN	42 (31)	44 (30)	42 (31)	0.111
Energy requirements met by EN+PN+propofol	56 (30)	59 (28)	55 (30)	0.006
Protein requirements met by EN+PN	52 (30)	53 (28)	52 (31)	0.205
EN interrupted during study, yes, n (%)	8796 (61)	1695 (72)	7103 (59)	<0.001
Reasons for interruptions, n (%)				
Fasting for procedure	5534 (63)	1173 (69)	4361 (61)	<0.001
Intolerance to EN	2291 (26)	418 (25)	1873 (26)	0.129
Other	2328 (26)	405 (24)	1923 (27)	0.387
Duration of interruptions to EN, hours, mean (SD)				
Total duration of EN interruptions	22 (18)	23 (19)	21 (18)	0.224
Duration of EN interruptions per 24	2.4 (1.9)	2.6 (2.0)	2.4 (1.9)	0.045

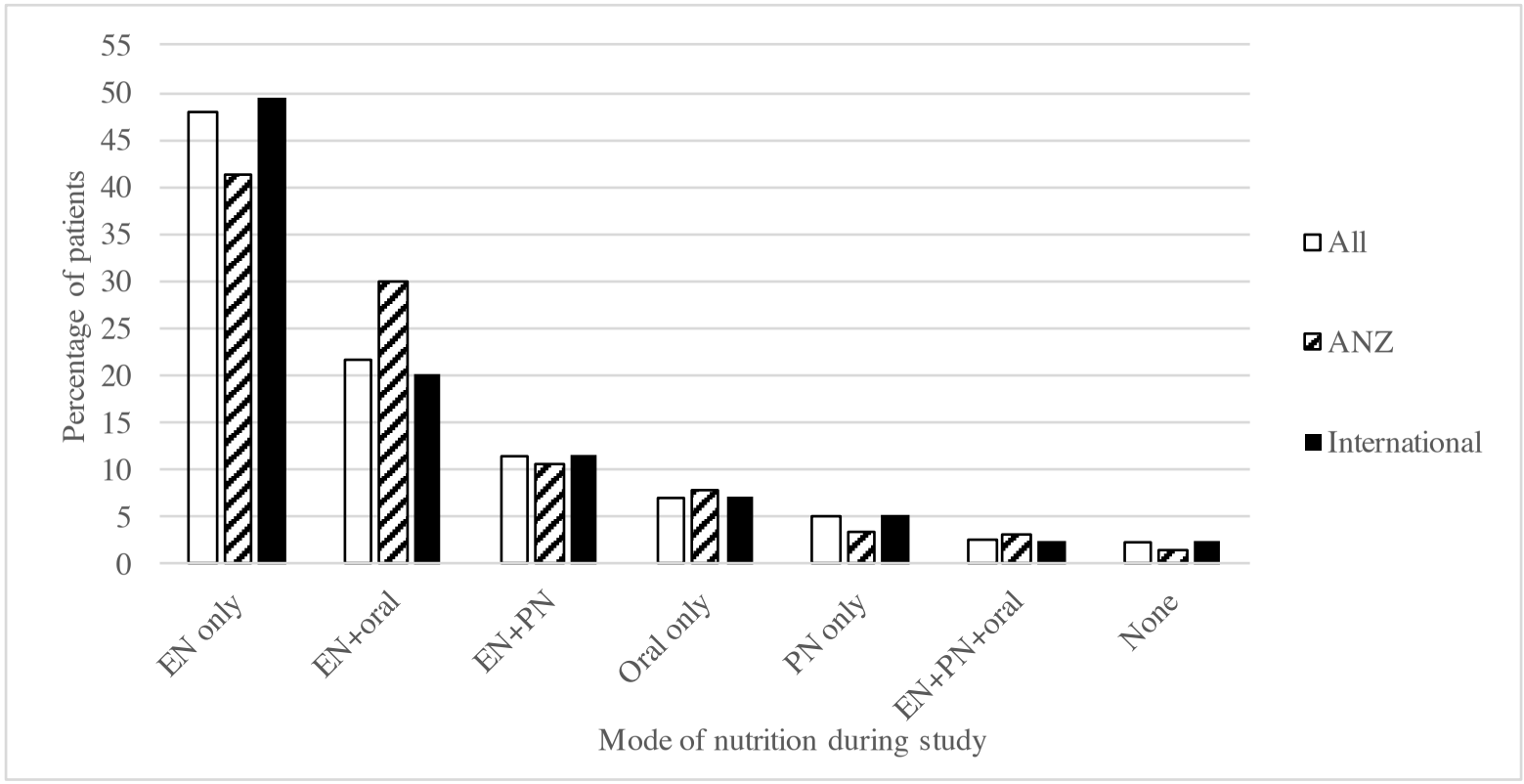
EN: Enteral nutrition; ICU: Intensive care unit; PN: Parenteral nutrition; kcal: Kilocalorie; SD: Standard deviation

Table 4: Outcomes

Characteristics	Overall	ANZ	International	P-value
Mortality to 60 days, died, n (%)	3299 (19)	383 (14)	2916 (20)	<0.001
ICU	4360 (25)	557 (20)	3803 (26)	<0.001
Hospital				
Duration of mechanical ventilation, days, median [IQR]	7[3-15]	6 [3-12]	7 [3-16]	<0.001
Length of stay, days				
ICU	10 [6 -19]	9 [5-17]	11 [6-20]	0.001
Hospital	24 [13-52]	26 [14- 49]	24 [13-53]	0.212
Time to discharge alive				
ICU	16 [7 – undefined]	11 [6- 28]	14 [7 – undefined]	<0.001
Hospital	38 [16-undefined]	34 [16- undefined]	40 [16 – undefined]	<0.001

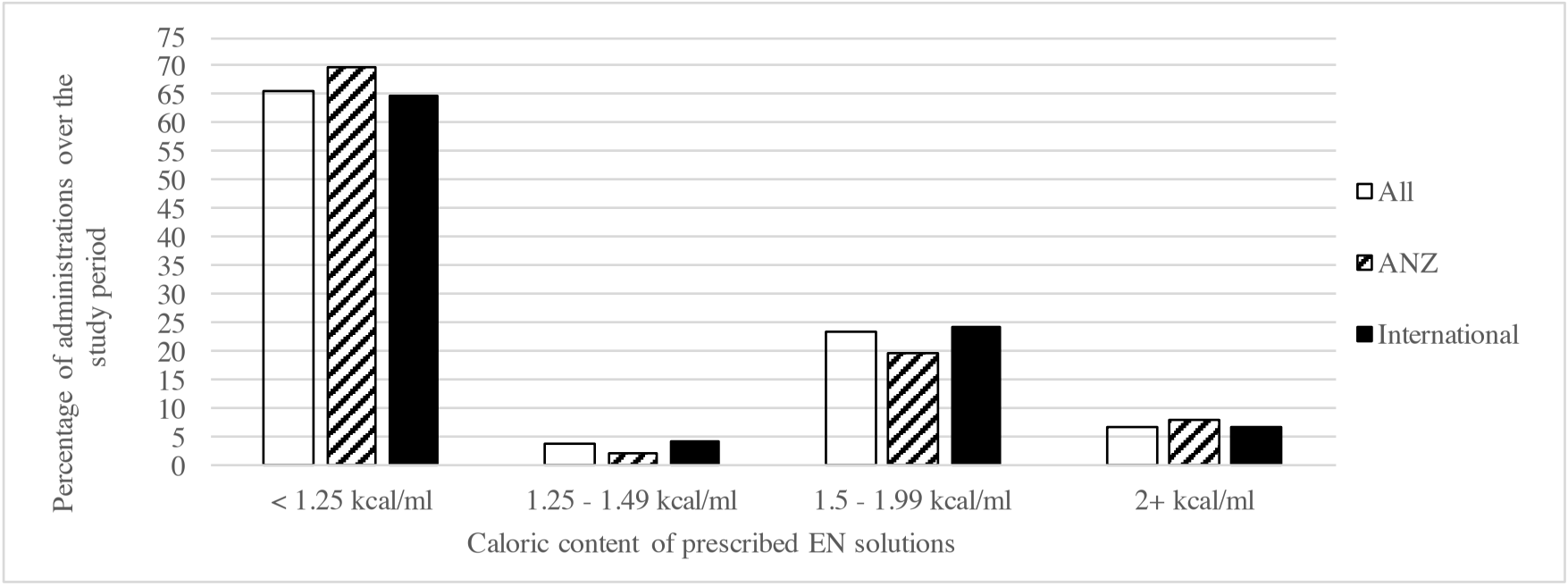
ICU: Intensive care unit; IQR: Interquartile range;

Figure 1: Mode of nutrition delivery during study period



ANZ: Australia and New Zealand; EN: Enteral nutrition; PN: Parenteral nutrition

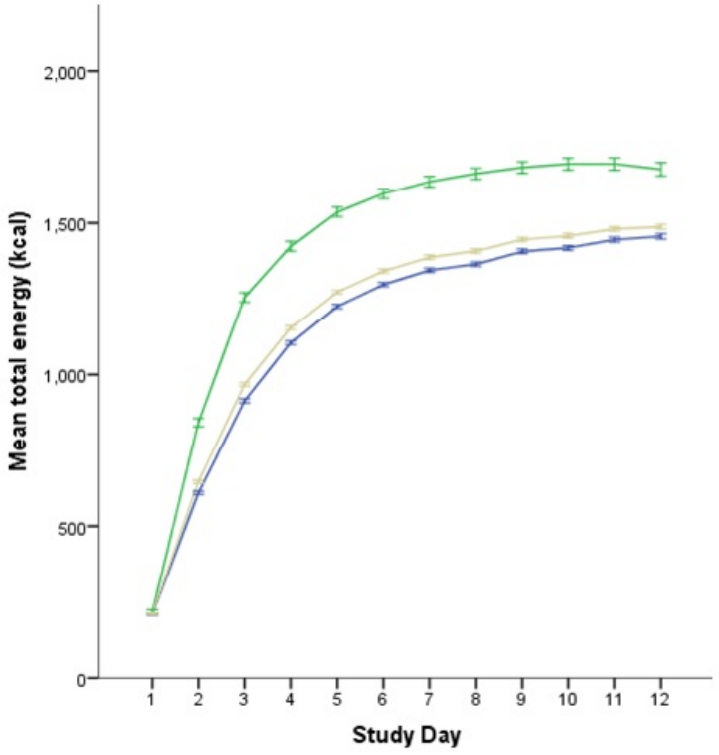
Figure 2: Caloric content of prescribed EN solutions during the study period



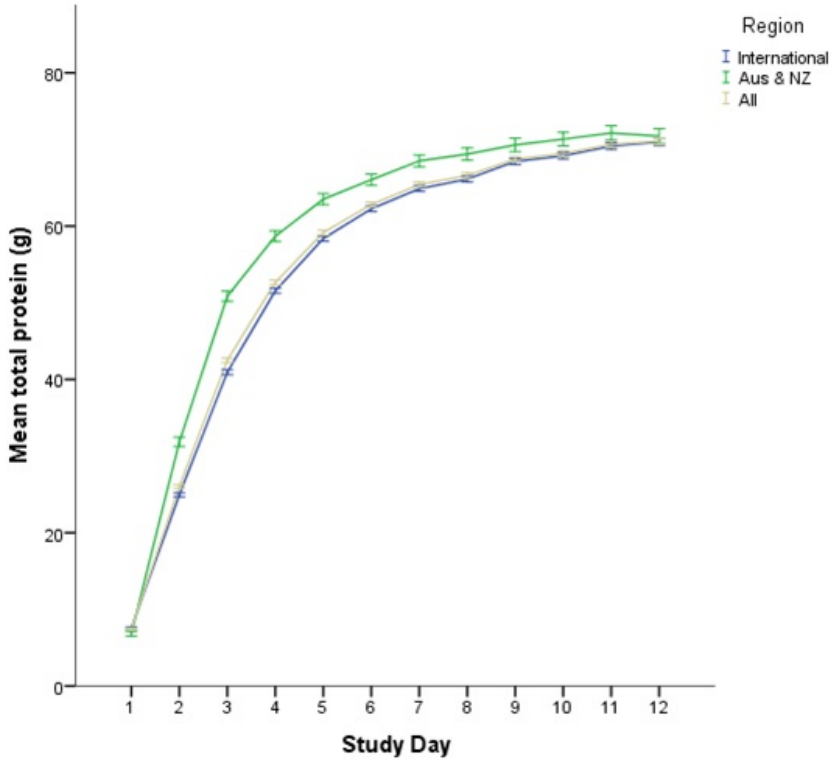
ANZ: Australia and New Zealand; EN: Enteral nutrition; kcal: kilocalorie

Figure 3: Daily energy (Panel A) and protein delivery (Panel B) over the study period from all sources in the whole cohort, Australia and New Zealand and international Intensive Care Units. Data is presented as mean (SE).

Panel A)



Panel B)



Chapter appendix

4.3 Case report form from the International Nutrition Survey (available from https://www.criticalcarenutrition.com/docs/INS2014/INS2014_burns_Instructions&CRFs_9June2014_final.pdf)

International Nutrition Survey 2014

ICU Name: ☐

Site Registration 1

1. Primary REDCap Users: *(Usernames and passwords to access the online data entry system will be assigned to each of the individuals listed below.)*

First name	Last name	Email	Phone	Role in ICU	Signature

To register your site, please provide the following information.

2. Did you require ethics approval to participate in INS 2014? ☐ Yes ☐ No

Hospital Information

3. Hospital Name: _____
4. Hospital Type: ☐ Teaching ☐ Non-teaching

5. City: _____ 6. Province/State: _____ 7. Country: _____

8. Size of Hospital (Number of Beds): _____

ICU Information

9. Does your hospital have multiple ICUs? ☐ Yes ☐ No

10. ICU Name: _____

11. Has this ICU participated in the International Nutrition Survey in previous years? ☐ Yes ☐ No

If yes, in which year(s) did you participate? (select all that apply)

☐ 2007 ☐ 2008 ☐ 2009 ☐ 2011 ☐ 2013

12. ICU Type:

☐ Open: Attending physician remains in charge, ICU physician consults.
☐ Closed: Care transferred or shared with ICU physician
☐ Other, *Please specify:* _____

13. Case Types (select all that apply):

☐ Medical ☐ Neurological ☐ Other, *Please Specify:*
☐ Surgical ☐ Neurosurgical _____
☐ Trauma ☐ Cardiac Surgery
☐ Pediatrics ☐ Burns

14. Is there a designated ICU Medical Director? ☐ Yes ☐ No

15. Is your unit specifically a burn unit? ☐ Yes ☐ No ***If no, use the Case Report Forms for Non Burn ICUs.***

16. Number of beds in ICU: _____

17. Do you have a Dietitian working in the ICU? ☐ Yes ☐ No

If yes: Amount of full time equivalent (FTE) dietitian: _____

International Nutrition Survey 2014

ICU Name: _____

Site Registration 2

18. What level of dietitian coverage is available in your ICU during weekends?

- ☐ Dietitian physically present in ICU
- ☐ Dietitian on call: comes in to ICU for consult on request
- ☐ Dietitian on call: telephone consult on request
- ☐ No dietitian available on weekends

19. Do you use a bedside feeding protocol/algorithm that allows the nurse to advance or withhold tube feedings as specified by the protocol/algorithm?

☐ Yes—We have a feeding protocol (not PEP uP) ☐ Yes—PEP uP Collaborative ☐ No

*If yes to "We have a feeding protocol" (**not** including PEP uP):*
Does your feeding protocol use an algorithm for: (check all that apply)

- ☐ Motility agents
- ☐ Small bowel feeding
- ☐ Withholding for procedures
- ☐ Head of bed elevation
- ☐ Other, *Please Specify:* _____

If yes to "PEP uP Collaborative", indicate which components you are implementing in your ICU (tick all that apply):

- ☐ A feeding strategy of volume based feeding, trophic feeds at 10 ml/hr and/or NPO
- ☐ Prophylactic use of motility agents starting day 1
- ☐ Protein supplements (24g protein/day) starting day 1

What type of formula are you using as part of your PEP uP feeding protocol (select only one)?

- ☐ Semi-elemental feeding formula
- ☐ Polymeric feeding formula
- ☐ Other type of formula , *Please Specify:* _____

20. Do you use a gastric residual volume threshold to adjust feeds? ☐ Yes ☐ No

If yes: What volume threshold do you use? _____ milliliters (ml)

21. Do you use a protocol to monitor blood sugar control or the administration of insulin?

☐ Yes ☐ No

If yes: What range do you target? Lower: _____ Upper: _____ *-OR-* What value do you target? Target: _____ *Units?* ☐ mmol/L ☐ mg/dL

22. Who conducts the nutritional assessment? Choose one option.

- ☐ Dietitian
- ☐ Nurse
- ☐ Physician
- ☐ Nutrition assessments are never completed
- ☐ Other, *please specify:* _____

23. What criteria are used for assessing malnutrition? Check all that apply.

- ☐ Weight loss
- ☐ Underweight status or low BMI
- ☐ Anthropometric assessment of skin-folds or circumferences
- ☐ Compromised dietary intake
- ☐ Low albumin or prealbumin
- ☐ Not applicable
- ☐ Other, *please specify:* _____

24. Do you monitor any laboratory indicators of inflammatory status in the ICU?

☐ Yes ☐ No

If yes, choose all that apply: ☐ C-reactive protein ☐ Other, *please specify:* _____

Filled out once for each ICU.

International Nutrition Survey 2014

ICU Name: [ ]

Site Registration 3

25. What is the average number of admissions to your burn unit each year? _____

26. What feeding practice are used in your unit to minimize the interruptions around burn related surgeries and/ or grafting? (Select all that apply)
    - ☐ No interruptions: feed patient through the OR and entire perioperative period (no interruptions for surgery)
    - ☐ Feed right up until the patient is transferred to the OR
    - ☐ Withhold feeds some hours before the OR
    - ☐ Withhold feeds at midnight the night before the OR
    - ☐ Other, please specify: _____

International Nutrition Survey 2014

ICU Name:

Screening Log

This log is for your own reference and will not be entered online. However, you will be asked to provide the total number of patients from the third, fourth and fifth column of your screening log to complete the Site Finalization form. Please use additional copies of this page as necessary.

Screening number *(for your reference only)*	Patient initials for all patients in the ICU on/ after first day of data collection	#1. **Patient is ≥18 years old (or ≥ 16, if applicable)**	#2. Patient meets criteria #1 and is **intubated and ventilated within the first 48 hours of admission to ICU** *(exclude mask ventilation)*	#3. Patient meets criteria #1 and #2 and **remained in ICU for ≥72 hours**	Patient eligible?	Head of the bed angle	REDCap Patient number *(automatically assigned in REDCap if patient included in survey)*
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
18							
19							
20							
21							
22							
23							
24							
25							
TOTAL							

International Nutrition Survey 2014

Patient Number: ☐

Patient Information 1

ICU Name: ☐

Sex: ☐ Male ☐ Female Age: _____

Does patient meet the inclusion criteria? **If no, do not proceed with data collection; patient is excluded from INS 2014.**

- ☐ Patient ≥18 years old (or ≥16, if approved locally at you site)
- ☐ Mechanically ventilated within 48 hours of admission to the ICU (duration does not matter)
- ☐ In the ICU for ≥72 hours from ICU admission

Hospital Admission Date (YYYY-MM-DD): _____ Time (HH:MM, 24h): _____

ICU Admission Date (YYYY-MM-DD): _____ Time (HH:MM, 24h): _____

Mechanical ventilation:

- ☐ Started prior to ICU admission
- ☐ Started in ICU: Date (YYYY-MM-DD): _____ Time (HH:MM, 24h): _____

Type of Admission: ☐ Medical ☐ Surgical Elective ☐ Surgical Emergency

Primary ICU Diagnosis: *(Select **one** item from the taxonomy)*

Medical

Cardiovascular/Vascular
- ☐ Acute myocardial infarction
- ☐ Aortic aneurysm
- ☐ Cardiac arrest
- ☐ Cardiogenic shock
- ☐ Congestive heart failure
- ☐ Hypertension
- ☐ Peripheral vascular disease
- ☐ Rhythm disturbance
- ☐ Other CV disease (specify)

Respiratory
- ☐ Aspiration pneumonia
- ☐ Asthma
- ☐ Bacterial / Viral pneumonia
- ☐ Chronic obstructive pulmonary disease
- ☐ Mechanical airway obstruction
- ☐ Parasitic pneumonia (ie.pneumocystis carinii)
- ☐ Pulmonary edema (non-cardiogenic)
- ☐ Pulmonary embolism
- ☐ Respiratory arrest
- ☐ Respiratory neoplasm (include larynx and trachea)
- ☐ Other respiratory disease (specify)

Gastrointestinal
- ☐ GI bleeding due to diverticulosis
- ☐ GI bleeding due to ulcer/laceration
- ☐ GI bleeding due to varices
- ☐ GI inflammatory disease (ulcerative colitis, crohn's disease)
- ☐ GI perforation/obstruction
- ☐ Hepatic failure
- ☐ Pancreatitis
- ☐ Other GI disease (specify)

Neurologic
- ☐ Intracerebral hemorrhage
- ☐ Neurologic infection
- ☐ Neurologic neoplasm
- ☐ Neuromuscular disease
- ☐ Seizure
- ☐ Stroke
- ☐ Subarachnoid hemorrhage
- ☐ Other neurologic disease (specify)

Sepsis
- ☐ Sepsis (other than urinary tract)
- ☐ Sepsis of urinary tract origin

Trauma
- ☐ Head trauma (with/without multiple trauma)
- ☐ Multiple trauma (excluding head trauma)

Metabolic
- ☐ Diabetic ketoacidosis
- ☐ Drug overdose
- ☐ Metabolic coma
- ☐ Other metabolic disease (specify)

Hematologic
- ☐ Coagulopathy / neutropeniathrombocyto-penia
- ☐ Other hematologic condition (specify)

Burns
- ☐ Burns

Other
- ☐ Renal disease (specify)
- ☐ Other medical disease (specify)

If you selected "other" in any of the above categories, specify here: _____

Surgical (elective or emergency)

Vascular/Cardiovascular
- ☐ CABG only
- ☐ Carotid endarterectomy
- ☐ Dissecting/ruptured aorta
- ☐ Elective abdominal aneurysm repair
- ☐ Peripheral artery bypass graft
- ☐ Peripheral vascular surgery (no bypass graft)
- ☐ Valvular heart surgery/CABG
- ☐ Valvular heart surgery only
- ☐ Other CV disease (specify)

Respiratory
- ☐ Lung neoplasm
- ☐ Respiratory infection
- ☐ Respiratory neoplasm (mouth, sinus, larynx, trachea)
- ☐ Other respiratory disease (specify)

Gastrointestinal
- ☐ GI bleeding
- ☐ GI cholecystitis / cholangitis
- ☐ GI inflammatory disease
- ☐ GI neoplasm
- ☐ GI obstruction
- ☐ GI perforation/rupture
- ☐ Liver transplant
- ☐ Pancreatitis
- ☐ Other GI disease (specify)

Neurologic
- ☐ Craniotomy for neoplasm
- ☐ Intracerebral hemorrhage
- ☐ Laminectomy/other spinal cord surgery
- ☐ Subarachnoid hemorrhage
- ☐ Subdural/epidural hematoma
- ☐ Other neurologic disease (specify)

Trauma
- ☐ Head trauma (with/without multiple trauma)
- ☐ Multiple trauma (excluding head trauma)

Renal
- ☐ Renal neoplasm
- ☐ Other renal disease (specify)

Gynecologic
- ☐ Hysterectomy

Orthopedic
- ☐ Hip or extremity fracture

Bariatric Surgery
- ☐ Laparoscopic Banding
- ☐ Laparoscopic Gastric Bypass
- ☐ Open Gastric Bypass (Roux-en-Y)
- ☐ Vertical Banded Gastroplasty

Other
- ☐ Other surgical disease (specify)

If you selected "other" in any of the above categories, specify here: _____

International Nutrition Survey 2014

Patient Number: ☐

Patient Information 2

ICU Name: ☐

Co-morbidities: ☐ Yes ☐ No

If yes, check all that apply:

Myocardial
- ☐ Angina
- ☐ Arrhythmia
- ☐ Congestive heart failure (or heart disease)
- ☐ Myocardial infarction
- ☐ Valvular

Vascular
- ☐ Cerebrovascular disease (Stroke or TIA)
- ☐ Hypertension
- ☐ Peripheral vascular disease or claudication

Pulmonary
- ☐ Asthma
- ☐ Chronic obstructive pulmonary disease (COPD, emphysema)

Neurologic
- ☐ Dementia
- ☐ Hemiplegia (paraplegia)
- ☐ Neurologic illnesses (such as Multiple sclerosis or Parkinsons)

Endocrine
- ☐ Diabetes Type I or II
- ☐ Diabetes with end organ damage
- ☐ Obesity and/or BMI > 30 (weight in kg/(ht in meters)^2)

Renal
- ☐ Moderate or severe renal disease

Gastrointestinal
- ☐ Gastrointestinal Disease (hernia or reflux)
- ☐ GI Bleeding
- ☐ Inflammatory bowel
- ☐ Mild liver disease
- ☐ Moderate or severe liver disease
- ☐ Peptic ulcer disease

Cancer/Immune
- ☐ AIDS
- ☐ Any Tumor
- ☐ Leukemia
- ☐ Lymphoma
- ☐ Metastatic solid tumor

Psychological
- ☐ Anxiety or Panic Disorders
- ☐ Depression

Muskoskeletal
- ☐ Arthritis (Rheumatoid or Osteoarthritis)
- ☐ Connective Tissue disease
- ☐ Degenerative Disc disease (back disease or spinal stenosis or severe chronic back pain)
- ☐ Osteoporosis

Substance Use
- ☐ Heavy alcohol use or binge drinking history
- ☐ Current smoker
- ☐ Drug abuse history

Miscellaneous
- ☐ Hearing Impairment (very hard of hearing even with hearing aids)
- ☐ Visual Impairment (cataracts, glaucoma, macular degeneration)

In your ICU, what units do you use to measure blood glucose?

☐ mmol/L ☐ mg/dL

Note: once you specify units here on the Patient Information Form on REDCap, these units will be assumed to be the same for **all other blood glucose fields for this patient**.

Was the patient's blood sugar recorded in the 1st 24 hours after admission? ☐ Yes ☐ No

If yes,

Highest blood glucose in 1st 24 hours: _____

Lowest blood glucose in 1st 24 hours: _____

Was ARDS present? ☐ Yes ☐ No

Was Head of Bed Elevation recorded? ☐ Yes (Actual) ☐ Yes (Estimated) ☐ Not available or not observed

If yes,

- ☐ Patient laying flat (0°)
- ☐ Patient sitting up (90°)
- ☐ Other angle: (specify) _____

APACHE II Score: _____

International Nutrition Survey 2014

Patient Number: ☐

Patient Information 3

ICU Name: ☐

Indicate the following burn injury details:

1) % total burn surface area (TBSA): _____

2) % 2nd degree burns:_____

3) % 3rd degree burns:_____

4) Date of burn injury: | 2 | 0 | Y | Y | M | M | D | D |

5) Type of burn: ☐ Scald ☐ Chemical ☐ Unknown
☐ Fire ☐ Radiation ☐ Other,
specify: _____

6) Is there presence of full thickness burn? ☐ Yes ☐ No

7) Is inhalation injury present? ☐ Yes ☐ No

If yes, please indicate the Inhalation Injury Severity Score: ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4

Filled out once for each patient.

International Nutrition Survey 2014

Patient Number: ☐

Baseline SOFA Score

ICU Name: ☐

1. Lowest PaO2/FiO2 Ratio (also known as P/F ratio):
   - ☐ ≥ 400 mmHg or N/A
   - ☐ 300 - 399 mmHg
   - ☐ 200 - 299 mmHg
   - ☐ 100 - 199 mmHg with respiratory support
   - ☐ < 100 mmHg with respiratory support

2. Lowest Platelets:
   - ☐ ≥ 150 $x10^3/mm^3$ or N/A
   - ☐ 100 - 149 $x10^3/mm^3$
   - ☐ 50 - 99 $x10^3/mm^3$
   - ☐ 20 - 49 $x10^3/mm^3$
   - ☐ < 20 $x10^3/mm^3$

3. Highest Bilirubin (total):
   - ☐ < 1.2 mg/dL (< 20 µmol/L) or N/A
   - ☐ 1.2 - 1.9 mg/dL (20 - 32 µmol/L)
   - ☐ 2.0 - 5.9 mg/dL (33 - 101 µmol/L)
   - ☐ 6.0 - 11.9 mg/dL (102 - 204 µmol/L)
   - ☐ ≥ 12.0 mg/dL (> 204 µmol/L)

4. Did the patient receive vasopressors today?

   If yes,
   - ☐ Dopamine ≤ 5 µg/kg/min or Dobutamine (any dose)
   - ☐ Dopamine >5 - 15 µg/kg/min or Epinephrine ≤ 0.1 µg/kg/min or Norepinephrine ≤ 0.1 µg/kg/min
   - ☐ Dopamine > 15 µg/kg/min or Epinephrine > 0.1 µg/kg/min or Norepinephrine > 0.1 µg/kg/min

   If no, mean arterial pressure (MAP):
   - ☐ < 70 mmHg
   - ☐ ≥ 70 mmHg

5. What is the patient's conscious state? (Choose option that gives the highest score)

Eye Opening	**Verbal Response**	**Best Motor Response**
☐ 1- None	☐ 1- None	☐ 1- None
☐ 2- To Pain	☐ 2- Incomprehensible words	☐ 2- Extension
☐ 3- To speech	☐ 3- Inappropriate words	☐ 3- Abnormal flexion
☐ 4-Spontanous	☐ 4- Confused	☐ 4- Withdraws from pain
	☐ 5- Oriented	☐ 5- Localizes to pain
		☐ 6- Obeys commands

6. a) Highest Creatinine:
   - ☐ < 1.2 mg/dL (< 110 µmol/L) or N/A
   - ☐ 1.2 - 1.9 mg/dL (110 - 170 µmol/L)
   - ☐ 2.0 - 3.4 mg/dL (171 - 299 µmol/L)
   - ☐ 3.5 - 4.9 mg/dL (300 - 440 µmol/L)

   b) Total urine output:
   - ☐ ≥ 500 mL/day or N/A
   - ☐ 200 - 499 mL/day
   - ☐ < 200 mL/day

Filled out once for each patient.

International Nutrition Survey 2014

Baseline Nutrition Assessment 1

Patient Number: ☐

ICU Name: ☐

Height (metres): _____ ☐ Actual ☐ Estimated

Dry Body Weight (kg): _____ ☐ Actual ☐ Estimated

Usual Weight (kg): _____

BMI = _____ kg/m^2

Was a nutrition assessment completed?

☐ Yes ☐ No

If yes:

Date of nutrition assessment: _____ Time: _____

Weight used in calculation of goal **calorie** requirements:

- ☐ Actual dry body weight
- ☐ Adjusted average [0.5(ABW + IBW)]
- ☐ Adjusted by 25% [0.25(ABW-IBW) + IBW]
- ☐ Adjusted by 40% [0.40(ABW-IBW) + IBW]
- ☐ Estimated dry body weight
- ☐ Ideal (IBW) based on Hamwi formula
- ☐ Ideal (IBW) based on BMI 20-25 kg/m^2
- ☐ Based on BMI: BMI range: _____ to _____
- ☐ No weight used in calculation
- ☐ Usual (UBW)
- ☐ Other (specify): _____

Weight used in calculation of goal **protein** requirements:

- ☐ Actual dry body weight
- ☐ Adjusted average [0.5(ABW + IBW)]
- ☐ Adjusted by 25% [0.25(ABW-IBW) + IBW]
- ☐ Adjusted by 40% [0.40(ABW-IBW) + IBW]
- ☐ Estimated dry body weight
- ☐ Ideal (IBW) based on Hamwi formula
- ☐ Ideal (IBW) based on BMI 20-25 kg/m^2
- ☐ Based on BMI: BMI range: _____ to _____
- ☐ No weight used in calculation
- ☐ Usual (UBW)
- ☐ Other (specify): _____

Method(s) used to calculate goal calorie requirements for this patient (select all that apply):

- ☐ Harris Benedict Equation with no adjustment for stress and/or activity
- ☐ Harris Benedict Equation with adjustment for stress and/or activity
- ☐ Schofield Equations with no adjustment for stress and/or activity
- ☐ Schofield Equation with adjustment for stress and/or activity
- ☐ Mifflin-St. Jeor Equation with no adjustment for stress and/or activity
- ☐ Mifflin-St. Jeor Equation with adjustment for stress and/or activity
- ☐ Ireton-Jones Equation with no adjustment for stress and/or activity
- ☐ Ireton-Jones Equation with adjustment for stress and/or activity
- ☐ Penn State Equation with no adjustment for stress and/or activity
- ☐ Penn State Equation with adjustment for stress and/or activity
- ☐ Modified Penn State Equation with no adjustment for stress and/or activity
- ☐ Modified Penn State Equation with adjustment for stress and/or activity
- ☐ Toronto Equation with no adjustment for stress and/or activity
- ☐ Toronto Equation with adjustment for stress and/or activity
- ☐ Weight based: _____kcal/kg to _____kcal/kg
- ☐ Provide 1200-1499 kcal as standard
- ☐ Provide 1500-2000 kcal as standard
- ☐ Indirect calorimetry
- ☐ Other (specify): _____

Goal Calorie Requirement: (kcal/day) _____ Goal Protein Requirement: (g/day) _____

International Nutrition Survey 2014

Baseline Nutrition Assessment 2

Patient Number: ☐

ICU Name: ☐

Has the patient lost weight unintentionally over the last 3 months?

- ☐ No
- ☐ Unsure
- ☐ Yes → *If yes,* how much?
  - ☐1-5 kg / 2-11 lbs
  - ☐6-10 kg / 13-22 lbs
  - ☐11-15 kg / 24-33 lbs
  - ☐>15 kg / >33 lbs
  - ☐Do not know

Has the patient's food intake declined over the past week due to loss of appetite?

- ☐ No
- ☐ Yes → *If yes,* What was your family member's food intake in the week prior to ICU admission?
  - ☐1/4 or less of what they usually eat
  - ☐1/4 to 1/2 of what they usually eat
  - ☐1/2 to 3/4 of what they usually eat
  - ☐3/4 to all of what they usually eat
- ☐ Do not know / can't estimate

When was EN first initiated?

- ☐ EN initiated prior to ICU admission
- ☐ EN initiated in ICU: *Date (YYYY-MM-DD):* _____ *Time (HH:MM, 24h):* _____
- ☐ EN not initiated during first 12 days in ICU

When was PN first initiated?

- ☐ PN intiated prior to ICU admission
- ☐ PN initiated in ICU: *Date (YYYY-MM-DD):* _____ *Time (HH:MM, 24h):* _____
- ☐ PN not initiated during first 12 days in ICU

If PN initiated in ICU or prior to ICU admission, specify reason PN initiated: (select only one)

- ☐ Bowel ischemia
- ☐ Gastrointestinal bleed
- ☐ Gastrointestinal perforation
- ☐ Gastrointestinal surgery
- ☐ Hemodynamic instability
- ☐ Mechanical bowel obstruction
- ☐ No access to small bowel
- ☐ Not tolerating enteral feeding
- ☐ Pancreatitis
- ☐ Proximal bowel anastomosis
- ☐ Short gut syndrome
- ☐ Small bowel ileus
- ☐ Small bowel fistulae
- ☐ No clinical reason
- ☐ Other (specify): _____

What was the nutrition delivery technique recommended by the physician or dietitian at the initial order?

- ☐ Initiate EN: start at low rate and progress to hourly goal rate
- ☐ Initiate EN: start at or progress to 24 hour volume goal based hourly rate
- ☐ Initiate EN: start at hourly goal rate
- ☐ Initiate EN: keep at low rate (trophic feeds: no progression)

If trophic feeds, please specify reason (select only one):

- ☐ Patient on vasopressors
- ☐ Surgically placed jejunostomy
- ☐ Impending intubation
- ☐ Ruptured abdominal aortic aneurysm (AAA)
- ☐ Upper intestinal anastomosis
- ☐ Risk of refeeding syndrome
- ☐ Other (specify): _____

- ☐ Initiate EN: bolus feeds
- ☐ Keep Nil Per Os (NPO) or Nil By Mouth → *If NPO, please specify reason (select only one):*
  - ☐ Bowel perforation
  - ☐ Bowel obstruction
  - ☐ Proximal high output fistula
  - ☐ Other (specify): _____
- ☐ Oral nutrition
- ☐ Parenteral Nutrition

International Nutrition Survey 2014

Patient Number: ☐

ICU Name: ☐

Daily Nutrition Data 1

Study Day:	1 *ICU Admission*	2	3	4	5	6	7	8	9	10	11	12
Was any nutrition received orally/by mouth?	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N
Morning Blood Glucose?	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
Hypoglycemic event? (<3.5mmol/L or <63mg/dL) (enter up to 3)	1. 2. 3.	1. 2. 3.	1. 2. 3.	1. 2. 3.	1. 2. 3.	1. 2. 3.	1. 2. 3.	1. 2. 3.	1. 2. 3.	1. 2. 3.	1. 2. 3.	1. 2. 3.
Insulin? *If yes:* Units/day:	☐ Y ☐ N _____	☐ Y ☐ N _____	☐ Y ☐ N _____	☐ Y ☐ N _____	☐ Y ☐ N _____	☐ Y ☐ N _____	☐ Y ☐ N _____	☐ Y ☐ N _____	☐ Y ☐ N _____	☐ Y ☐ N _____	☐ Y ☐ N _____	☐ Y ☐ N _____
Propofol (≥ 6 hours) *If yes:* Amount given: Units? ☐ kcal ☐ mL	☐ Y ☐ N _____	☐ Y ☐ N _____	☐ Y ☐ N _____	☐ Y ☐ N _____	☐ Y ☐ N _____	☐ Y ☐ N _____	☐ Y ☐ N _____	☐ Y ☐ N _____	☐ Y ☐ N _____	☐ Y ☐ N _____	☐ Y ☐ N _____	☐ Y ☐ N _____
Location of Feeding Tube: *(Select one)*												
Gastric	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Small bowel	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
No tube in place	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Motility Agents *If yes, select all that apply:*	☐Y ☐N	☐Y ☐N	☐Y ☐N	☐Y ☐N	☐Y ☐N	☐Y ☐N	☐Y ☐N	☐Y ☐N	☐Y ☐N	☐Y ☐N	☐Y ☐N	☐Y ☐N
Alizapride	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Cinitapride	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Cisapride	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Domperidone	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Erythromycin	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Itopride	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Lesuride	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Methylnaltrexon	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Metoclopramide	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Mosapride	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Naloxone	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Other (specify)	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____

International Nutrition Survey 2014

Daily Nutrition Data 2

Patient Number: ☐

ICU Name: ☐

Study Day:	**1** ***ICU Admission***	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Did the goal nutrition requirements change today…	…from baseline? ☐ Y ☐ N	…from yesterday? ☐ Y ☐ N	…from yesterday? ☐ Y ☐ N	…from yesterday? ☐ Y ☐ N	…from yesterday? ☐ Y ☐ N	…from yesterday? ☐ Y ☐ N	…from yesterday? ☐ Y ☐ N	…from yesterday? ☐ Y ☐ N	…from yesterday? ☐ Y ☐ N	…from yesterday? ☐ Y ☐ N	…from yesterday? ☐ Y ☐ N	…from yesterday? ☐ Y ☐ N
If yes, specify new nutrition goals:	Kcal: _____ Protein: (g) _____	Kcal: _____ Protein: (g) _____	Kcal: _____ Protein: (g) _____	Kcal: _____ Protein: (g) _____	Kcal: _____ Protein: (g) _____	Kcal: _____ Protein: (g) _____	Kcal: _____ Protein: (g) _____	Kcal: _____ Protein: (g) _____	Kcal: _____ Protein: (g) _____	Kcal: _____ Protein: (g) _____	Kcal: _____ Protein: (g) _____	Kcal: _____ Protein: (g) _____
Were oral nutritional supplements received?	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N
If yes, specify total kilocalories (kcal) and protein (g) received from oral nutrition supplements	Kcal: _____ Protein: (g) _____	Kcal: _____ Protein: (g) _____	Kcal: _____ Protein: (g) _____	Kcal: _____ Protein: (g) _____	Kcal: _____ Protein: (g) _____	Kcal: _____ Protein: (g) _____	Kcal: _____ Protein: (g) _____	Kcal: _____ Protein: (g) _____	Kcal: _____ Protein: (g) _____	Kcal: _____ Protein: (g) _____	Kcal: _____ Protein: (g) _____	Kcal: _____ Protein: (g) _____
Did the patient receive IV glucose?	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N
If yes, specify kilocalories received from IV glucose source	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
Medication received: Oxandrolone Propanolol	☐ Y ☐ N ☐ Y ☐ N	☐ Y ☐ N ☐ Y ☐ N	☐ Y ☐ N ☐ Y ☐ N	☐ Y ☐ N ☐ Y ☐ N	☐ Y ☐ N ☐ Y ☐ N	☐ Y ☐ N ☐ Y ☐ N	☐ Y ☐ N ☐ Y ☐ N	☐ Y ☐ N ☐ Y ☐ N	☐ Y ☐ N ☐ Y ☐ N	☐ Y ☐ N ☐ Y ☐ N	☐ Y ☐ N ☐ Y ☐ N	☐ Y ☐ N ☐ Y ☐ N

International Nutrition Survey 2014

Daily Nutrition: Enteral Nutrition 1

Patient Number: ☐

ICU Name: ☐

Study Day:	**1** *ICU Admission*	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Was enteral nutrition received?	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N
If yes:												
Enteral formula(s): *(Select up to 3, see taxonomy)*[1]	1. 2. 3.	1. 2. 3.	1. 2. 3.	1. 2. 3.	1. 2. 3.	1. 2. 3.	1. 2. 3.	1. 2. 3.	1. 2. 3.	1. 2. 3.	1. 2. 3.	1. 2. 3.
Kilocalories received from enteral formula(s):	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
Protein (g) received from enteral formula(s):	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
Supplemental protein? Specify: *(see taxonomy)*	☐ Y ☐ N _____	☐ Y ☐ N _____	☐ Y ☐ N _____	☐ Y ☐ N _____	☐ Y ☐ N _____	☐ Y ☐ N _____	☐ Y ☐ N _____	☐ Y ☐ N _____	☐ Y ☐ N _____	☐ Y ☐ N _____	☐ Y ☐ N _____	☐ Y ☐ N _____
Kilocalories received from supplemental protein:	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
Protein (g) received from supplemental protein:	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
Other non-protein modular supplements? Specify (up to 2): *(see taxonomy)*	☐ Y ☐ N 1. 2.	☐ Y ☐ N 1. 2.	☐ Y ☐ N 1. 2.	☐ Y ☐ N 1. 2.	☐ Y ☐ N 1. 2.	☐ Y ☐ N 1. 2.	☐ Y ☐ N 1. 2.	☐ Y ☐ N 1. 2.	☐ Y ☐ N 1. 2.	☐ Y ☐ N 1. 2.	☐ Y ☐ N 1. 2.	☐ Y ☐ N 1. 2.
Kilocalories received from other non-protein modular supplements:												

[1] If on any of the above days an enteral nutrition formula(s) was/were provided which is/are not found in the International Nutrition Survey taxonomy, specify:

Company/manufacturer name: _____ Product name: _____

Is the formula polymeric? ☐ Yes ☐ No *Does the formula contain:* ☐ Fish oil ☐ Supplemental glutamine (>10g/L or powder) ☐ Supplemental arginine (>4.5 g/L)

International Nutrition Survey 2014

Patient Number: ☐

Daily Nutrition: Enteral Nutrition 2

ICU Name: ☐

Study Day:	**1** *ICU Admission*	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Was EN interrupted today?	☐Y ☐N	☐Y ☐N	☐Y ☐N	☐Y ☐N	☐Y ☐N	☐Y ☐N	☐Y ☐N	☐Y ☐N	☐Y ☐N	☐Y ☐N	☐Y ☐N	☐Y ☐N
If yes: Total time interrupted: (hh:mm)	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
Are the reason(s) EN was interrupted known? *If yes, select all that apply:*	☐Y ☐N	☐Y ☐N	☐Y ☐N	☐Y ☐N	☐Y ☐N	☐Y ☐N	☐Y ☐N	☐Y ☐N	☐Y ☐N	☐Y ☐N	☐Y ☐N	☐Y ☐N
Fasting for extubation/intubation/trach procedure	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Fasting for other bedside procedure	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Fasting for operating room procedure	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Fasting for radiology suite procedure	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Fasting for administration of medications	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Intolerance to enteral feeding - high gastric residuals	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Intolerance to enteral feeding - increased abdominal girth or abdominal distension	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Intolerance to enteral feeding - vomiting/ emesis	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Intolerance to enteral feeding - diarrhea	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Intolerance to enteral feeding - subjective discomfort	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Necrotic bowel/gut ischemia	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
No enteral access available/enteral access lost, displaced or malfunctioning	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Inotropes, vasopressor requirement	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Subject deemed too sick to continue enteral feeding	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Enteral feeding formula not available	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
New contraindication to EN	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Trial of oral intake	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Other *(specify)*	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____

Filled out on each day this patient received enteral nutrition.

International Nutrition Survey 2014

Daily Nutrition: Parenteral Nutrition

Patient Number: ____

ICU Name: ____

Study Day:	**1** *ICU Admission*	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Was parenteral nutrition received?	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N
If yes:												
Parenteral solution(s): [1] *(See PN taxonomy)* Multi-chamber bag:												
OR												
Admixture *or* single bottle system: Amino Acid:												
Dextrose:												
Lipid: [1] *(If lipid is "other," specify lipid type)*												
Kilocalories received from parenteral formula(s):												
Protein (g) received from parenteral formula(s):												
If no:												
Did the patient receive IV amino acids **only?** *If yes,*	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N
Amino acid solution: *(See PN taxonomy)*												
Kcal received:												
Protein (g) received:												
Did the patient receive IV lipids **only**? *If yes,*	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N	☐ Y ☐ N
Lipid solution: [1] *(See PN taxonomy)*												
Kcal received:												

[1] If on any of the above days an parenteral nutrition formula(s) was/were provided which is/are not found in the International Nutrition Survey taxonomy, specify:

Company/manufacturer name: _____ Product name: _____ Lipid type: ☐Olive oil based ☐ Soybean oil based ☐ MCT/LCT Physical Mixture ☐ MCT/LCT Structured Form ☐ Mixture of soy, MCTs, olive and fish oil ☐ Fish oil based ☐ Other, specify: _____

Filled out on each day this patient received parenteral nutrition.

International Nutrition Survey 2014

Daily Nutrition: Supplemental Nutrients

Patient Number: ☐

ICU Name: ☐

Did the patient receive any of the following on any of the first 12 days in ICU?

Study Day:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
IV Supplemental Vitamin C *If yes,* dose (mg):	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____
EN/PO Supplemental Vitamin C *If yes,* dose (mg):	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____
IV Supplemental Zinc *If yes,* dose (mg):	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____
EN/PO Supplemental Zinc *If yes,* dose (mg):	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____
IV Supplemental glutamine *If yes,* dose (grams):	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____
EN/PO Supplemental glutamine *If yes,* dose (grams):	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____
IV Supplemental selenium *If yes,* dose (µg):	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____
EN/PO Supplemental selenium *If yes,* dose (µg):	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____	☐Y ☐N _____
Supplemental Probiotics	☐Y ☐N	☐Y ☐N	☐Y ☐N	☐Y ☐N	☐Y ☐N	☐Y ☐N	☐Y ☐N	☐Y ☐N	☐Y ☐N	☐Y ☐N	☐Y ☐N	☐Y ☐N

Filled out each day.

International Nutrition Survey 2014

Outcomes Information

Patient Number: ☐☐☐☐

ICU Name: ☐☐☐☐☐☐☐☐☐☐

1) Did the patient die in the ICU?

☐ **Yes** → Date of death: 2 0 Y Y M M D D Time: H H M M

Was mechanical ventilation discontinued prior to ICU death?

☐ Yes → Date discontinued: 2 0 Y Y M M D D Time: H H M M (**END OF FORM**)

☐ No (**END OF FORM**)

☐ **No** → Patient in ICU at day 60?

☐ Yes → Was mechanical ventilation discontinued in ICU?

☐ Yes → Date discontinued: 2 0 Y Y M M D D Time: H H M M (**END OF FORM**)

☐ No (**END OF FORM**)

☐ No → Date of ICU discharge: _____ Time: _____ (proceed to question #2)

2) Did the patient die in hospital?

☐ **Yes** → Date of death: 2 0 Y Y M M D D Time: H H M M

Was mechanical ventilation discontinued in ICU?

☐ Yes → Date discontinued: 2 0 Y Y M M D D Time: H H M M (**END OF FORM**)

☐ No → Was mechanical ventilation discontinued prior to hospital death?

☐ Yes → Date discontinued: 2 0 Y Y M M D D Time: H H M M (**END OF FORM**)

☐ No (**END OF FORM**)

☐ **No** → Patient in hospital at day 60?

☐ Yes → Was mechanical ventilation discontinued in ICU?

☐ Yes → Date discontinued: 2 0 Y Y M M D D Time: H H M M (**END OF FORM**)

☐ No → Was mechanical ventilation discontinued in hospital?

☐ Yes → Date discontinued: 2 0 Y Y M M D D Time: H H M M (**END OF FORM**)

☐ No (**END OF FORM**)

☐ No → a) Date of hospital discharge: 2 0 Y Y M M D D Time: H H M M

b) Was mechanical ventilation discontinued in ICU?

☐ Yes → Date discontinued: 2 0 Y Y M M D D Time: H H M M (**END OF FORM**)

☐ No → Was mechanical ventilation discontinued in hospital?

☐ Yes → Date discontinued: 2 0 Y Y M M D D Time: H H M M (**END OF FORM**)

☐ No → Patient was transferred while still mechanically ventilated: (**END OF FORM**)

☐ To an ICU in another hospital ☐ Home

☐ To a ward in another hospital ☐ To another location, *specify:* _____

☐ To a long term care facility

Chapter 5: A randomised controlled trial to optimise energy provision in critically ill adults

5.1 Chapter summary

This chapter describes a randomised controlled pilot trial of 100 critically ill adults, conducted in six ICUs in Australia and New Zealand. The aim of this trial was to determine if an individually titrated supplemental PN strategy commenced 48–72 hours after ICU admission and continued for up to seven days would increase energy delivery in critically ill adults closer to estimated requirements than usual care EN delivery. Secondary aims were to determine rates of enrolment, feasibility of trial processes and to estimate sample size to assist planning a large randomised trial. The work in this Chapter relates to thesis aim 2 and hypothesis 3.

5.2 Manuscript: "Supplemental parenteral nutrition in critically ill patients: a study protocol for a phase II randomised controlled trial" (open access) [68]

Ridley *et al. Trials* (2015) 16:587
DOI 10.1186/s13063-015-1118-y

Trials

STUDY PROTOCOL Open Access

Supplemental parenteral nutrition in critically ill patients: a study protocol for a phase II randomised controlled trial

Emma J. Ridley[1,2*], Andrew R. Davies[1], Rachael Parke[1,3,5,6], Michael Bailey[1], Colin McArthur[7], Lyn Gillanders[6,7,8], David J. Cooper[1,4], Shay McGuinness[1,3,5] and For the Supplemental Parenteral Nutrition Clinical Investigators

Abstract

Background: Nutrition is one of the fundamentals of care provided to critically ill adults. The volume of enteral nutrition received, however, is often much less than prescribed due to multiple functional and process issues. To deliver the prescribed volume and correct the energy deficit associated with enteral nutrition alone, parenteral nutrition can be used in combination (termed "supplemental parenteral nutrition"), but benefits of this method have not been firmly established. A multi-centre, randomised, clinical trial is currently underway to determine if prescribed energy requirements can be provided to critically ill patients by using a supplemental parenteral nutrition strategy in the critically ill.

Methods/design: This prospective, multi-centre, randomised, stratified, parallel-group, controlled, phase II trial aims to determine whether a supplemental parenteral nutrition strategy will reliably and safely increase energy intake when compared to usual care. The study will be conducted for 100 critically ill adults with at least one organ system failure and evidence of insufficient enteral intake from six intensive care units in Australia and New Zealand. Enrolled patients will be allocated to either a supplemental parenteral nutrition strategy for 7 days post randomisation or to usual care with enteral nutrition. The primary outcome will be the average energy amount delivered from nutrition therapy over the first 7 days of the study period. Secondary outcomes include protein delivery for 7 days post randomisation; total energy and protein delivery, antibiotic use and organ failure rates (up to 28 days); duration of ventilation, length of intensive care unit and hospital stay. At both intensive care unit and hospital discharge strength and health-related quality of life assessments will be undertaken. Study participants will be followed up for health-related quality of life, resource utilisation and survival at 90 and 180 days post randomisation (unless death occurs first).

Discussion: This trial aims to determine if provision of a supplemental parenteral nutrition strategy to critically ill adults will increase energy intake compared to usual care in Australia and New Zealand. Trial outcomes will guide development of a subsequent larger randomised controlled trial.

Trial registration: NCT01847534 (First registered 5 February 2013, last updated 14 October 2015)

Keywords: Clinical nutrition, Nutrition therapy, Enteral nutrition, Parenteral nutrition, Critical care, Randomised controlled trials

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Background

In critical illness, enteral nutrition (EN) is usually delivered to provide estimated daily nutrition requirements via a gastric tube [1–3]. EN is the preferred choice of nutrition for critically ill adults because it mimics normal nutritional intake in health, preserves gastrointestinal tract (GIT) function, is relatively inexpensive and has been associated with a reduced incidence of pneumonia and mortality when started early after intensive care unit (ICU) admission [4–6]. The alternative to EN is parenteral nutrition (PN), which is a specialised solution designed to provide daily nutrition requirements intravenously. PN is used when a patient does not have a functioning GIT or when a clinical preference for use of PN exists [1, 7]. Until recently it was thought that PN was associated with an increased risk of infectious complications and mortality, although new data indicates that these risks may have reduced with contemporary care in the ICU [8, 9].

It has been reported that only 45–60 % [10] of energy is provided when EN is used alone due to delivery and tolerance problems [11], resulting in failure to meet daily energy requirements with unknown consequences. The strategy of "supplemental PN" aims to correct the energy deficit from inadequately delivered EN with a supply of PN, to meet 100 % of daily energy requirements in combination. This approach is based on the premise that delivery of close to 100 % of estimated daily nutrition requirements may improve patient outcomes. Whilst the strategy has been demonstrated to deliver close to 100 % of estimated energy needs, the effects on clinical outcomes have been contradictory [12–14]. A prospective randomised control trial (RCT) which investigated supplemental PN initiated early (within 48 hours of ICU admission) versus late (8 days after ICU admission) demonstrated that late supplemental PN resulted in patients being more likely to be discharged earlier from the ICU, with fewer infections when compared to patients in the early arm. However, late supplemental PN led to a higher proportion of hypoglycaemia, a more pronounced inflammatory response and did not affect overall hospital, 90-day mortality or functional status [15]. The outcomes from this study appear to be contradictory and may relate to the use of aggressive insulin therapy, which is not practiced in Australia and New Zealand (ANZ) [16]. Furthermore, the population in this RCT were largely patients undergoing cardiac surgery, and of low to moderate acuity. This patient group can usually return to volitional oral intake quickly and do not often require artificial nutrition due to their short duration of ICU stay; thus, it would seem there may be a low likelihood of benefit from supplemental PN in this population. Another RCT investigating supplemental PN from admission to ICU versus usual care found that the supplemental PN group received more energy (28 kcal/kg per day versus 20 kcal/kg per day) and had fewer nosocomial infections compared with the usual care group (27 % versus 38 %, respectively), but only on days 9–28 of ICU admission [14]. This finding may be explained by the positive effect of adequately delivered nutrition on immunity later in the ICU stay, which is also a biologically plausible explanation.

Thus, it seems that supplemental PN in addition to standard EN may be able to deliver increased energy to critically ill adults, but the exact clinical effects and the population that may benefit most remain undefined. Our aim is to determine if a supplemental PN strategy commenced 48–72 hours following ICU admission will deliver increased amounts of energy to adults with severe critical illness, when compared with usual care in six ANZ tertiary ICUs.

Methods

Design and study participants

A stratified, prospective, multi-centre, unblinded, randomised, parallel-group phase II study will be undertaken.

Inclusion criteria

1) Admitted to intensive care between 48 hours and 72 hours previously
2) Mechanically ventilated at the time of enrolment and expected to remain ventilated until the day after tomorrow
3) At least 16 years of age
4) Have central venous access suitable for PN solution administration
5) Have one or more organ system failure related to their acute illness defined as:

a) $PaO_2/FiO_2 \leq 300$ mmHg
b) Currently on one or more continuous vasopressor infusions which were started at least 4 hours ago at a minimum dose of:

- Dopamine ≥ 5 mcg/kg/min
- Noradrenaline ≥ 0.1 mcg/kg/min
- Adrenaline ≥ 0.1 mcg/kg/min
- Any dose of vasopressin
- Milrinone > 0.25 mcg/kg/min)

6) Renal dysfunction defined as

In patients without known renal disease:

a) Serum creatinine > 171 mmol/L OR
b) Currently receiving renal replacement therapy

In patients with known renal disease:

a) An absolute increase of > 50 % in serum creatinine from baseline OR
b) Currently receiving renal replacement therapy

7) Currently has an intracranial pressure monitor or ventricular drain in situ
8) Currently receiving extracorporeal membrane oxygenation
9) Currently has a ventricular assist device.

Exclusion criteria

Patients will be excluded if:

1) Both EN and PN cannot be delivered at enrolment (that is, either an enteral tube or a central venous catheter cannot be placed or clinicians feel that EN or PN cannot be safely administered due to any other reason)
2) Currently receiving PN
3) Standard PN solutions cannot be delivered at enrolment (that is, clinicians believe that a patient definitely needs a specific parenteral nutrition formulation (for example, glutamine supplementation or specific lipid formulation)
4) Death is imminent or deemed highly likely in the next 96 hours
5) There is a current treatment limitation in place or the patient is unlikely to survive to 6 months due to underlying illness
6) More than 80 % of energy requirements have been satisfactorily delivered via the enteral route in the last 24 hours
7) Are known to be pregnant
8) The treating clinician does not believe the study to be in the best interest of the patient.

Randomisation, allocation concealment and blinding

Concealed randomisation will be performed via a web-based system which includes randomisation in blocks of 6 at each site. Treatment allocation will be stratified by site. The trial is unblinded.

Trial intervention and comparator

The intervention is the delivery of a supplemental PN strategy using Olimel N9-840E/Triomel 9, manufactured and supplied by Baxter Healthcare Corporation, Old Toongabbie NSW 2146, Australia. A multi-trace element solution (10 ml), multi-vitamin (Cernevit, Baxter Healthcare Corporation, 5 ml) and ascorbate (300 milligrams) for stability will be added to the intervention in a Baxter Healthcare Corporation compounding centre following good manufacturing practice.

Further details on the interventional product can be viewed at Additional file 1.

The comparator arm will be usual care, with provision and management of nutrition as per local practice at each participating site.

The intervention period is defined as 7 days from the day of randomisation.

Study procedures common to both arms

Patients will be screened for eligibility by research coordinators/medical staff at each site when they are between 48 and 72 hours of their first admission to the ICU. Those that are found to meet all the inclusion and none of the exclusion criteria will be randomised using a web-based randomisation system.

At randomisation, the body weight of study participants will be standardised using calculated body weight (CBW). To determine CBW, actual or estimated weight and height will be required to allow calculation of body mass index (BMI). The weight used to determine BMI will be defined according to the following hierarchy:

a) Actual body weight if it has been recorded in the previous 6 weeks
b) Estimated dry weight if actual weight is not known.

Height will be estimated using demi arm span [17].

CBW will be the patient's actual weight if their BMI is deemed to be <25 kg/m^2. If their BMI is ≥25 kg/m^2, the CBW will be set to the patient's ideal weight at a BMI of 23 kg/m^2. Once the CBW has been determined, it will not be changed for the study duration.

Daily energy requirements will be estimated using CBW with a fixed prescription. The daily energy requirements will be set at 25 kcal/kg CBW unless the patient is receiving renal replacement therapy (RRT) and/or extracorporeal membrane therapy (ECMO), where 30 kcal/kg of CBW will be used. The daily energy requirement will only be changed during the study period if the patient commences or discontinues ECMO and/or RRT (with the two requirement options being 30 kcal/kg CBW or 25 kcal/kg CBW, respectively). A higher energy requirement has been chosen during RRT and/or ECMO due to the potential for increased metabolic stress and inflammation associated with the delivery of both therapies and the underlying disease processes that require these treatments [18]. Once randomised, the target rate for continuous EN delivery will be calculated by the treating clinical team to match the daily energy

requirement, with the assumption that all patients should receive 100 % of their daily energy requirements from administration of EN and rounded up to the nearest 5 ml/hour. The choice of EN formula, protein requirement estimation and management of blood glucose levels will be according to local protocols.

Figure 1 demonstrates the study processes from screening to study completion.

Study procedures in the intervention arm

Day of randomisation:

The interventional product will be administered to intervention patients within 2 hours of randomisation via a central venous catheter (including long-term central catheters, for example, a Hickman catheter if already in situ) or a peripherally inserted central catheter. Management of the line will be as per the participating hospital's usual procedure. Due to the increased risk of overfeeding with energy when PN is used, the intervention strategy has been designed to minimise this risk. Thus, the maximum amount of energy provided by the intervention will be 20 kcal/kg/day (or 24 kcal/kg/day for those on RRT and/or ECMO), which equals 80 % of the daily energy requirement set at 25 or 30 kcal/kg/day, respectively. This will allow for small amounts of energy provided by EN, 25/50 % glucose and propofol (non-nutritional energy sources) in addition to interventional product in the intervention arm.

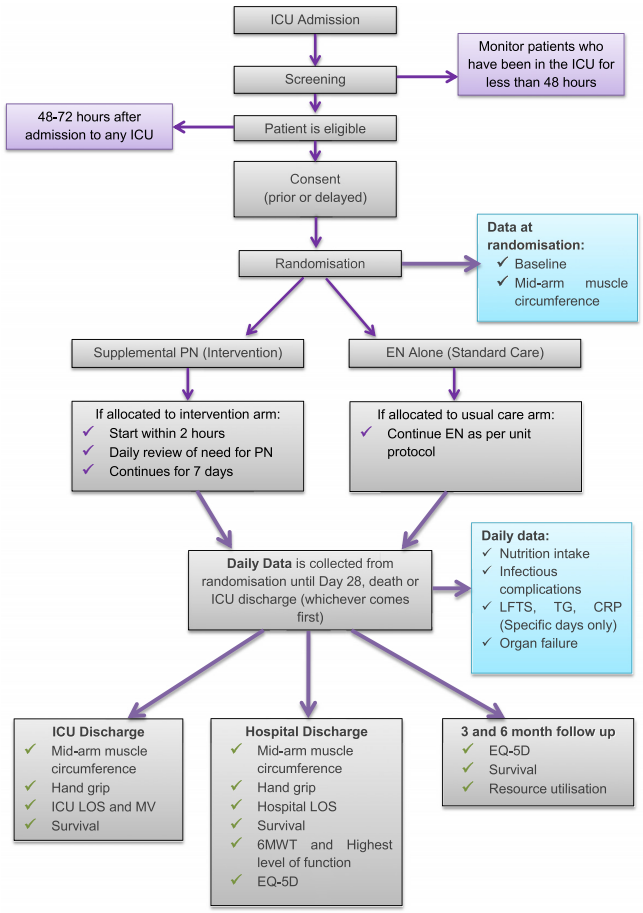

Fig. 1 Study overview. CRP: C-reactive protein; EN: enteral nutrition; EQ-5D: EuroQuol 5 dimension; ICU: intensive care unit; LFTs: liver function tests; LOS: length of stay; MV: mechanical ventilation; PN: parenteral nutrition; 6MWT: 6-minute walk test

The starting rate of PN will be determined by the amount of energy received via the enteral route in the 24 hours prior to randomisation:

a) Between 40–80 % of daily energy requirement received from EN: PN rate will equal delivery of 10 kcal/kg of CBW/day (or 12 kcal/kg of CBW/day for those on RRT and/or ECMO)
b) Less than 40 % of daily energy requirement received from EN: PN rate will equal delivery of 20 kcal/kg of CBW/day (or 24 kcal/kg of CBW/day for those on RRT and/or ECMO).

Management of EN in the intervention arm will be according to unit protocol. Every attempt will be made by the treating clinical team to achieve delivery of EN in the intervention arm to provide 100 % of daily energy requirements. Importantly, EN must not be reduced based on the amount of intervention being administered.

Daily review of intervention:

From study day 2 until study day 7 (or ICU discharge, whichever occurs first), the adequacy of energy from EN and non-nutritional sources will be assessed at bkmidday by a member of the site research team. Total energy intake will be determined for the 24 hours prior to review and used to determine the rate of delivery bkof study PN for the subsequent 24 hours (Fig. 2). Once the rate is set for the following 24 hours by the research team, it should not be altered by the treating team unless deemed necessary for patient safety.

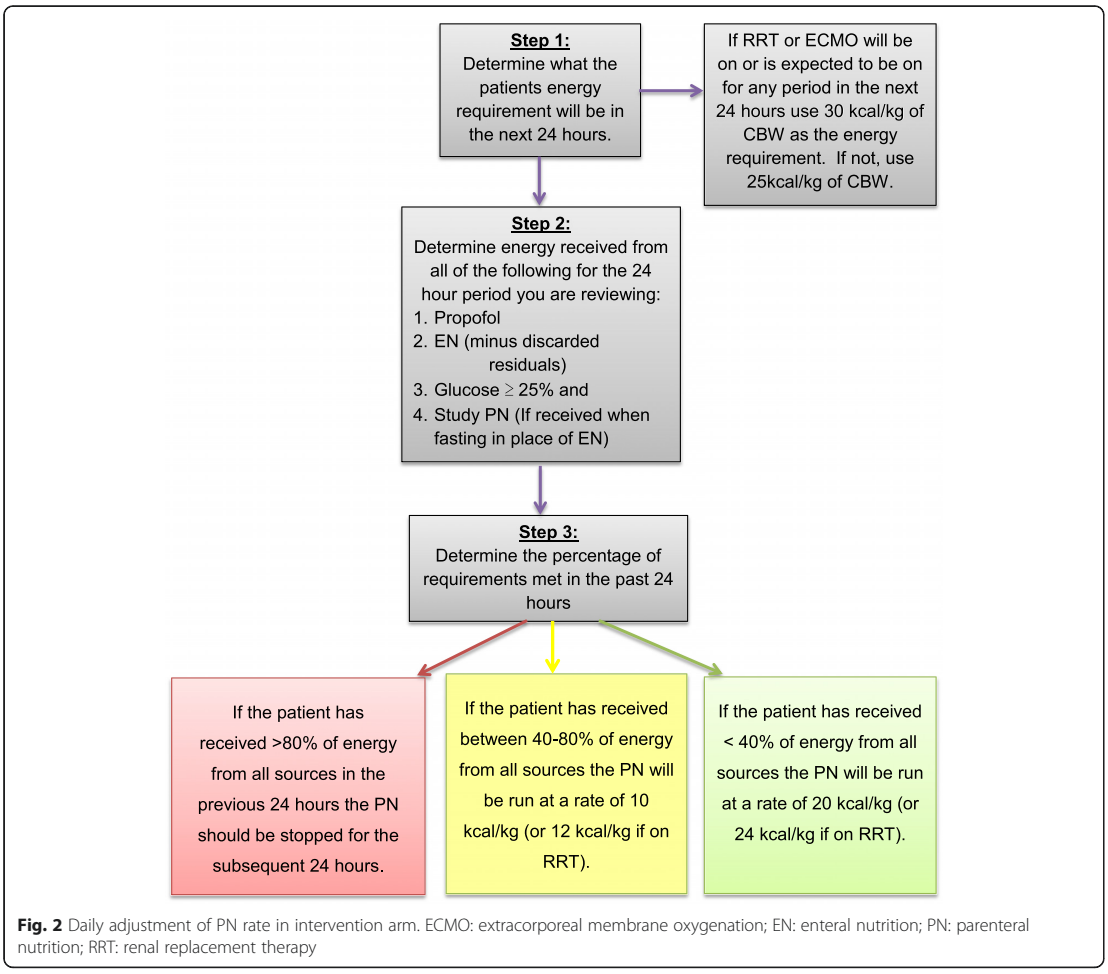

Fig. 2 Daily adjustment of PN rate in intervention arm. ECMO: extracorporeal membrane oxygenation; EN: enteral nutrition; PN: parenteral nutrition; RRT: renal replacement therapy

Management of interruptions to EN in the intervention arm:

In the event of an anticipated or actual interruption to EN for a period of 2 hours or more in the intervention arm, the interventional strategy will be adjusted to minimise energy deficit for the period of the interruption. During the interruption period, the intervention will be run at the hourly rate corresponding to 20 kcal/kg or 24 kcal/kg for those on RRT and/or ECMO. If the patient is already receiving the highest rate of the intervention, there will be no change to the rate during the interruption period. As soon as is practical, EN should be recommenced as per local protocol and the intervention returned to the rate determined as per the midday assessment.

Cessation of study intervention prior to the end of the study period:

The intervention will cease either prior to ICU discharge or 7 days following enrolment if energy from EN and non-nutritional sources provides more than 80 % of estimated energy requirements on any day. Cessation on any one day will not preclude recommencement in the following 24 hours should the strategy be indicated based on the procedures previously outlined, until study day 7.
Should a patient commence oral intake during the 7-day study period, the intervention will cease when it is deemed that the patient will resume oral intake with the intent to provide nutrition, that is, not only to provide water or fluid intake.

Usual care arm

After enrolment, patients allocated to the usual care arm will commence or continue EN via an enteral tube to a target rate aimed to provide 100 % of daily energy requirements. All other aspects of nutrition therapy will be managed according to local unit protocol and, if required, include the use of promotility agents and the placement of nasojejunal feeding tubes prior to commencement of PN. PN will only be used in the usual care arm if the above methods have been attempted, or if an absolute contraindication to EN develops. The interventional product will be used in the usual care arm should PN be required within 7 days of randomisation. If PN is required after study day 7, it will be the usual hospital PN formula, managed by the treating clinicians as clinically appropriate.

Outcome measures

The primary outcome of this trial is the mean energy amount in calories delivered from nutrition therapy over the first 7 days of the study period.

Secondary outcomes include:

1) Total protein amount delivered in the first 7 days of the study period
2) Total energy amount delivered in the ICU stay (up to 28 days)
3) Total protein amount delivered in the ICU stay (up to 28 days)
4) Total antibiotic usage
5) Sequential Organ Failure Assessment scores
6) Duration of mechanical ventilation
7) Duration of ICU and hospital stay
8) Mortality to 180 days post randomisation
9) Functional and quality of life to 180 days post randomisation

Study management and data collection

This trial will be coordinated by the Australian and New Zealand Intensive Care Research Centre (ANZIC-RC), Monash University, Melbourne, Australia. Dedicated study tools will be provided to participating sites to standardise all study procedures. Data will be collected at each site by dedicated and trained research staff using a paper case report form. Study variables collected will include baseline demographics such as anthropometric measurements, admission diagnoses, physiological parameters, Acute Physiology and Chromic Health Evaluation II, daily information including nutrition therapy, antibiotic use, blood tests and outcome data such as mortality, protocol deviations and serious adverse events (SAEs). At ICU and hospital discharge, functional, strength and health-related quality of life (HRQOL) assessments will be undertaken using the 6-minute walk test if possible and/or the highest level of function scale [19], hand grip strength and the EuroQol 5 dimension 5 level (EQ-5D-5 L) tools, respectively. Study participants will be contacted at 90 and 180 days post randomisation (unless previously deceased) to assess HRQOL, resource utilisation and survival. Follow-up assessments will be conducted via telephone by the research staff at the randomising site using a pre-prepared script to obtain the assessment using the EQ-5D-5 L. In the event that the patient is unable to complete the assessment at any time point, a relative or friend for the patient will be used as per the instructions for the EQ-5D-5 L. Data will be entered by the research staff at each participating site into a web-based database developed by Spiral Web Solutions, Wellington, New Zealand. Table 1 details the full table of events from baseline to outcome assessment.

Ethical considerations

The study protocol has been approved by The Alfred Hospital Ethics Committee in Australia and the Multi-Region Ethics Committee in New Zealand.

Table 1 Table of events: usual care and intervention arms

Study day	Baseline	1	2	3	4	5	6	7	8	9	10	11	12	13	14	21	28	ICU D/C	Ward	Hospital D/C	90 days post D/C	180 days post D/C
Incl. and excl. criteria	X																					
Consent	X																					
Randomisation	X																					
Demographics	X																					
Apache II score	X																					
Apache III diagnosis	X																					
Daily data[a] (ICU)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
LFTs, WBC	X	x	x	x	x	x	x	X	x	x	x	x	x	x	X	X	X					
Use of new antibiotics	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
SOFA score	X	X	X	X				X							X	X	X					
TG	X			X				X							X							
CRP	X							X							X		X					
Dur MV																		X				
LOS ICU																		X				
LOS hospital																				X		
Survival status																		X		X	X	X
Mid-upper arm muscle circumference	X									Measured once patient is ready for ICU D/C										X		
Hand grip										Measured once patient is ready for ICU D/C										X		
6-minute walk test																				X		
QOL																				X	X	X

X denotes must be collected on specified day
x denotes collect only if measured, no need to specially collect
Abbreviations used in table: *CRP* C-reactive protein, *EN* enteral nutrition, *ICU* intensive care unit, *LOS* length of stay, *MV* mechanical ventilation, *PN* parenteral nutrition, *QOL* quality of life, *SOFA* Sequential Organ Failure Assessment, *TG* triglycerides
[a]Daily data: The following variables will be collected daily: target energy and protein requirements, received energy and protein amounts, received EN and PN volumes, AM BGL levels, units of insulin delivered, gastric residual volumes, documented episodes of vomiting, documented episode of abdominal distension, documented episode of witnessed aspiration

Participants in this trial will be unable to provide informed consent for themselves to participate in the study at the time of enrolment. A delayed consent model has been approved by the responsible ethics committees, which means a patient's legal surrogate, relative/friend or whanau member will be approached for consent to participate in the study. Following consent from a patient's legal surrogate, relative/friend or whanau member, the patient will be approached to give consent to continue in the trial if they recover the ability to do so and the timing is appropriate.

Sample size and power

Using two published RCTs on nutrition therapy in ANZ critically ill patients, we estimated that the usual care group would receive an average of 1,400 kcal/day. We aim to deliver an additional 420 kcal/day (using a standard deviation of 600 kcal/day) to the intervention group, which is a 30 % relative increase in energy delivery and requires a sample size of 100 patients (80 % power, significance 0.05).

This sample size will also provide baseline rates of other key secondary outcomes which could be used in the future to inform sample size estimations for larger RCTs assessing clinical outcomes.

Statistical analysis plan

Statisticians at the Australian and New Zealand Intensive Care Research Centre (ANZIC-RC) will perform statistical analysis using the intention-to-treat principle. All data will initially be assessed for normality and will be log-transformed as appropriate. Baseline variables and single measure outcomes will be compared using chi-square tests for equal proportion (or Fisher's exact tests if numbers are small), Student's *t*-test for normally distributed outcomes and Wilcoxon rank-sum tests otherwise. Continuously normally distributed repeated measure outcomes will be compared between groups using longitudinal mixed modelling fitting main effects

for treatment and time with an interaction between treatment and time to determine if groups behave differently over time. Sensitivity analysis accounting for site, known covariates and baseline imbalances will also be performed for all outcomes, using logistic regression for binomial outcomes and mixed linear or non-linear modelling for continuous outcomes. Analysis will be performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), and a two-sided p-value of 0.05 will be considered statistically significant.

Data and safety monitoring

Given the size of the trial, there are no planned interim analyses, and there is no dedicated data safety monitoring board. Safety will be monitored by reported adverse events and SAEs and reviewed by the study management committee (listed in Appendix 1) and Baxter Healthcare Corporation. All study sites will have an initial monitoring visit conducted by the project manager after two to five patients have been recruited. At this site visit, one intervention and one usual care arm patient will have 100 % source data verification at this visit; all other patients monitored at the visit will have consent procedures and eligibility criteria checked. Furthermore, intervention patients monitored at this initial visit will also have intervention delivery reviewed for adherence to the study protocol. Additional monitoring visits will be completed based on recruitment rates per site and any identified issues which need review after the initial monitoring visit.

The project manager will conduct remote monitoring of data completeness via the study website, and any data queries will be sent to the site for review.

Discussion

Nutrition is a commonly used therapy in the ICU. It is relatively inexpensive compared to other treatments and, if used correctly, may positively affect clinical and functional outcomes, although this remains to be definitively determined. Large-scale RCTs to date have failed to deliver EN to meet estimated energy requirements, or have delivered nutrition in a population or manner that makes the evidence difficult to translate into clinical practice. This study aims to determine if a supplemental PN strategy will safely deliver close to 100 % of energy requirements compared to usual care, identify a patient population who may benefit most and minimise the risks of overfeeding. This information will assist in the development of future studies to provide definitive answers on the role of energy intake in critical illness.

Trial status

The trial commenced recruitment on 17 February 2014. Final recruitment is expected to be achieved in late 2015 with 6 month outcomes available by early 2016.

Appendix 1

Management committee of the Supplemental Parenteral Nutrition in Critically Ill Patients Phase II Randomised Controlled Trial

Shay McGuinness, Emma Ridley, Andrew Davies, Rachael Parke, David (Jamie) Cooper, Lyn Gillanders, Colin McArthur, Neil Orford, Owen Roodenburg.

Additional file

Additional file 1: Detailed product information for the interventional product. (DOCX 14 kb)

Abbreviations

ANZ: Australia and New Zealand; ANZIC-RC: Australian and New Zealand Intensive Care Research Centre; BMI: body mass index; CBW: calculated body weight; CI: confidence interval; ECMO: extracorporeal membrane therapy; EN: enteral nutrition; EQ-5D-5 L: EuroQol 5 dimension 5 level; FiO_2: fraction of inspired oxygen; GIT: gastrointestinal tract; HRQOL: health-related quality of life; ICU: intensive care unit; kcal: kilocalorie; kg: kilogram; mcg: microgram; min: minute; mmHg: millimetre of mercury; mmol: millimole; PaO_2: partial pressure of oxygen; PN: parenteral nutrition; RCT: randomised controlled trial; RRT: renal replacement therapy; SAE: serious adverse event.

Competing interests

AD does sessional work with Baxter Healthcare Corporation independently of this trial.

SM has received speaking fees from Baxter Healthcare Corporation. Research in the Cardiothoracic and Vascular Intensive Care Unit, Auckland City Hospital is supported in part by an unrestricted grant from Fisher & Paykel Healthcare, New Zealand.

Authors' contributions

ER contributed to the original trial concept, development of trial concept including statistical analysis plans, funding acquisition, drafting of the manuscript, trial management, is a management committee member, a site investigator and will assist with statistical analysis. AD contributed to the original trial concept, development of trial concept including statistical analysis plans, funding acquisition, drafting of the manuscript, trial management and is a management committee member. RP contributed to the development of trial concept including statistical analysis plans, drafting of the manuscript, trial management, is a management committee member and a senior site research coordinator. MB contributed to the development of the trial statistical analysis plan and will oversee analysis and assisted with drafting of the manuscript. CM contributed to the original trial concept, development of trial concept, drafting of the manuscript, trial management, is a management committee member and a principal investigator. LG contributed to the original trial concept, development of trial concept, drafting of the manuscript, trial management, is a management committee member and a site investigator. DJC contributed to the original trial concept, funding acquisition, is a management committee member and assisted with drafting of the manuscript. SM is the chief investigator, contributed to the development of trial concept including statistical analysis plans, drafting of the manuscript, trial management, is a management committee member and principal investigator. Members of the Supplemental Parenteral Nutrition Clinical Investigators contributed to trial management, study conduct at individual sites and drafting of the manuscript. All named and group authors read and approved the final version of the manuscript.

Acknowledgements

This trial is funded by an unrestricted research grant by Baxter Healthcare Corporation. The study PN is provided at no charge for the study. Baxter Healthcare Corporation has not been involved in the original trial concept, development of the trial concept, trial management, data collection, analysis plans, interpretation of the data or preparation of the manuscript. Members of the Supplemental Parenteral Nutrition Clinical Investigators are as follows

(listed as participating sites, principal investigators, research coordinators, dietitians and method centre staff):
Auckland City Hospital, Auckland New Zealand: Cardiothoracic and Vascular Intensive Care Unit; Shay McGuinness, Rachael Parke, Eileen Gilder, Lianne McCarthy, Keri-Anne Cowdrey, Rebecca Baskett
Auckland City Hospital, Auckland, New Zealand: Department of Critical Care Medicine; Colin McArthur, Lynette Newby, Lyn Gillanders, Varsha Asrani
Christchurch Hospital, Christchurch, New Zealand: Seton Henderson, Jan Mehrtens, Anna Morris, Emmeline Minto
University Hospital Geelong, Geelong, Australia: Neil Orford, Allison Bone, Tania Elderkin, Tania Salerno, Roy Hoevenaars
The Alfred, Melbourne, Australia: Owen Roodenburg, Meredith Young, Phoebe McCracken, Jasmin Board, Shirley Vallance, Emma Ridley, Eleanor Capel
Wellington Hospital, Wellington, New Zealand: Paul Young, Leanlove Navarra, Anna Hunt, Sally Hurford, Lynn Andrews, Diane Mackle, Catherine Boulton
Australian and New Zealand Intensive Care Research Centre: Michael Bailey, Andrew Davies, Adam Deane, Carol Hodgson, Emma Ridley.
The members of the management committee are listed in Appendix 1.

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Received: 3 August 2015 Accepted: 14 December 2015
Published online: 24 December 2015

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5.3 Manuscript: "Supplemental parenteral nutrition versus usual care in critically ill adults: a pilot randomised controlled study" (open access) [69]

Ridley *et al. Critical Care* (2018) 22:12
DOI 10.1186/s13054-018-1939-7

Critical Care

RESEARCH Open Access

Supplemental parenteral nutrition versus usual care in critically ill adults: a pilot randomized controlled study

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Abstract

Background: In the critically ill, energy delivery from enteral nutrition (EN) is often less than the estimated energy requirement. Parenteral nutrition (PN) as a supplement to EN may increase energy delivery. We aimed to determine if an individually titrated supplemental PN strategy commenced 48–72 hours following ICU admission and continued for up to 7 days would increase energy delivery to critically ill adults compared to usual care EN delivery.

Methods: This study was a prospective, parallel group, phase II pilot trial conducted in six intensive care units in Australia and New Zealand. Mechanically ventilated adults with at least one organ failure and EN delivery below 80% of estimated energy requirement in the previous 24 hours received either a supplemental PN strategy (intervention group) or usual care EN delivery. EN in the usual care group could be supplemented with PN if EN remained insufficient after usual methods to optimise delivery were attempted.

Results: There were 100 patients included in the study and 99 analysed. Overall, 71% of the study population were male, with a mean (SD) age of 59 (17) years, Acute Physiology and Chronic Health Evaluation II score of 18.2 (6.7) and body mass index of 29.6 (5.8) kg/m^2. Significantly greater energy (mean (SD) 1712 (511) calories vs. 1130 (601) calories, $p < 0.0001$) and proportion of estimated energy requirement (mean (SD) 83 (25) % vs. 53 (29) %, $p < 0.0001$) from EN and/or PN was delivered to the intervention group compared to usual care. Delivery of protein and proportion of estimated protein requirements were also greater in the intervention group (mean (SD) 86 (25) g, 86 (23) %) compared to usual care (mean (SD) 53 (29) g, 51 (25) %, $p < 0.0001$). Antibiotic use, ICU and hospital length of stay, mortality and functional outcomes were similar between the two groups.

Conclusions: This individually titrated supplemental PN strategy applied over 7 days significantly increased energy delivery when compared to usual care delivery. Clinical and functional outcomes were similar between the two patient groups.

Trial registration: Clinical Trial registry details: NCT01847534 (First registered 22 April 2013, last updated 31 July 2016)

Keywords: Enteral nutrition, Parenteral nutrition, Randomized controlled trial, Nutrition therapy, Clinical nutrition, Critical care, Intensive care

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Background

Best practice guidelines for energy delivery in critical illness often recommend that energy delivery be aimed to meet energy requirements, usually estimated using standard equations, and most often using enteral nutrition (EN) [1–4]. However, energy delivery in critically ill patients when using EN alone is almost always less than estimated requirements [5, 6]. Parenteral nutrition (PN), delivered in addition to EN, is a strategy which may increase energy delivery more closely to estimated energy requirements, however recommendations for use differ and evidence is controversial [1–4, 7–12]. Previously, the use and infective risk of PN has been a concern when compared to standard care nutrition, however, this has been challenged in more recent trials which investigated PN in a modern-day ICU setting [13, 14].

Observational studies have suggested an association between higher energy delivery and improved clinical outcomes. [15–18]. And, prospective randomized controlled trials (RCTs) addressing this question have been limited by either trial size, or by methodological concerns [19]. One randomized trial found that supplemental PN was associated with decreased infective complications later in ICU stay (however this endpoint was not in the original study protocol), and another found a trend to improved outcomes in nutritionally at-risk patients [8, 11]. The largest randomized trial indicated harm with early supplemental PN delivery, despite only achieving 74% of estimated energy requirements in the early PN arm [7, 10]. Further, interpretation of this trial was complicated by the parallel use of an intensive insulin therapy strategy, which has since been found to impair patient outcomes [20].

We aimed to determine if an individually titrated supplemental PN strategy commenced 48–72 hours following ICU admission and continued for up to 7 days would increase energy delivery closer to estimated requirements in critically ill adults compared to usual care delivery. Secondary aims (which are not reported in this article) were to determine rates of enrolment, feasibility of trial processes and estimate sample size to assist planning a large randomized trial.

Methods

Design

We conducted a prospective, unblinded, parallel group, block randomized phase II pilot trial in six ICUs in Australia and New Zealand.

Patients

Patients aged ≥ 16 years, admitted to ICU in the previous 48–72 hours, who were receiving mechanical ventilation (MV) and expected to continue until the day after randomization, with central venous access and one or more defined organ system failure were eligible. Patients were excluded if they could not receive EN and/or PN at the time of randomization, were already receiving PN, had a requirement for a specific PN solution (e.g. glutamine containing), had received more than 80% of their estimated nutrition requirements from EN in the 24 hours prior to randomization, seemed not likely to survive the subsequent 96 hours, had a treatment limitation in place or a high likelihood of terminal illness, were pregnant or the treating clinician did not believe that study participation was in the best interests of the patient. There was a modification to the inclusion criteria after the first 6 months of recruitment. Details of the full inclusion and exclusion criteria can be viewed in Additional file 1.

Eligible patients were randomly assigned in a 1:1 ratio via a web-based randomization system. Randomization was stratified by site and allocation occurred in permuted blocks of two, four or six. Recruitment began on 17 February 2014 and was completed on 6 January 2016 with the final outcome determined 180 days later. Ethics approval was obtained from The Alfred Hospital Research and Ethics committee for Australia and the Northern A Health and Disability Ethics Committee in New Zealand, as well as the Monash University Research and Ethics Committee. As participants were unable to provide consent for participation at the time of enrolment, the patient's legal surrogate, relative/friend or whanau member was approached for consent or agreement to participate in the study. Patients were approached at a later time if it was appropriate and they regained the capacity to provide consent to continue to participate. The full protocol for this RCT was pre-published and registered (NCT01847534) [21].

Study processes

Common to both groups

Body weight was standardized in both groups using 'calculated body weight' (CBW) as follows:

Body mass index (BMI) < 25 kg/m^2: actual body weight was equal to CBW BMI ≥ 25 kg/m^2: CBW was an ideal body weight set at a body mass index (BMI) of 23 kg/m^2 using the patient's height.

Actual body weight was preferred to estimated weight if it was current within 6 weeks and height was estimated using demi-arm span [22]. Once set, the CBW was not changed for the duration of the study.

Energy requirements were determined on a daily basis using a fixed prescription method of 25 kilocalories (kcal)/kg CBW or 30 kcal/kg CBW if the patient was receiving renal replacement therapy or extracorporeal membrane oxygenation on that day. The daily nutrition target was 100% of estimated energy requirement in both groups. Estimated protein requirements and the

choice of EN formula followed usual practice at the participating ICU and recorded as part of study data collection. To determine the volume of EN received over 24 hours, discarded gastric residual volumes were deducted from the total volume of EN received. Blood glucose level (BGL) management followed the participating ICUs usual practice, which was usually based on the control group strategy in a recently conducted trial [20].

Management of the usual care group

Nutrition therapy in the usual care group followed clinical practice at the participating ICU. PN was only used when EN delivery remained insufficient despite attempts to improve it with strategies recommended in best practice guidelines [1, 3, 4]. If PN was required during the first 7 days of the study in the usual care group, the same PN formulation used in the intervention group was provided. If PN was required in usual care after the first 7 days the usual hospital PN formulation was used. Micronutrients were provided as part of the standard EN solutions provided in usual care. Additional micronutrients could be provided if deemed necessary by the treating clinical team.

Management of the intervention group

The intervention group received a supplemental PN strategy, delivered for up to 7 days after randomization, using Olimel N9-840/Triomel with added multi-trace elements and multi-vitamins (manufactured and supplied by Baxter Healthcare Corporation, Sydney, Australia). On randomization, intervention PN was commenced within 2 hours, at a rate based on the percentage of estimated energy requirements received from EN in the 24 hours prior to randomization. These rates corresponded to either 40% or 80% of the estimated requirement (Fig. 1, panel A in Additional file 1 demonstrates study processes at randomization). The intervention strategy was designed to increase average delivery towards 100% of the estimated energy requirement but avoid overfeeding by (1) using ideal body weight in those who were overweight or obese, (2) having variable PN rates which were individually titrated, reviewed daily and based on the percentage estimated energy requirement delivered, (3) accounting for additional energy from EN, intravenous glucose solutions ≥ 25% and propofol and (4) never providing more than 80% of the estimated energy requirement by the intervention PN.

After the day of randomization, total energy received from EN, propofol and intravenous glucose solutions ≥ 25% were assessed daily for up to 7 days by a dietitian, research coordinator or investigator at the site. Based on the percentage of estimated energy requirement received, the intervention PN was individually titrated on a daily basis, with three rates possible for the following 24 hours (corresponding to 0%, 40% or 80% of estimated requirements). Once set, the PN was continued at that rate for

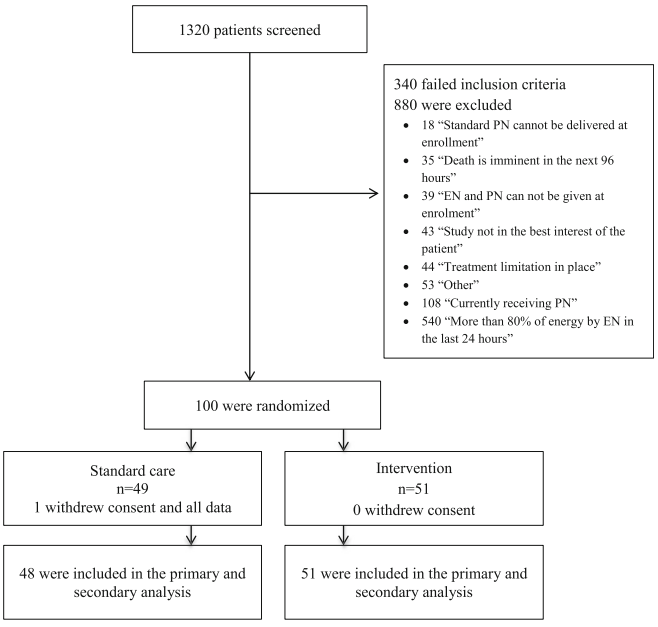

Fig. 1 Participant flow diagram

the next 24 hours and EN was managed as per standard practice in the participating ICU and not reduced based on the intervention strategy. If there was a discontinuation of EN ≥ 2 hours, the intervention PN was run at a rate corresponding to 80% of the estimated energy requirement for the duration of the interruption and once EN was recommenced, returned to the last rate determined. The intervention period ceased at the end of study day 7 or earlier if the patient was discharged from the ICU or oral nutrition was commenced.

Details on the interventional product and daily management of intervention PN can be viewed in Additional file 1 (Table 1 and Fig. 1, panel B).

Data collection

Baseline data included nutrition information, patient and ICU admission demographics, severity of illness characteristics and standard blood test results. Daily data included nutrition requirements and intake (including energy from propofol and intravenous glucose solutions ≥ 25%); morning BGL level; number of episodes of hypoglycaemia; complications associated with nutrition delivery and antibiotic usage. On specific days Sequential Organ Failure Assessment (SOFA) score, liver function tests, white cell count, serum triglyceride, and C-reactive protein were collected.

Outcomes

The primary outcome was mean energy delivered from both EN and/or PN therapy through the first 7 days of the study (the intervention period). Secondary outcomes included: (1) total protein delivered in the first 7 days of the study period; (2) total energy and protein delivered in the ICU stay (up to 28 days); (3) number of new antibiotics commenced while in ICU to day 28; (4) SOFA scores; (5) duration of MV to day 28; (6) duration of ICU and hospital stay; (7) mortality to 180 days post randomization; (8) assessment of physical function using the ICU mobility scale (or 6-minute walk test where possible) at hospital discharge (D/C), hand grip strength (HGS) at ICU and hospital D/C and (9) quality of life with the EuroQuol-5 Dimension 3 Level (EQ-5D-3L) at hospital D/C, 90 and 180 days post randomization [23, 24].

Statistical analysis

A sample size of 100 patients was calculated on a mean (SD) daily delivery of 1400 (600) calories in the usual care group, estimated from work previously conducted by our group [25, 26]. This provided an 80% power (two-sided p value of 0.05) to detect a 30% relative increase (1400 vs. 1820 kcal) in calories delivered.

Daily data were collected until the patient was discharged from ICU, died or was censored at day 28 (whichever occurred first). We conducted all analyses according to the intention-to-treat principle and there were no planned interim analyses. Baseline and outcome variables were compared using chi-square 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 [interquartile range (IQR)] respectively. Longitudinal analysis of total energy was performed using mixed linear modelling with patients treated as random effects, fitting main effect for treatment and time and an interaction between the two to determine if treatment behaved differently over time. Missing data were not imputed and no assumptions were made relating to missingness. All analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and a two-sided p value of 0.05 was considered to be statistically significant.

Results

Patients

Of 1320 patients screened for eligibility, 100 patients were randomized over 24 months. One patient in the usual care group withdrew consent for follow-up and use of all data (Fig. 1).

Baseline characteristics

The two groups were comparable at baseline (Table 1). The mean (SD) age was 59 (17) years, 71% were male and the mean Acute Physiology and Chronic Health Evaluation II score was 18.2 (6.7). Fewer patients with a diagnostic category of 'sepsis' were randomized to usual care than the intervention group (one and seven patients respectively). Prior to randomization, more patients in the usual care group (44 (91%)) had commenced EN compared to the intervention group (40 (78%)). The median [IQR] energy received in the usual care group was less (394 [67–1020] kcal) than the intervention group (605 [75–1270] kcal) prior to randomization. The mean overall estimated energy and protein requirements in both groups at randomization were 2092 (392) kcal and 103 (21) g.

Nutrition delivery

The median time from randomization to commencing the intervention was 1.2 [0.5–1.8] hours. Over the 7-day intervention period, the mean daily energy delivery from EN, PN or both in usual care was 1130 (601) kcal and 1712 (511) kcal in the intervention group, $p = < 0.0001$. When energy from nutrition, propofol and intravenous glucose solutions ≥ 25% were included the mean daily intake increased to 1298 (671) kcal in the usual care group and 1892 (540) kcal in the intervention group, $p < 0.0001$. Those in the usual care group were delivered a mean 53 (29) g of protein daily compared to 86 (35) g of protein daily in the intervention group,

Table 1 Baseline characteristics

Variable	Usual care ($n = 48$)	Intervention ($n = 51$)
Age, years, mean (SD)	60 (17)	59 (17)
Sex, male, n (%)	35 (73)	35 (69)
BMI, kg/m^2, mean (SD)	30 (6)	29 (6)
APACHE II score, mean (SD)	19 (7)	18 (7)
APACHE III diagnosis code, n (%)		
Cardiovascular	29 (59)	31 (61)
Trauma	7 (14)	6 (12)
Respiratory	6 (12)	3 (6)
Sepsis	1 (2)	7 (14)
Gastrointestinal	1 (2)	2 (4)
Musculoskeletal	2 (4)	0 (0)
Renal	1 (2)	1 (2)
Unknown	1 (2)	1 (2)
Neurological	1 (2)	0 (0)
Location prior to ICU admission, n (%)		
Elective surgery	20 (42)	22 (43)
ICU	9 (19)	7 (14)
Emergency surgery	9 (19)	5 (10)
ED	5 (10)	8 (16)
Ward	4 (8)	6 (12)
Other hospital	1 (2)	3 (6)
Time from hospital admission to randomization, days, median [IQR]	3 [3–6]	3 [3–4]
Time from ICU admission to randomization, days, mean (SD)	2.5 (0.4)	2.5 (0.4)
Baseline total SOFA, mean (SD)	10 (3)	10 (4)
Bloods, median [IQR]		
ALT, U/L	25 [11–103]	40 [18–108]
ALP, U/L	67 [49–97]	72 [50–89]
GGT, U/L, mean (SD)	44 [27–79]	41 [28–98]
Bilirubin, mmol/L	21 [10–41]	24 [11–47]
WCC, 0^9/L	13 [10–15]	17 [11–23]
TG, mmol/L	2 [1–3]	2 [1–3]
CRP, mg/L	209 (97)	217 (111)
Mid arm muscle circumference, cm, mean (SD)	34 (5)	34 (4)

APACHE Acute Physiology and Chronic Health Evaluation II, *ALP* alkaline phosphatase, *ALT* alanine aminotransferase, *BMI* body mass index, *CRP* C-reactive protein, *ED* Emergency department, *GGT* gamma-glutamyltransferase, *ICU* intensive care unit, *IQR* interquartile range, *SD* standard deviation, *SOFA* Sequential Organ Failure Assessment, *TG* triglyceride, *WCC* white cell count

$p < 0.0001$. Figure 2, panels A, B and C demonstrate energy and protein intake on a daily basis over the 7-day intervention period. On study day 2, those in the intervention group received a mean proportion of estimated energy requirement of 105% (5%) and when energy from all sources were accounted for this increased to 117% (5%) (Fig. 2, Panel D). On all other study days, the proportion of estimated energy requirement provided was less than 100%. Figure 2 in the Additional file 1 shows the proportion of daily energy delivery by EN and PN in the usual care (Panel A) and the intervention (Panel B) groups. Over the duration of ICU stay, mean energy and protein from nutrition were 1212 (676) kcal and 57 (33) g protein in the usual care group compared to 1599 (458) kcal and 79 (23) g protein in the intervention group, ($p = 0.001$ and < 0.0001, respectively). Including all energy sources for the duration of ICU stay increased the mean energy to 1331 (720) kcal and 1718 (468) kcal in the usual and intervention groups,

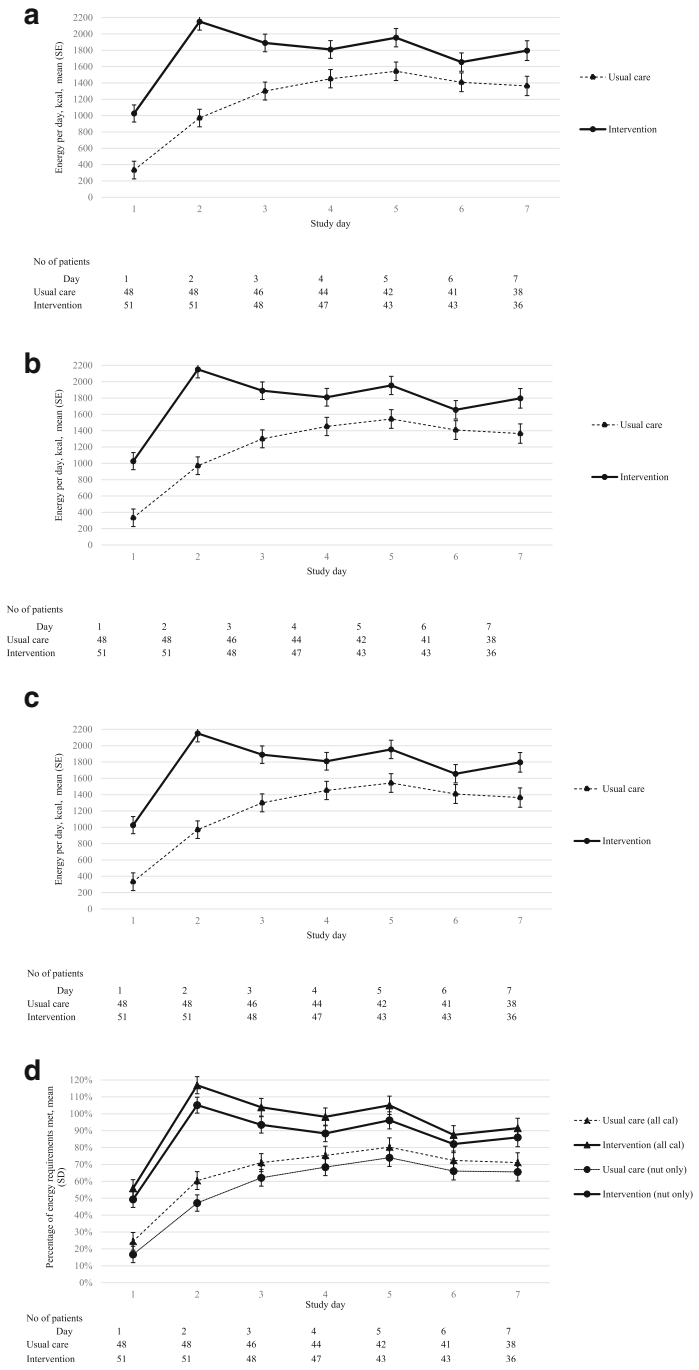

Fig. 2 Daily energy and protein intake during the 7-day intervention period. Mean standard error (SE) daily energy and protein intake during the 7-day intervention period: Panel (**a**) Energy from nutrition only (kcal); Panel (**b**) energy from all sources (kcal); Panel (**c**) protein from nutrition (g); Panel (**d**) percentage of estimated energy requirements received from nutrition and all sources

respectively, $p < 0.0001$. Table 2 provides further information about energy delivery during the intervention period and ICU stay. There were ten patients in the usual care group who received PN during the intervention period; the median time to commencement was 3 [1–4] days.

Other outcomes

Morning BGL was lower in the usual care (mean 7.9 (1.9) mmol/L) compared to the intervention (8.5 (1.2) mmol/L, $p = 0.03$) group, as was daily insulin dose (median 8 [0–35] compared to 24 [4–69] units in the usual care and intervention groups, respectively, $p = 0.03$). There were 16 (33%) and 18 (35%) patients in the usual care and intervention groups, respectively, who received at least one new antibiotic during the study period, $p = 0.84$. There were no significant differences between the two groups in the duration of mechanical ventilation, ICU or hospital stay, mortality, witnessed complications of feeding or functional outcomes (Table 3).

Discussion

Key findings

Our multicentre, pilot, randomized trial in 100 critically ill adults receiving EN, found that an individually titrated supplemental PN strategy was feasible and effective in delivering increased energy, closer to estimated requirements than usual care. There were no differences between our two groups in any clinical outcomes.

Previous studies have found that use of supplemental PN can deliver additional energy in critical illness when combined with EN [8, 11, 27, 28]. However, the largest randomized trial addressing this question, achieved no more than approximately 74% of estimated energy requirements [7]. Our trial found that a supplemental PN strategy could instead be used to increase energy delivery closer to the patient's estimated energy requirement and includes several different approaches to help protect against overfeeding, an essential element of any supplemental PN intervention.

Despite many interventions aiming to improve energy delivery, the timing, and the amount of energy to provide in critical illness remains uncertain. Recently, a U-shaped relationship between energy needs and clinical outcomes has been suggested, with just 70% of the measured requirement being optimal for patient outcomes in a cohort trial [29]. It has been suggested that increased macronutrient delivery early in ICU admission may be harmful by inhibiting autophagy, an important and protective cell process for maintenance of organ function [7, 30]. These factors may explain indications of harm in patients who received early supplemental PN (74% of energy requirement) compared to those who received late PN (30% of energy requirement) in a large

Table 2 Energy and protein delivery during the 7-day intervention and ICU stay

Variable	Usual care ($n = 48$)	Intervention ($n = 51$)	p value
7-day intervention period, mean (SD)			
Delivery of energy from EN and PN, kcal	1130 (601)	1712 (511)	<0.0001
Proportion of energy from EN and PN, %	54 (28)	83 (22)	<0.0001
Energy from EN and PN, kcal/kg	13 (6.6)	20.6 (6.3)	<0.0001
Delivery of energy from all sources, kcal	1298 (671)	1892 (540)	<0.0001
Proportion of energy from all sources, %	62 (31)	92 (22)	<0.0001
Energy from all sources, kcal/kg	16.8 (8.2)	24.9 (6.4)	<0.0001
Delivery of protein, g	53.3 (28.5)	85.6 (25.4)	<0.0001
Proportion of protein, %	51 (25)	86 (23)	<0.0001
Protein delivery, g/kg	0.6 (0.3)	1.0 (0.3)	<0.0001
ICU stay, mean (SD)			
Delivery of energy from EN and PN, kcal	1212 (676)	1599 (458)	0.001
Proportion of energy from EN and PN, %	58 (30)	78 (21)	<0.0001
Energy from EN and PN, kcal/kg	13.9 (7.4)	19.2 (5.7)	<0.0001
Delivery of energy from all sources, kcal	1331 (720)	1718 (468)	0.002
Proportion of energy from all sources, %	63 (32)	84 (21)	<0.0001
Energy from all sources, kcal/kg	15.3 (7.8)	20.6 (5.7)	<0.0001
Delivery of protein, g	57 (33)	79 (23)	<0.0001
Proportion of protein, %	54 (29)	80 (22)	<0.0001
Protein delivery, g/kg	0.7 (0.3)	1.0 (0.3)	<0.0001

EN enteral nutrition, *PN* parenteral nutrition; *kcal* kilocalorie, *SD* standard deviation

Table 3 Clinical outcomes

Variable	n	Usual care	n	Intervention	*p* value
Patients with reported complications during study period, n (%)					
GRV > 300 ml on study days 1–7	48	23 (48)	51	28 (55)	0.49
Abdominal distention		14 (29)		16 (31)	0.81
Vomiting		8 (17)		13 (26)	0.28
Calories from propofol over the study period, kcal, median [IQR]	48	0 [0-110]	51	0 [0-160]	0.48
Blood test results on study day 7:					
ALP, U/L, mean (SD)	38	165 (81)	33	183 (103)	0.40
ALT, U/L, median [IQR]	38	50 [23-86]	34	58 [30-102]	0.54
GGT, U/L, mean (SD)	38	196 (125)	34	216 (126)	0.51
Bilirubin, mmol/L, median [IQR]	38	15 [11-29]	35	24 [14-53]	0.47
WCC, 0^9/L, mean (SD)	38	18 (10)	36	20 (10)	0.18
TG, mmol/L, median [IQR]	37	2 [1-3]	32	2 [2-4]	0.18
CRP, mg/L, median [IQR]	37	110 [78-185]	32	153 [105-216]	0.06
Mean SOFA over study duration, mean (SE)	48	8.0 (0.4)	51	8.2 (0.4)	0.75
Duration of mechanical ventilation, days, median [IQR]	48	8 [5-18]	51	10 [6-15]	0.68
Duration of ICU stay, days, median [IQR]	48	11 [6-17]	51	11 [5-17]	0.83
Duration of hospital stay, days, mean (SD)	48	23 (17)	51	22 (21)	0.85
Survival					
ICU D/C, n (%)		37 (77)		36 (71)	0.46
Hospital D/C, n (%)	48	37 (77)	51	35 (67)	0.37
90 days, n (%)		35 (73)		32 (63)	0.28
180 days, n (%)		35 (73)		32 (63)	0.28
EQ-5D-3L					
Hospital D/C, mean (SD)	17	0.32 (0.36)	27	0.25 (0.34)	0.54
90 days, median [IQR]	29	0.76 (0.23)	35	0.69 (0.24)	0.29
180 days, mean (SD)	29	0.77 (0.24)	35	0.75 (0.26)	0.76
Hand grip strength at hospital D/C, kg, mean (SD)	24	20 (8)	19	19 (13.5)	0.71
ICU mobility scale at hospital D/C, median [IQR]	33	8 [4-10]	25	9 [5-10]	0.58
Mid arm muscle circumference, hospital D/C, cm, mean (SD)	25	30 (5)	22	30 (5)	0.91

The highest level of function scale ranges from 0 to 10 with 0 being 'no mobility' (lying in bed) and 10 being 'Walking independently without a gait aid' [23].
ALT alanine aminotransferase, *ALP* alkaline phosphatase, *BMI* body mass index, *CRP* C-reactive protein, *D/C* discharge, *ED* Emergency department, *EQ-5D-3L* EuroQuol-5 Dimension 3 Level, *GGT* gamma glutamyltransferase, *GRV* gastric residual volume, *ICU* intensive care unit, *IQR* interquartile range, *SD* Standard deviation, *SOFA* Sequential Organ Failure Assessment, *TG* triglyceride, *WCC* white cell count

RCT [7]. Furthermore, a recent randomized trial found no advantage from increasing energy delivery using PN to requirements guided by indirect calorimetry during the first week of critical illness, although the trial was likely to be underpowered for clinical outcomes [28]. And a recent meta-analysis suggested higher infectious complications in a sub-group of studies where patients received considerably more energy from PN compared to EN alone [31].

It is also possible that energy requirements during critical illness vary during the time course of critical illness. Early in ICU admission, endogenous glucose supplies are mobilised (up to 1500 kcal/day) and metabolic rate reduces as a result of the metabolic response to illness [32]. Less energy from exogenous sources may then be required early in critical illness, and this may explain why studies of short duration hypocaloric nutrition, early in illness, have suggested equivalence to usual care [7, 33, 34]. We found no indicators of overfeeding in our trial but indirect calorimetry was not used. Later in the time course of critical illness, energy requirements may change and increase as a patient's metabolism switches from a catabolic to anabolic state. It is plausible that provision of nutrition in this anabolic phase may be more important than in the early phase. These factors may partially explain why nutrition trials, which have predominately investigated the early phase of illness, have been unable to demonstrate patient benefit to date.

Furthermore, the use of predictive equations to estimate energy expenditure during critical illness is known to be inaccurate when compared to indirect calorimetry [35–37]. Use of indirect calorimetry to guide energy delivery may result in improved clinical and functional outcomes; however, this remains to be determined in future prospective controlled trials.

Despite these concerns, many observational studies have suggested higher energy delivery is positively associated with improved clinical outcomes [15–18, 38]. And, even in the absence of randomized trial data in support, some best practice guidelines recommend the delivery of energy to approximate estimated energy requirements [1–4]. The recommendations from best practice nutrition guidelines need to be interpreted carefully however; some have not been updated in recent years (when critical care nutrition research has been prolific), and all are developed with different methodologies. Both of these factors complicate comparisons and interpretation of the evidence [1–4, 12].

Strengths and limitations

Our usual care patients received energy delivery comparable with current clinical practice as reported in recent cohort studies and multiple approaches to reduce the risk of overfeeding were used [5, 6]. We did observe a significantly higher dose of insulin in our intervention group, which could simply reflect the increased dextrose load or which instead could be an early indication of overfeeding. Rates of hypoglycemia were not different between our groups. On only 1 of 7 intervention days, was energy delivery greater than the estimated requirements (117% of estimated energy requirements on day 3) and the effect of this single day on overall trial outcomes cannot be determined. After study day 3, while still remaining statistically significant, the energy difference between our two groups was relatively small at approximately 200 kcal/day. Though this did remain statistically significant this relatively small difference may not be clinically significant. Our trial was designed as a feasibility study, has small patient numbers, and therefore was not powered to detect differences in clinical outcomes. Our significant proportion of cardiovascular patients may also limit generalizability. We used 'administration of new antibiotics' as a surrogate marker for development of infective complications; however, the safety of PN when applied in a modern ICU setting has recently been challenged in two large RCTs [13, 14]. Our loss to follow-up for our functional secondary outcomes measured at ICU and hospital discharge was also significant as patients were often unable to participate in the assessments. Finally, data collection on nutrition intake ceased when oral intake commenced in ICU, however the contribution of this oral intake to overall energy balance is likely to be small and balanced between the two groups.

Conclusions

Our individually titrated supplemental PN strategy was feasible and effective at increasing energy delivery closer to estimated requirements in critically ill adults. To determine the impact of this strategy on patient outcomes, or to determine the optimal timing for such a strategy during the changing time course of critical illness would require substantially larger, carefully timed, randomized trials.

Additional file

Additional file 1: Supplemental parenteral nutrition versus usual care in critically ill adults: a pilot randomized controlled study. (DOCX 94 kb)

Abbreviations

APACHE: Acute Physiology and Chronic Health Evaluation II; BGL: Blood glucose level; CBW: Calculated body weight; D/C: Discharge; ED: Emergency department; EN: Enteral nutrition; EQ-5D-3L: EuroQuol-5 Dimension 3 Level; ICU: Intensive care unit; kcal: Kilocalorie; LOS: Length of stay; MV: Mechanical ventilation; PN: Parenteral nutrition; RCT: Randomized controlled trial; SOFA: Sequential Organ Failure Assessment

Acknowledgements

Thank you to Baxter Healthcare Corporation for the funding associated with this trial. Thank you to all participating staff and centers.
Members of the Supplemental Parenteral Nutrition Clinical Investigators for PubMed indexing are as follows (listed as participating sites, principal investigators, research coordinators, dietitians and method center staff):
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Christchurch Hospital, Christchurch, New Zealand: Seton Henderson, Jan Mehrtens, Anna Morris, Emmeline Minto.
University Hospital Geelong, Geelong, Australia: Neil Orford, Allison Bone, Tania Elderkin, Tania Salerno, Roy Hoevenaars.
The Alfred, Melbourne, Australia: Owen Roodenburg, Meredith Young, Phoebe McCracken, Jasmin Board, Shirley Vallance, Emma Ridley, Eleanor Capel.
Wellington Hospital, Wellington, New Zealand: Paul Young, Leanlove Navarra, Anna Hunt, Sally Hurford, Lynn Andrews, Diane Mackle, Catherine Boulton.
Australian and New Zealand Intensive Care Research Centre: Michael Bailey, Andrew Davies, Adam Deane, Carol Hodgson, Emma Ridley.
The study management committee members were:
Shay McGuinness, Emma Ridley, Andrew Davies, Rachael Parke, David (Jamie) Cooper, Lyn Gillanders, Colin McArthur, Neil Orford, Owen Roodenburg

Funding

This investigator-initiated study was funded by an unrestricted research grant from Baxter Healthcare Corporation. The interventional PN was manufactured by Baxter Healthcare Corporation and provided at no charge. Baxter Healthcare Corporation was not involved in the original development of the trial concept, trial management, data collection, analysis or interpretation of the data. The final version of the study manuscript was reviewed by Baxter Healthcare Corporation prior to submission as per the funding agreement.

Availability of data and materials

On reasonable request, data from this study are available from the corresponding author.

Authors' contributions
ER, AD, RP, CM, LG, DJC, and SM were responsible for research design, research conduct and writing of the manuscript. MB was responsible for data analysis and writing of the manuscript. ER and SM had primary responsibility for final content of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Ethics approval was obtained from The Alfred Hospital Research and Ethics committee for Australia (HREC/12/Alfred/68) and the Northern A Health and Disability Ethics Committee in New Zealand (13/NTA/52), as well as the Monash University Research and Ethics Committee (CF13/3812 – 2013001928). Written informed consent or agreement to participate was obtained from the patient's legal surrogate, relative/friend or whanau member at the time of enrolment. Patients were approached at a later time if it was appropriate and they regained the capacity to provide consent to continue to participate.

Consent for publication
Not applicable

Competing interests
AD is an employee of Baxter Healthcare Corporation, Australia. This position commenced in September 2015, which was after the trial had been designed and recruitment had begun. There are no other competing interests for any other authors.

Publisher's Note

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Received: 21 September 2017 Accepted: 2 January 2018
Published online: 23 January 2018

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5.4 Additional File for manuscript "Supplemental parenteral nutrition versus usual care in critically ill adults: a pilot randomised controlled study"

ADDITIONAL FILE

Supplemental parenteral nutrition in critically ill adults: a pilot randomized controlled study

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[7] Nutrition and Dietetics, Auckland City Hospital, Park Road, Grafton, Auckland New Zealand

[8] Faculty of Medical and Health Sciences, University of Auckland, Park Road, Grafton, Auckland, New Zealand

Contents

1. Inclusion and exclusion criteria

Inclusion criteria

Patients in intensive care who meet all of the following:

- Admitted to intensive care between 48 hours and 72 hours previously
- Mechanically ventilated at the time of enrolment and expected to remain ventilated until the day after tomorrow
- At least 16 years of age
- Have central venous access suitable for parenteral nutrition (PN) solution administration
- Have 1 or more organ system failure (respiratory, cardiovascular or renal) related to their acute illness defined as:
    1. $PaO_2/FiO_2 \leq 300$ mmHg*
    2. Currently on 1 or more continuous vasopressor infusion which were started at least 4 hours ago at a minimum dose of :
        a. Dopamine greater than 5 mcg/kg/min
        b. Noradrenaline ≥ 0.1mcg/kg/min
        c. Adrenaline ≥ 0.1 mcg/kg/min
        d. Any dose of total vasopressin
        e. Milrinone >0.25mcg/kg/min)
    3. Renal dysfunction defined as

        In patients without known renal disease:
        a. Serum Creatinine > 171 mmol/l OR
        b. Currently receiving renal replacement therapy

        In patients with known renal disease:
        a. an absolute increase of > 50% in serum Creatinine from baseline OR
        b. Currently receiving renal replacement therapy
    4. Currently has an intracranial pressure monitor or ventricular drain in situ*
    5. Currently receiving extracorporeal membrane oxygenation*
    6. Currently has a ventricular assist device*

Exclusion criteria

Patients will be excluded if:

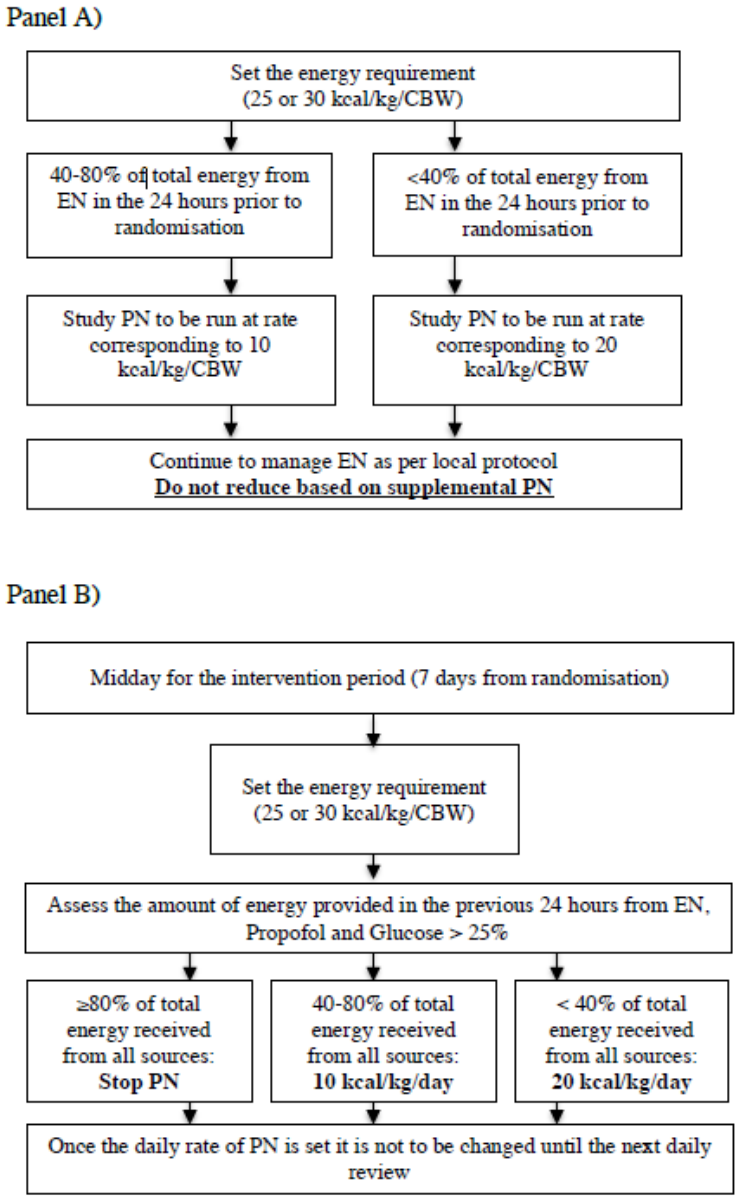
- Both enteral nutrition (EN) and PN cannot be delivered at enrolment (i.e. either an enteral tube or a central venous catheter cannot be placed or clinicians feel that EN or PN cannot be safely administered due to any other reason).
- Currently receiving PN
- Standard PN solutions cannot be delivered at enrolment (i.e. clinicians believe that a patient definitely needs a specific parenteral nutrition formulation (e.g. glutamine-supplementation or specific lipid formulation).
- Death is imminent or deemed highly likely in the next 96 hours.
- There is a current treatment limitation in place or the patient is unlikely to survive to 6 months due to underlying illness
- More than 80% of energy requirements have been satisfactorily delivered via the enteral route in the last 24 hours.
- Are known to be pregnant
- The treating clinician does not believe the study to be in the best interest of the patient

·Modified from $PaO_2/FiO_2 \leq 200$ mmHg during protocol amendment, after recruitment commenced

·Added during protocol amendment, after recruitment commenced

2. Figure 1: Study processes in the intervention arm

Panel A) Study processes at randomization; Panel B) Daily adjustment of intervention



CBW: Calculated body weight; EN: Enteral *nutrition*; PN: Parenteral nutrition; kcal: Kilocalorie

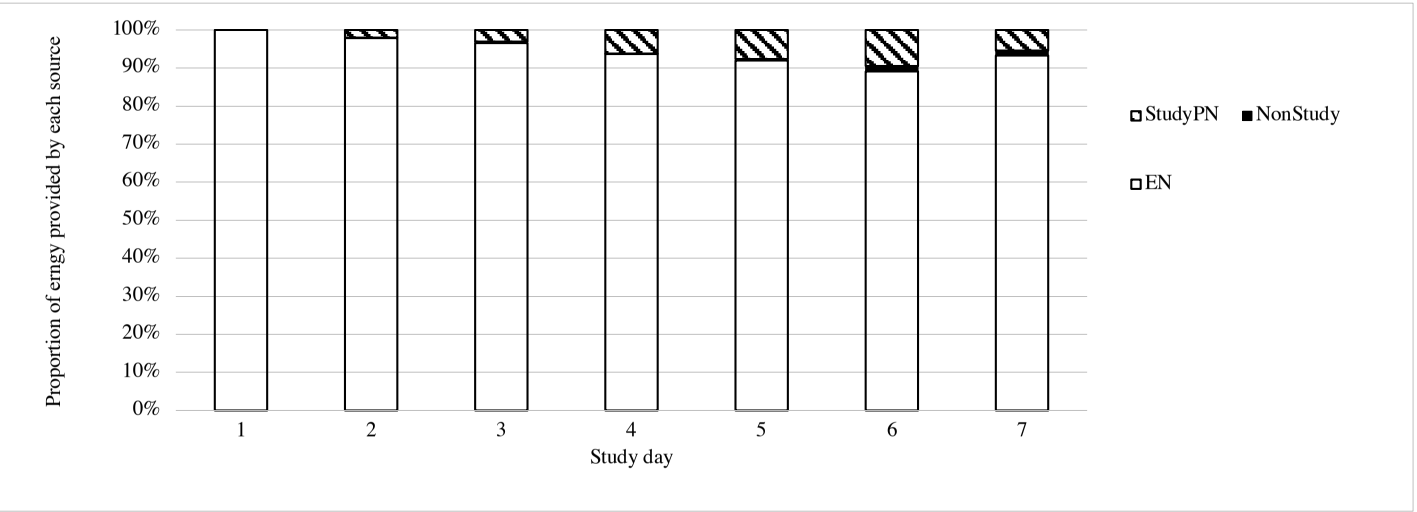
3. Table 1: Product information for Olimel N9-840E/Triomel 9 with electrolytes and additions

Contents	Compounded Ready To Use Parenteral Nutrition (per 1500ml bag)
Total nitrogen (g)	13.5
Amino acid (g)	85.4
Glucose (g) (Hydrous)	181.5 (equal to Anhydrous 165 g labelled on compounded bag)
Lipid as ClinOleic (g)	60
Total energy (kcal)	1600
Non protein energy (kcal)	1260
Glucose energy (kcal)	660
Lipid energy (kcal)	600
Sodium (mmol)	52.5 (New Zealand) 54 (Australia - includes 1.5 mmol from Sodium Ascorbate)
Potassium (mmol)	45
Magnesium (mmol)	6.0
Calcium (mmol)	5.3
Phosphate (mmol)	22.5
Acetate (mmol)	80
Chloride (mmol)	68
Osmolarity (mOsm/L)	1310
Additions per bag of parenteral nutrition	
Baxter's Multiple Trace Elements with Iron (mcg)	Per ml (note 10ml is added to each parenteral nutrition bag)
Zinc	650
Copper	130
Manganese	27
Chromium	1
Selenium	3.2
Iodide	13
Molybdenum	1.9
Iron	120
Ascorbate (Vitamin C) for stability (mg per bag) Sodium Ascorbate in Australia and Ascorbate acid in NZ	300
Cernevit (ml per bag)	5

4. <u>Figure 2: Mean proportion of daily energy intake provided by enteral and parenteral nutrition during the 7 day intervention period</u>

Panel A) Components of total energy intake from EN, PN and non-study PN in usual care arm; Panel B) Components of total energy intake from EN, PN and non-study PN in intervention arm

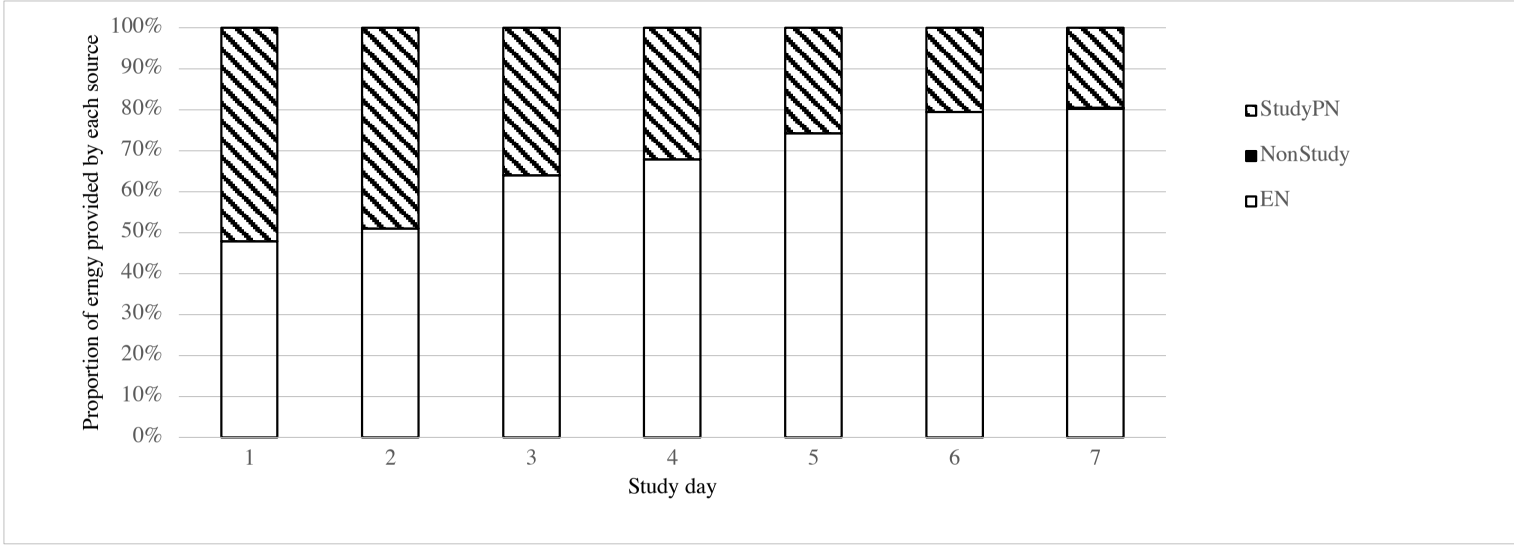
Panel A)



EN: Enteral nutrition; PN: Parenteral nutrition

Day	1	2	3	4	5	6	7
Usual care (n)	48	48	46	44	42	41	38
Proportion of energy requirement provided in total	24%	60%	71%	75%	80%	72%	71%

Panel B)



EN: Enteral *nutrition*; PN: Parenteral nutrition

Day	1	2	3	4	5	6	7
Intervention (n)	51	51	48	47	43	43	36
Proportion of energy requirement provided in total	56%	117%	104%	98%	105%	88%	91%

5. Protocol deviations during study period

Deviation explanation	Times occurred during study
Patient randomised but not eligible	3 (2 intervention arm and 1 usual care)
Study PN not given when indicated (Supp PN group only)	10
Other types	11
Study PN run at the incorrect rate i.e. run at 10kcal/kg when it should have been 20kcal/kg	0

6. Adverse events

Event explanation	Times occurred during study	Related to the study
Medically unstable patient with PEA arrest	1 (Intervention arm)	Unrelated
Persistent hyperglycaemia	1 (Intervention arm)	Possibly related

Chapter appendices:

5.4.1 Clinicaltrials.gov trial registration

ClinicalTrials.gov PRS
Protocol Registration and Results System

ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: July 31, 2016

ClinicalTrials.gov ID: NCT01847534

Study Identification

Unique Protocol ID:	ANZIC RC AD 003
Brief Title:	Supplemental Parenteral Nutrition in Critically Ill Adults: A Pilot Randomised Controlled Trial
Official Title:	Supplemental Parenteral Nutrition in Critically Ill Adults: A Pilot Randomised Controlled Trial
Secondary IDs:	

Study Status

Record Verification:	July 2016
Overall Status:	Completed
Study Start:	February 2014 []
Primary Completion:	January 2016 [Actual]
Study Completion:	July 2016 [Actual]

Sponsor/Collaborators

Sponsor:	Australian and New Zealand Intensive Care Research Centre
Responsible Party:	Sponsor
Collaborators:	Baxter Healthcare Corporation

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Unapproved/Uncleared Device:	No
U.S. FDA IND/IDE:	No
Human Subjects Review:	Board Status: Approved Approval Number: HREC/12/Alfred/68 Board Name: Alfred Health Human Ethics Committee Board Affiliation: Alfred Health Phone: 03 90763619 Email: research@alfred.org.au Address:

Data Monitoring:	No
FDA Regulated Intervention:	Yes
Section 801 Clinical Trial:	Yes

Study Description

Brief Summary: One of the essential treatments for assisting patients in their recovery from illness is the provision of nutrition in a liquid form which is delivered into the stomach or as a fluid into the vein. Until recently the benefits of nutrition were undervalued in the critically ill, however, it has now become clear that targeted nutrition can positively affect a person's outcome. This is particularly important for patients who are significantly unwell and require increased amounts of nutrition to support recovery. Inadequate nutrition therapy leads them to rapidly lose weight, predominantly in the form of muscle loss which greatly contributes to their poor recovery.

Whilst nutrition is essential for recovery, there are several issues with the delivery of nutrition via the stomach (the most commonly used method of delivering nutrition in the critically ill). For many reasons, patients are unable to tolerate large quantities of nutrition via the stomach and in addition to this there are hospital or procedural reasons for nutrition being turned off for lengthy periods of time. As such, this results in patients being delivered only about half of the nutrition that is planned. One potential way to overcome this is to deliver nutrition via the vein, whilst nutrition into the stomach continues, with the aim to meet the energy gap that is lost by inadequate nutrition via the stomach.

In this study of 100 patients, we will deliver combined nutrition via the vein and stomach in 50 patients and the other 50 patients will receive nutrition as per normal practice. We will measure important outcomes for these patients to determine if this allows us to meet significantly more of their nutrition needs. This study will also help us determine how best to design a larger study of this strategy.

Detailed Description: The principal objectives are:

1. To determine whether the supplemental Parenteral Nutrition (PN) strategy leads to the delivery of increased amounts of total nutrition (measured as energy delivered), and is safe in regards to adverse effects.
2. To measure the clinical outcomes in patients receiving both study strategies to provide information to assist design of a larger randomized controlled trial.

Secondary objectives in a sub-set of patients are:

3. To determine whether the supplemental PN strategy leads to improved nitrogen balance.
4. To determine both the nutritional requirements and nutritional intake of critically ill patients during the period of hospitalization after transfer from the Intensive Care Unit (ICU).

Conditions

Conditions:	Multiple Organ Failure Critical Illness
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Supportive Care
Study Phase:	Phase 2/Phase 3
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	None (Open Label)
Allocation:	Randomized
Enrollment:	100 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Standard Care Standard care: Nutrition will be managed as per best practice and local policy including the use of small bowel feeding tubes, prokinetics and PN if required to meet nutrition needs.	Standard Care
Experimental: Supplemental PN Supplemental PN to complete inadequate EN provision 1. Patients allocated to the supplemental PN (intervention) group will have PN commenced within 2 hours of randomisation. The starting dose of PN will be determined by the amount of energy received in the 24 hours prior to randomisation. 2. EN will be managed as per local protocol however EN must not be reduced based on the supplemental PN being administered. 3. The adequacy of nutrition provision from both PN and EN will be assessed at midday each day for 7 days or until ICU discharge. The dose of PN will be adjusted according to a prespecified schedule.	Supplemental PN

Outcome Measures

Primary Outcome Measure:

1. Total energy amount delivered
   The primary outcome for this pilot study is the total energy amount delivered from nutrition therapy (ie. from Enteral Nutrition (EN) and from supplemental PN, if delivered) over the first 7 days of the study period.

   [Time Frame: First 7 days of the study period]

Eligibility

Minimum Age:	16 Years
Maximum Age:	

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

Patients in intensive care who meet all of the following:

- Admitted to intensive care between 48 hours and 72 hours previously
- Mechanically ventilated at the time of enrollment and expected to remain ventilated until the day after tomorrow
- At least 16 years of age
- Have central venous access suitable for PN solution administration
- Have 1 or more organ system failure (respiratory, cardiovascular or renal) related to their acute illness defined as:

1. Partial pressure of oxygen (PaO2) / Fraction of Inspired oxygen (FiO2) ratio ≤ 300 mmHg
2. Currently on 1 or more continuous vasopressor infusion which were started at least 4 hours ago at a minimum dose of :

    a. Dopamine greater than 5 mcg/kg/min
    b. Noradrenaline ≥ 0.1mcg/kg/min
    c. Adrenaline ≥ 0.1 mcg/kg/min
    d. Any dose of total vasopressin
    e. Milrinone >0.25mcg/kg/min)
3. Renal dysfunction defined as

    In patients without known renal disease:

    a. serum creatinine > 171 mmol/l OR
    b. Currently receiving renal replacement therapy

    In patients with known renal disease:
    c. an absolute increase of > 50% in creatinine from baseline OR
    d. Currently receiving renal replacement therapy
4. Currently has an intracranial pressure monitor or ventricular drain in situ
5. Currently receiving extracorporeal membrane oxygenation
6. Currently has a ventricular assist device

Exclusion Criteria:

- Both EN and PN cannot be delivered at enrollment (i.e. either an enteral tube or a central venous catheter cannot be placed or clinicians feel that EN or PN cannot be safely administered due to any other reason).
- Currently receiving PN
- Standard PN solutions cannot be delivered at enrolment (i.e. clinicians believe that a patient definitely needs a specific parenteral nutrition formulation (e.g. glutamine-supplementation or specific lipid formulation).
- Death is imminent or deemed highly likely in the next 96 hours.
- There is a current treatment limitation in place or the patient is unlikely to survive to 6 months due to underlying illness
- More than 80% of energy requirements have been satisfactorily delivered via the enteral route in the last 24 hours.
- Are known to be pregnant

Contacts/Locations

Central Contact Person: Emma Ridley, MPH

Email: [redacted]

Central Contact Backup: Shay McGuinness, Dr

Study Officials:

Locations: Australia, VIC
The Alfred Hospital
Melbourne, VIC, Australia, 3004
Principal Investigator: Owen Roodenburg
Sub-Investigator: Emma Ridley
Sub-Investigator: Ibolya Nyulasi
Sub-Investigator: Carlos Scheinkestel

Australia
Geelong Hospital
Geelong, Australia
Principal Investigator: Neil Orford

New Zealand
Auckland City Hospital (CVICU)
Auckland, New Zealand
Principal Investigator: Shay McGuinness

Auckland City Hospital (DCCM)
Auckland, New Zealand
Principal Investigator: Colin McArthur

Christchurch Hospital
Christchurch, New Zealand
Contact: Seton Henderson Seton.Henderson@cdhb.health.nz
Principal Investigator: Seton Henderson

Wellington Hospital
Wellington, New Zealand
Contact: Paul Young
Principal Investigator: Paul Young

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

5.4.2 Health and Research Ethics Committee Approvals: Monash University, The Alfred Health Research and Ethics Committee (Victorian approval) and the Health and Disability Ethics Board (New Zealand approval)

MONASH University

Monash University Human Research Ethics Committee (MUHREC)
Research Office

Human Ethics Certificate of Approval

This is to certify that the project below has been approved by the Monash University Human Research Ethics Committee under the Memorandum of Agreement with the Alfred

Project Number:	**CF13/3812 - 2013001928**
Project Title:	**Supplemental parenteral nutrition in critically ill patients: A pilot randomised controlled study**
Chief Investigator:	**Dr Owen Roodenburg**
Approved:	**From: 16 December 2013 to 16 December 2018**

Terms of approval - ***Failure to comply with the terms below is in breach of your approval and the Australian Code for the Responsible Conduct of Research.***

1. Approval is only valid whilst you hold a position at Monash University and approval at the primary HREC is current.
2. **Future correspondence:** Please quote the project number and project title above in any further correspondence.
3. **Final report:** A Final Report should be provided at the conclusion of the project. MUHREC should be notified if the project is discontinued before the expected date of completion.
4. **Retention and storage of data:** The Chief Investigator is responsible for the storage and retention of original data pertaining to a project for a minimum period of five years.

[redacted]

Professor Nip Thomson
Chair, MUHREC

cc: Ms Emma Ridley; Dr Neil Orford; Assoc Prof Ibolya Nyulasi; Prof Jamie Cooper; Prof Carlos Scheinkestel;

Postal – Monash University, Vic 3800, Australia
[redacted]
ABN 12 377 614 012 CRICOS Provider #00008C

TheAlfred

ETHICS COMMITTEE CERTIFICATE OF APPROVAL

This is to certify that

Project No: HREC/12/Alfred/68 (Local Reference: Project 19/13)

Project Title: Supplemental Parenteral Nutrition in Critically Ill Patients: A Pilot Randomised Controlled Study

Principal Researcher: Dr Owen Roodenburg

*was considered by the Ethics Committee on **24-Jan-2013**, meets the requirements of the National Statement on Ethical Conduct in Human Research (2007) and was **APPROVED** on **18-Jul-2013***

It is the Principal Researcher's responsibility to ensure that all researchers associated with this project are aware of the conditions of approval and which documents have been approved.

The Principal Researcher is required to notify the Secretary of the Ethics Committee, via amendment or progress report, of

- Any significant change to the project and the reason for that change, including an indication of ethical implications (if any);
- Serious adverse effects on participants and the action taken to address those effects;
- Any other unforeseen events or unexpected developments that merit notification;
- The inability of the Principal Researcher to continue in that role, or any other change in research personnel involved in the project;
- Any expiry of the insurance coverage provided with respect to sponsored clinical trials and proof of re-insurance;
- A delay of more than 12 months in the commencement of the project; and,
- Termination or closure of the project.

Additionally, the Principal Researcher is required to submit

- A Progress Report on the anniversary of approval and on completion of the project *(forms to be provided)*;

The Ethics Committee may conduct an audit at any time.

All research subject to the Alfred Hospital Ethics Committee review must be conducted in accordance with the National Statement on Ethical Conduct in Human Research (2007).

The Alfred Hospital Ethics Committee is a properly constituted Human Research Ethics Committee in accordance with the National Statement on Ethical Conduct in Human Research (2007).

SPECIAL CONDITIONS

A report to be submitted to the Ethics Committee over the first three months after ethics approval and covering all Victorian Sites covered by this application detailing:

1. *The total number of participants enrolled.*
2. *Of those, how many were enrolled:*
    a. *Under procedural authorisation (PA)*
    b. *By person responsible (PR)*
3. *Of those enrolled under PA:*
    a. *In how many instances was PR subsequently sought?*
    b. *In how many instances was continuing consent from the participant subsequently sought?*
4. *Of those enrolled under PA:*
    a. *The average timeframe during which attempts were made to contact the PR.*
    b. *The average number of attempts made to contact the PR.*

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Ethics Committee

Certificate of Approval of Amendments

This is to certify that amendments to

Project: **HREC/12/Alfred/68 (Local Reference: Project 19/13) Supplemental Parenteral Nutrition in Critically Ill Patients: A Pilot Randomised Controlled Study**

Principal Researcher: **Dr Owen Roodenburg**

Protocol: **AD003**
Amendment: **Protocol Version 7**
Protocol Amendment dated: **17-May-2013**
Sub-study to be conducted at Alfred Health only

Master PICFs:
Master Participant Information & Consent Form – Participant post Procedural Authorisation: **Version 3** dated: **13-Aug-2013**
Master Participant Information & Consent Form – Participant post Person Responsible: **Version 3** dated: **13-Aug-2013**
Master Participant Information & Consent Form – Mature Minor post Parent/Guardian: **Version 2** dated: **13-Aug-2013**
Master Participant Information & Consent Form –Parent/Guardian: **Version 3** dated: **13-Aug-2013**
Master Participant Information & Consent Form – Person Responsible: **Version 3** dated: **13-Aug-2013**
Master Participant Information & Consent Form – Person Responsible post Procedural Authorisation: **Version 3** dated: **13-Aug-2013**

The Alfred Hospital Master PICFs:
Master Participant Information & Consent Form – Participant post Procedural Authorisation: **Version 3** dated: **13-Aug-2013** Local Governance date: **13-Aug-2013**
Master Participant Information & Consent Form – Participant post Person Responsible: **Version 3** dated: **13-Aug-2013** Local Governance date: **13-Aug-2013**
Master Participant Information & Consent Form – Mature Minor post Parent/Guardian: **Version 2** dated: **13-Aug-2013** Local Governance date: **13-Aug-2013**
Master Participant Information & Consent Form –Parent/Guardian: **Version 3** dated: **13-Aug-2013** Local Governance date: **13-Aug-2013**
Master Participant Information & Consent Form – Person Responsible: **Version 3** dated: **13-Aug-2013** Local Governance date: **13-Aug-2013**
Master Participant Information & Consent Form – Person Responsible post Procedural Authorisation: **Version 3** dated: **13-Aug-2013** Local Governance date: **13-Aug-2013**

have been approved under the Consultative Council for Clinical Trial Research (CCCTR) Streamlined Ethics Review Program (SERP) in accordance with your amendment

application dated **19-Aug-2013** on the understanding that you observe the National Statement on Ethical Conduct in Human Research.

It is now your responsibility to ensure that all people associated with this particular research project are made aware of what has actually been approved and any caveats specified in correspondence with the Ethics Committee. Any further change to the application which is likely to have a significant impact on the ethical considerations of this project will require approval from the Ethics Committee.

Chair, Ethics Committee (or delegate) Date: **08-Oct-2013**

R Frew
Secretary, Ethics Committee

All research subject to Alfred Hospital Ethics Committee review must be conducted in accordance with the National Statement on Ethical Conduct in Human Research (2007).

The Alfred Ethics Committee is a properly constituted Human Research Ethics Committee operating in accordance with the National Statement on Ethical Conduct in Human Research (2007).

TheAlfred

Ethics Committee

Certificate of Approval of Amendments

This is to certify that amendments to

Project: **HREC/12/Alfred/68 (Local Reference: Project 19/13) Supplemental Parenteral Nutrition in Critically Ill Patients: A Pilot Randomised Controlled Study**

Principal Researcher: **Dr Owen Roodenburg**

Protocol: **AD003**
Amendment: **Protocol Version 8**
Protocol Amendment dated: **10-Jul-2014**

Master Person Responsible PICF **Version 4** dated: **10-Jul-2014**
Master Person Responsible PICF: Alfred Health **Version 4** dated: **10-Jul-2014**
Master PICF following PR **Version 4** dated: **10-Jul-2014**
Master PICF following PR: Alfred Health **Version 4** dated: **10-Jul-2014**
Master PICF for participant following 42T **Version 4** dated: **10-Jul-2014**
Master PICF for participant following 42T: Alfred Health **Version 4** dated: **10-Jul-2014**
Master PICF for PR following 42T **Version 4** dated: **10-Jul-2014**
Master PICF for PR following 42T: Alfred Health **Version 4** dated: **10-Jul-2014**
Master PICF Parent and guardian **Version 4** dated: **10-Jul-2014**
Master PICF Parent and guardian: Alfred Health **Version 4** dated: **10-Jul-2014**
Master PICF following consent by parent or guardian **Version 4** dated: **10-Jul-2014**
Master PICF following consent by parent or guardian: Alfred Health **Version 4** dated: **10-Jul-2014**

have been approved under *the Consultative Council for Clinical Trial Research (CCCTR) Victorian Streamlined Ethical Review Program (SERP)* in accordance with your amendment application dated **28-Jul-2014** on the understanding that you observe the National Statement on Ethical Conduct in Human Research.

It is now your responsibility to ensure that all people associated with this particular research project are made aware of what has actually been approved and any caveats specified in correspondence with the Ethics Committee. Any further change to the application which is likely to have a significant impact on the ethical considerations of this project will require approval from the Ethics Committee.

Professor John J. McNeil
Chair, Ethics Committee

Date: **16-Sep-2014**

All research subject to Alfred Hospital Ethics Committee review must be conducted in accordance with the National Statement on Ethical Conduct in Human Research (2007).

The Alfred Ethics Committee is a properly constituted Human Research Ethics Committee operating in accordance with the National Statement on Ethical Conduct in Human Research (2007).

TheAlfred

Ethics Committee

Certificate of Approval of Amendments

This is to certify that amendments to

Project: **HREC/12/Alfred/68 (Local Reference: Project 19/13) Supplemental Parenteral Nutrition in Critically Ill Patients: A Pilot Randomised Controlled Study**

Principal Researcher: **Dr Owen Roodenburg**

Protocol: **Version 4**
Amendment: Section 42T SOP Supplemental PN **Version 2** dated: **06-Nov-2014**

have been approved under the Consultative Council for Clinical Trial Research (CCCTR) Streamlined Ethics Review Program (SERP) in accordance with your amendment application dated **17-Feb-2015** on the understanding that you observe the National Statement on Ethical Conduct in Human Research.

It is now your responsibility to ensure that all people associated with this particular research project are made aware of what has actually been approved and any caveats specified in correspondence with the Ethics Committee. Any further change to the application which is likely to have a significant impact on the ethical considerations of this project will require approval from the Ethics Committee.

[redacted]

Professor John J. McNeil
Chair, Ethics Committee

Date: **23-Mar-2015**

All research subject to Alfred Hospital Ethics Committee review must be conducted in accordance with the National Statement on Ethical Conduct in Human Research (2007).

The Alfred Ethics Committee is a properly constituted Human Research Ethics Committee operating in accordance with the National Statement on Ethical Conduct in Human Research (2007).

Health and Disability Ethics Committees
Ministry of Health
[redacted]
0800 4 ETHICS
[redacted]

21 May 2013

Dr Shay McGuinness
CVICU - Ward 48
Auckland City Hospital
Private Bag 92024
Auckland 1142

Dear Dr McGuinness

Re:	**Ethics ref:**	**13/NTA/52**
	Study title:	Supplemental Parenteral Nutrition in Critically Ill Patients: A Pilot Randomized Controlled Study

I am pleased to advise that this application has been *approved* by the Northern A Health and Disability Ethics Committee. This decision was made through the HDEC-Full Review pathway.

- This is a feasibility study which will inform a larger study.
- The Committee queried if participants will undergo any additional tests from standard practice. Dr McGuiness confirmed there is one additional test that is non-invasive and is required to draw accurate conclusions from the study.
- The Committee queried the risks involved in the study. Dr McGuiness stated that there are standard risks with TPN however the participants involved in this study are not at risk as the group has already undergone successful IV feeding. Participants who cannot have TPN are excluded (F.2.1).
- The Committee queried the safety monitoring plan *(Ethical Guidelines for Intervention Studies 2012 para 6.38)*. Dr McGuiness clarified that internal data monitoring will identify risks and SAEs.
- Please ensure 'medical complications' are explained to participants, in particular when unpublished information that is not in the PIS is relevant to patient safety.
- Please submit a copy of the family assent form.
- The Committee requested the following changes to the Participant Information Sheet and Consent Form:
  - please include information about the sub study,
  - please proof read,
  - please include contact details for Maori support.

Conditions of HDEC approval

HDEC approval for this study is subject to the following conditions being met prior to the commencement of the study in New Zealand. It is your responsibility, and that of the

study's sponsor, to ensure that these conditions are met. No further review by the Northern A Health and Disability Ethics Committee is required.

Standard conditions:

1. Before the study commences at *any* locality in New Zealand, all relevant regulatory approvals must be obtained.

2. Before the study commences at *any* locality in New Zealand, it must be registered in a WHO-approved clinical trials registry (such as the Australia New Zealand Clinical Trials Registry, www.anzctr.org.au).

3. Before the study commences at *a given* locality in New Zealand, it must be authorised by that locality in Online Forms. Locality authorisation confirms that the locality is suitable for the safe and effective conduct of the study, and that local research governance issues have been addressed.

After HDEC review

Please refer to the *Standard Operating Procedures for Health and Disability Ethics Committees* (available on www.ethics.health.govt.nz) for HDEC requirements relating to amendments and other post-approval processes.

Participant access to ACC

The Northern A Health and Disability Ethics Committee is satisfied that your study is not a clinical trial that is to be conducted principally for the benefit of the manufacturer or distributor of the medicine or item being trialled. Participants injured as a result of treatment received as part of your study may therefore be eligible for publicly-funded compensation through the Accident Compensation Corporation (ACC).

Please don't hesitate to contact the HDEC secretariat for further information. We wish you all the best for your study.

Yours sincerely,

Dr Brian Fergus
Chairperson
Northern A Health and Disability Ethics Committee

Encl: appendix A: documents submitted
appendix B: statement of compliance and list of members

Appendix A
Documents submitted

Document	*Version*	*Date*
Protocol	v6	22 April 2013
CV for CI	1	04 March 2013
Evidence of CI indemnity	1	06 July 2012
CVs for other Investigators	1	27 March 2013
Survey/questionnaire	1	22 April 2013
PIS/CF	1	04 April 2013
PIS/CF for persons interested in welfare of non-consenting participant	1	04 April 2013
Evidence of scientific review	1	22 April 2013
Reciept of clinical trials registration	1	22 April 2013
Application	1	
Covering Letter	1	23 April 2013

Health and Disability Ethics Committees
Ministry of Health
C/- MEDSAFE, Level 6, Deloitte House
[redacted]
0800 4 ETHICS
[redacted]

15 April 2014

Dr Shay McGuinness
Auckland City Hospital
Cardiothoracic and Vascular Intensive Care Unit
Park Road
Auckland 1023

Dear Dr McGuinness

Re:	**Ethics ref:**	**13/NTA/52/AM03**
	Study title:	Supplemental Parenteral Nutrition in Critically Ill Patients:A Pilot Randomized Controlled Study

I am pleased to advise that this amendment has been *approved* by the Northern A Health and Disability Ethics Committee. This decision was made through the HDEC Expedited Review pathway.

Please don't hesitate to contact the HDEC secretariat for further information. We wish you all the best for your study.

Yours sincerely,

[redacted]

Dr Brian Fergus
Chairperson
Northern A Health and Disability Ethics Committee

Encl: appendix A: documents submitted
appendix B: statement of compliance and list of members

Appendix A
Documents submitted

Document	Version	Date
PIS/CF for persons interested in welfare of non-consenting participant: ICF v3 WgtnChCh_track changes	3	27 March 2014
PIS/CF for persons interested in welfare of non-consenting participant: v3 CVICU_DCCM_track changes	3	27 March 2014
Post Approval Form	1	28 March 2014

Appendix B
Statement of compliance and list of members

Statement of compliance

The Northern A Health and Disability Ethics Committee:

- is constituted in accordance with its Terms of Reference
- operates in accordance with the *Standard Operating Procedures for Health and Disability Ethics Committees*, and with the principles of international good clinical practice (GCP)
- is approved by the Health Research Council of New Zealand's Ethics Committee for the purposes of section 25(1)(c) of the Health Research Council Act 1990
- is registered (number 00008714) with the US Department of Health and Human Services' Office for Human Research Protection (OHRP).

List of members

Name	*Category*	*Appointed*	*Term Expires*
Dr Brian Fergus	Lay (consumer/community perspectives)	01/07/2012	01/07/2015
Dr Karen Bartholomew	Non-lay (intervention studies)	01/07/2013	01/07/2016
Ms Susan Buckland	Lay (consumer/community perspectives)	01/07/2012	01/07/2015
Ms Shamim Chagani	Non-lay (health/disability service provision)	01/07/2012	01/07/2014
Dr Christine Crooks	Non-lay (intervention studies)	01/07/2013	01/07/2015
Mr Kerry Hiini	Lay (consumer/community perspectives)	01/07/2012	01/07/2014
Dr Etuate Saafi	Non-lay (intervention studies)	01/07/2012	01/07/2014
Ms Michele Stanton	Lay (the law)	01/07/2012	01/07/2014

http://www.ethics.health.govt.nz

Health and Disability Ethics Committees
Ministry of Health
C/- MEDSAFE, Level 6, Deloitte House
[redacted]
0800 4 ETHICS
[redacted]

21 August 2014

Dr Shay McGuinness
Auckland City Hospital
Cardiothoracic and Vascular Intensive Care Unit
Park Road
Auckland 1023

Dear Dr McGuinness

Re:	**Ethics ref:**	**13/NTA/52/AM05**
	Study title:	Supplemental Parenteral Nutrition in Critically Ill Patients:A Pilot Randomized Controlled Study

I am pleased to advise that this amendment has been *approved* by the Northern A Health and Disability Ethics Committee. This decision was made through the HDEC Expedited Review pathway.

Please don't hesitate to contact the HDEC secretariat for further information. We wish you all the best for your study.

Yours sincerely,

[redacted]

Dr Brian Fergus
Chairperson
Northern A Health and Disability Ethics Committee

Encl: appendix A: documents submitted
appendix B: statement of compliance and list of members

Appendix A
Documents submitted and approved

Document	Version	Date
Protocol: Amended protocol	8	10 July 2014
Track changes to protocol amendment	8.1	10 July 2014
Summary of protocol changes	1	10 July 2014
Post Approval Form	05	29 July 2014

Appendix B
Statement of compliance and list of members

Statement of compliance

The Northern A Health and Disability Ethics Committee:

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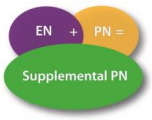
Ms Shamim Chagani	Non-lay (health/disability service provision)	01/07/2012	01/07/2015
Dr Christine Crooks	Non-lay (intervention studies)	01/07/2013	01/07/2015
Mr Kerry Hiini	Lay (consumer/community perspectives)	01/07/2012	01/07/2015
Ms Michele Stanton	Lay (the law)	01/07/2012	01/07/2015

http://www.ethics.health.govt.nz

5.5 Study Case Report Forms for "Supplemental parenteral nutrition in critically ill adults: a pilot randomised controlled trial"



PATIENT STUDY NUMBER |__| |__| |__| - |__| |__| |__|__| |__|

PATIENT INITIALS |__| |__| |__|

1 Baseline data

This paper form can be used to keep all baseline data together. Please remember to enter it into the website.

Demographics				
Where was the patient before this ICU admission?	|__|	Emergency Department		
	|__|	Hospital Ward		
	|__|	Transfer from other ICU		
	|__|	Transfer from another hospital		
	|__|	Operating theatre following EMERGENCY surgery		
	|__|	Operating theatre following ELECTIVE surgery		
Date and time of first hospital admission	|__|__| / |__|__| / |__|__|__|__| [dd/mm/yyyy]		|__|__| - |__|__| (24 hr clock)	
Date and time of first ICU admission	|__|__| / |__|__| / |__|__|__|__| [dd/mm/yyyy]		|__|__| - |__|__| (24 hr clock)	
Date and time of MV commenced	|__|__| / |__|__| / |__|__|__|__| [dd/mm/yyyy]		|__|__| - |__|__| (24 hr clock)	
APACHE III diagnosis code	|__|__|__|__|			
APACHE II score	|__|__|			
SOFA				
Cardiovascular	|__|	Not measured	|__|	
Respiratory	|__|	Not measured	|__|	
Liver	|__|	Not measured	|__|	
Renal	|__|	Not measured	|__|	
Coagulation	|__|	Not measured	|__|	
Baseline bloods				
ALT	|__|__|__|__| U/L		Not measured	|__|
GGT	|__|__|__|__| U/L		Not measured	|__|
ALP	|__|__|__|__| U/L		Not measured	|__|
Bilirubin	|__|__|__|__| µmol/L		Not measured	|__|
White Cell Count	|__|__|__|.|__| 10^9/L		Not measured	|__|
Triglycerides	|__|__|.|__| mmol/L		Not measured	|__|
C-Reactive Protein	|__|__|__|__| mg/L		Not measured	|__|
Baseline Nutrition assessment				
Total Protein requirements	|__|__|__| g/day			
Was EN commenced prior to enrolment into the study	|Y| / |N|			
How much energy from all sources was received from hospital admission to randomisation?	EN Kcal	|__|__|__|__| kcal		
	Glucose Kcal	|__|__|__|__| kcal		
	Propofol Kcal	|__|__|__|__| kcal		
Mid arm muscle circumference	|__|__|__| cm (can also be recorded on the physical measurement log)			
Sub study only	Nitrogen intake |__|__| g/day	Urinary nitrogen |__|__|__| g/day		

PATIENT STUDY NUMBER|__|__|__| - |__|__|__|__|__|

PATIENT INITIALS |__|__|__|

2 Daily Data

This paper form can be used to keep all daily data together. Please remember to enter it into the website

Part 1: Complete for ALL patients

Study Day	|__|__|	|__|__|	|__|__|	|__|__|	|__|__|
Date [dd/mm/yyyy]	|__|__|/|__|__|/|__|__|__|__|	|__|__|/|__|__|/|__|__|__|__|	|__|__|/|__|__|/|__|__|__|__|	|__|__|/|__|__|/|__|__|__|__|	|__|__|/|__|__|/|__|__|__|__|
Was the energy requirement changed today? **Note: This should only change it ECMO or RRT starts or stops**	|Y|/|N| If Yes: |__| 25 kcal/kg |__| 30 kcal/kg	|Y|/|N| If Yes: |__| 25 kcal/kg |__| 30 kcal/kg	|Y|/|N| If Yes: |__| 25 kcal/kg |__| 30 kcal/kg	|Y|/|N| If Yes: |__| 25 kcal/kg |__| 30 kcal/kg	|Y|/|N| If Yes: |__| 25 kcal/kg |__| 30 kcal/kg
Current energy and protein requirement?	|__|__|__|__| kcal	|__|__|__|__| kcal	|__|__|__|__| kcal	|__|__|__|__| kcal	|__|__|__|__| kcal
	|__|__|__| g/day	|__|__|__| g/day	|__|__|__| g/day	|__|__|__| g/day	|__|__|__| g/day
Morning blood glucose level (closest to 8am)	|__|__|.|__| mmol/L	|__|__|.|__| mmol/L	|__|__|.|__| mmol/L	|__|__|.|__| mmol/L	|__|__|.|__| mmol/L
Enter the number of blood glucose levels less than 2.1 mmol/L today	|__|__|	|__|__|	|__|__|	|__|__|	|__|__|
Total insulin received today	|__|__|__| units	|__|__|__| units	|__|__|__| units	|__|__|__| units	|__|__|__| units
Total amount of Propofol received today	|__|__|__| ml	|__|__|__| ml	|__|__|__| ml	|__|__|__| ml	|__|__|__| ml
Glucose concentration (excluding PN glucose)	None |__|	None |__|	None |__|	None |__|	None |__|
	25 % |__|__|__|__| ml	25 % |__|__|__|__| ml	25 % |__|__|__|__| ml	25 % |__|__|__|__| ml	25 % |__|__|__|__| ml
	50% |__|__|__|__| ml	50% |__|__|__|__| ml	50% |__|__|__|__| ml	50% |__|__|__|__| ml	50% |__|__|__|__| ml
How many gastric aspirates were above 300ml today?	|__|__|	|__|__|	|__|__|	|__|__|	|__|__|
	|__| NG on FD	|__| NG on FD	|__| NG on FD	|__| NG on FD	|__| NG on FD
Were prokinetics given today?	|Y|/|N|	|Y|/|N|	|Y|/|N|	|Y|/|N|	|Y|/|N|
If Y: Metoclopramide dose	|__|__|__|mg	|__|__|__|mg	|__|__|__|mg	|__|__|__|mg	|__|__|__|mg
If Y: Erythromycin dose	|__|__|__|__| mg	|__|__|__|__| mg	|__|__|__|__| mg	|__|__|__|__| mg	|__|__|__|__| mg
Witnessed complications	|__| Abdominal distention	|__| Abdominal distention	|__| Abdominal distention	|__| Abdominal distention	|__| Abdominal distention
	|__| Vomiting	|__| Vomiting	|__| Vomiting	|__| Vomiting	|__| Vomiting
	|__| Witnessed aspiration	|__| Witnessed aspiration	|__| Witnessed aspiration	|__| Witnessed aspiration	|__| Witnessed aspiration
	|__| None	|__| None	|__| None	|__| None	|__| None
How many new antibiotics were prescribed today?	|__|__|	|__|__|	|__|__|	|__|__|	|__|__|

PATIENT STUDY NUMBER|__| |__| |__| - |__| |__| |__| |__| |__|

PATIENT INITIALS |__| |__| |__|

Part 2: Please fill this out the relevant sections pending the type of nutrition that is received each day for ALL PATIENTS

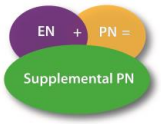
Study Day	|__| |__|	|__| |__|	|__| |__|	|__| |__|	|__| |__|
	Fill out the following section if your patient has received: ✓ EN (alone or in combination with any other nutrition)	Fill out the following section if your patient has received: ✓ EN (alone or in combination with any other nutrition)	Fill out the following section if your patient has received: ✓ EN (alone or in combination with any other nutrition)	Fill out the following section if your patient has received: ✓ EN (alone or in combination with any other nutrition)	Fill out the following section if your patient has received: ✓ EN (alone or in combination with any other nutrition)
Volume of EN nutrition	|__| |__| |__| |__| ml	|__| |__| |__| |__| ml	|__| |__| |__| |__| ml	|__| |__| |__| |__| ml	|__| |__| |__| |__| ml
Location of the feeding tube	|__| Gastric |__| Post-pyloric	|__| Gastric |__| Post-pyloric	|__| Gastric |__| Post-pyloric	|__| Gastric |__| Post-pyloric	|__| Gastric |__| Post-pyloric
Code of EN product	1. |__| |__| 2. |__| |__| 3. |__| |__|	1. |__| |__| 2. |__| |__| 3. |__| |__|	1. |__| |__| 2. |__| |__| 3. |__| |__|	1. |__| |__| 2. |__| |__| 3. |__| |__|	1. |__| |__| 2. |__| |__| 3. |__| |__|
	Fill out the following information if your patient has received: ✓ Study PN (alone or in combination with any other nutrition	Fill out the following information if your patient has received: ✓ Study PN (alone or in combination with any other nutrition	Fill out the following information if your patient has received: ✓ Study PN (alone or in combination with any other nutrition	Fill out the following information if your patient has received: ✓ Study PN (alone or in combination with any other nutrition	Fill out the following information if your patient has received: ✓ Study PN (alone or in combination with any other nutrition
Date and Time PN was commenced **ONLY COLLECTED ON STUDY DAY 1**	|__| |__| / |__| |__| / |__| |__| |__| |__| [dd/mm/yyyy] |__| |__| - |__| |__| (24 hr clock)				
Volume of study PN received?	|__| |__| |__| |__| ml	|__| |__| |__| |__| ml	|__| |__| |__| |__| ml	|__| |__| |__| |__| ml	|__| |__| |__| |__| ml
Oral only	|__| No further info required.	|__| No further info required.	|__| No further info required.	|__| No further info required.	|__| No further info required.
No nutrition (none)	|__| No further info required	|__| No further info required	|__| No further info required	|__| No further info required	|__| No further info required

PATIENT STUDY NUMBER|__| |__| |__| - |__| |__| |__||__| |__|

PATIENT INITIALS |__| |__| |__|

Part 3: Only fill this section out if <u>NON STUDY PN</u> was delivered, otherwise leave blank

Study Day	|__| |__|	|__| |__|	|__| |__|	|__| |__|	|__| |__|
Was non study PN delivered today?	|Y| / |N|	|Y| / |N|	|Y| / |N|	|Y| / |N|	|Y| / |N|
Lipid percent in PN bag	|__| |__|%	|__| |__|%	|__| |__|%	|__| |__|%	|__| |__|%
Lipid volume in PN bag	|__| |__| |__| |__| ml	|__| |__| |__| |__| ml	|__| |__| |__| |__| ml	|__| |__| |__| |__| ml	|__| |__| |__| |__| ml
Glucose concentration in PN bag	|__| None |__| 5% |__| 10% |__| 25% |__| 50%	|__| None |__| 5% |__| 10% |__| 25% |__| 50%	|__| None |__| 5% |__| 10% |__| 25% |__| 50%	|__| None |__| 5% |__| 10% |__| 25% |__| 50%	|__| None |__| 5% |__| 10% |__| 25% |__| 50%
Glucose volume in PN bag	|__| |__| |__| |__| ml	|__| |__| |__| |__| ml	|__| |__| |__| |__| ml	|__| |__| |__| |__| ml	|__| |__| |__| |__| ml
Protein g in bag	|__| |__|__|g	|__| |__|__|g	|__| |__|__|g	|__| |__|__|g	|__| |__|__|g
Volume of PN provided to the patient	|__| |__| |__| |__| ml	|__| |__| |__| |__| ml	|__| |__| |__| |__| ml	|__| |__| |__| |__| ml	|__| |__| |__| |__| ml



PATIENT STUDY NUMBER |__| |__| |__| - |__| |__| |__| |__| |__|

PATIENT INITIALS |__| |__| |__|

3 Physical measurements and anthropometry record form

This paper form can be used to keep all measurements together. Please remember to enter them onto the study website.

	Baseline	**ICU Discharge** On the website, these items are entered on the daily data form under **'physical assessment'** on the day the patient is ready for ICU discharge	**Hospital Discharge** On the website, these items are entered on the **hospital outcomes form** on the day the patient is ready for hospital discharge.
Mid Arm Muscle Circumference	|__| |__| |__| cm	|__| |__| |__| cm	|__| |__| |__| cm
Handgrip strength		Attempt: 1. |__| |__| kg 2. |__| |__| kg 3. |__| |__| kg Record the best attempt in the website. If the patient is unable to complete the assessment at ICU discharge, record why not: |__| Clinician Unavailable |__| Patient discharge prior |__| Patient unable to complete the assessment |__| Other-free text reason _____ _____	Attempt: 1. |__| |__| kg 2. |__| |__| kg 3. |__| |__| kg Record the best attempt in the website. If the patient is unable to complete the assessment at hospital discharge, record why not: |__| Clinician Unavailable |__| Patient discharge prior |__| Patient unable to complete the assessment |__| Other-free text reason _____ _____
6MWT On the website, this item is entered on the **hospital outcomes form** on the day the patient is ready for hospital discharge.			Distance |__| |__| |__| m If the patient is unable to complete the assessment at hospital discharge, record why not: |__| Clinician Unavailable |__| Patient discharge prior |__| Patient unable to complete the assessment |__| Other-free text reason _____ _____ Please ensure you **ALSO** complete the highest level of function scale
Highest level of function scale On the website, this item is entered on the **hospital outcomes form** on the day the patient is ready for hospital discharge.			Number |__| If you are unable to complete the assessment at hospital discharge, record why not: |__| Clinician Unavailable |__| Patient discharge prior |__| Patient unable to complete the assessment |__| Other-free text reason _____ _____

PATIENT STUDY NUMBER |__| |__| |__|- |__| |__| |__| |__| |__|

PATIENT INITIALS |__| |__| |__|

4 SOFA SCORE WORKSHEET AND RECORD FORM

This paper form can be used to keep all data together. Please remember to enter it into the website

This data is considered mandatory on the pre populated study days while the patient remains in ICU

ORGAN SYSTEM	0	1	2	3	4
Cardiovascular Hypotension	MAP > 70 mm Hg without vasopressors	MAP <70 mm Hg without vasopressors	Dopamine ≤5 or dobutamine (any dose)"	Dopamine >5 or adr ≤0.1 or noradr ≤0.1"	Dopamine >15 or adr >0.1 or noradr >0.1"
Respiration PaO_2/FIO_2 (in mmHg)	>400	301-400	<301 The highest score for someone **without** respiratory support is **2**.	≤200 With Respiratory Support*	≤100 With Respiratory Support*
Liver Bilirubin (mg/dL) (µmol/L)	<1.2 <20	1.2 - 1.9 20 - 32	2.0 - 5.9 33 - 101	6.0 - 11.9 102 - 204	>12.0 >204
Renal Creatine (mg/dL) (µmol/L) or urine output	<1.2 <110	1.2 - 1.9 110 - 170	2.0 - 3.4 171 - 299	3.5 - 4.9 300 – 440 or <500 mL/day	>5.0 >440 or <200 mL/day
Coagulation Platelets ($x10^3/mm^3$)	>150	101-150	51-100	21-50	≤20

adr, adrenaline = epinephrine; noradr, noradrenaline = norepinephrine. "Adrenergic agents administered for at least 1 hr (doses given are in µg/kg/min).
*Respiratory support is defined as any form of invasive or non-invasive ventilation including mask CPAP or CPAP delivered through a tracheostomy/tracheotomy or endotracheal tube. PLEASE NOTE: The highest score for someone **without** respiratory support is **2**.

Study Day	1			2			3			7			14			21			28		
Cardiovascular	|__|	N/M	|_|	|__|	N/M	|_|	|__|	N/M	|_|	|__|	N/M	|_|	|__|	N/M	|_|	|__|	N/M	|_|	|__|	N/M	|_|	|__|	N/M	|_|
Respiratory	|__|	N/M	|_|	|__|	N/M	|_|	|__|	N/M	|_|	|__|	N/M	|_|	|__|	N/M	|_|	|__|	N/M	|_|	|__|	N/M	|_|	|__|	N/M	|_|
Liver	|__|	N/M	|_|	|__|	N/M	|_|	|__|	N/M	|_|	|__|	N/M	|_|	|__|	N/M	|_|	|__|	N/M	|_|	|__|	N/M	|_|	|__|	N/M	|_|
Renal	|__|	N/M	|_|	|__|	N/M	|_|	|__|	N/M	|_|	|__|	N/M	|_|	|__|	N/M	|_|	|__|	N/M	|_|	|__|	N/M	|_|	|__|	N/M	|_|
Coagulation	|__|	N/M	|_|	|__|	N/M	|_|	|__|	N/M	|_|	|__|	N/M	|_|	|__|	N/M	|_|	|__|	N/M	|_|	|__|	N/M	|_|	|__|	N/M	|_|

If a variable is not measured it will be entered into the database using the 'not measured' (N/M) option

SOFA_Paper CRF V3 01 08 14

PATIENT STUDY NUMBER |__| |__| |__| - |__| |__| |__||__| |__|

PATIENT INITIALS |__| |__| |__|

Blood Test Record Form

This paper form can be used to keep all data together. Please remember to enter it into the website

PART 1: ALL PATIENTS

- **Where the patient remains in ICU, all patients must have blood tests recorded on the days where the fields are available for data entry.**
- **<u>If bloods are not completed as part of routine care then they must be ordered on these specific days</u>**
- **Record blood tests to one decimal place if available. Insert the decimal in the appropriate spot on the paper CRF**
- **REMEMBER: If bloods are ordered as routine practice on days other than that specified, please collect this data (PART 2 of CRF)**

Study Day	ALT	GGT	ALP	Bilirubin	White Cell Count	Triglycerides	C-reactive Protein
Baseline/ Study 1							
3						|__|__|.__| mmol/L	
7	|__|__|__|__| U/L	|__|__|__|__| U/L	|__|__|__|__| U/L	|__|__|__|__| µmol/L	|__|__|__|.__| 10^9/L	|__|__|__|.__| mmol/L	|__|__|__| mg/L
14	|__|__|__|__| U/L	|__|__|__|__| U/L	|__|__|__|__| U/L	|__|__|__|__| µmol/L	|__|__|__|.__| 10^9/L	|__|__|__|.__| mmol/L	|__|__|__| mg/L
21	|__|__|__|__| U/L	|__|__|__|__| U/L	|__|__|__|__| U/L	|__|__|__|__| µmol/L	|__|__|__|.__| 10^9/L		
28	|__|__|__|__| U/L	|__|__|__|__| U/L	|__|__|__|__| U/L	|__|__|__|__| µmol/L	|__|__|__|.__| 10^9/L		|__|__|__| mg/L

PATIENT STUDY NUMBER |__| |__| |__|- |__| |__| |__| |__| |__|

PATIENT INITIALS |__| |__| |__|

6 Consent record form

This paper form can be used to keep all information together. Please remember to enter this into the study website.

Consent		
Date Consent Given	|__| |__| / |__| |__| / |__| |__| |__| |__| [dd/mm/yyyy]	
Who Gave Consent (circle relevant)	|__|	Prior Consent from patient
	|__|	Prior consent from person responsible
	|__|	Delayed consent from person responsible
	|__|	Delayed consent from patient
	|__|	Patient died before consent could be obtained, permission to keep data
Date Consent Given	|__| |__| / |__| |__| / |__| |__| |__| |__| [dd/mm/yyyy]	
Who Gave Consent (circle relevant)	|__|	Prior Consent from patient
	|__|	Prior consent from person responsible
	|__|	Delayed consent from person responsible
	|__|	Delayed consent from patient
	|__|	Patient died before consent could be obtained, permission to keep data
Withdrawal of consent		
Who withdrew consent (circle relevant)	|__|	Patient
	|__|	Relative/friend
	|__|	Physician
Date consent withdrawn	|__| |__| / |__| |__| / |__| |__| |__| |__| [dd/mm/yyyy]	
Has the patient agreed to ongoing follow-up?	|__|	Yes
	|__|	No
Has the patient agreed to the use of the data already collected?	|__|	Yes
	|__|	No

PATIENT STUDY NUMBER |__| |__| |__|-|__| |__| |__| |__| |__|

PATIENT INITIALS |__| |__| |__|

Outcomes record form

This paper form can be used to keep all measurements together. Please remember to enter them onto the study website.

Part 1: ICU Discharge- ALL PATIENTS

ICU Discharge		
Date and time of ICU discharge	|__| |__| / |__| |__| / |__| |__| |__| |__| [dd/mm/yyyy]	
	Time|__| |__| - |__| |__| (24 hr clock)	
Survival status	|__|	Alive
	|__|	Deceased
Date and time MV was ceased	|__| |__| / |__| |__| / |__| |__| |__| |__| [dd/mm/yyyy]	
	Time|__| |__| - |__| |__| (24 hr clock)	
	MV never ceased |__|	
Discharge destination	|__|	Home
	|__|	Rehabilitation centre
	|__|	Other ward
	|__|	Other ICU
	|__|	Long term care facility- high care
	|__|	Long term care facility- low care
	|__|	Other
	|__|	Unknown
PN status	|__|	Never started
	|__|	Never ceased
	|__|	Ceased:
	If ceased, Date |__| |__| / |__| |__| / |__| |__| |__| |__| [dd/mm/yyyy]	
EN status	|__|	Never started
	|__|	Never ceased
	|__|	Ceased:
	If ceased, Date |__| |__| / |__| |__| / |__| |__| |__| |__| [dd/mm/yyyy]	

DON'T FORGET: Functional/anthropometry outcomes required at ICU Discharge:

- ✓ Mid-arm muscle circumference
- ✓ Hand Grip Strength

These can be kept on the 'Physical Measurements Log'.

PATIENT STUDY NUMBER |__| |__| |__|-|__| |__| |__| |__| |__|

PATIENT INITIALS |__| |__| |__|

Part 2: Hospital Discharge- ALL PATIENTS

Hospital Discharge		
Date and time of hospital discharge		__|__| / |__|__| / |__|__|__|__| [dd/mm/yyyy]
	Time |__|__| - |__|__| (24 hr clock)	
Survival status	|__|	Alive
	|__|	Deceased If deceased: Date of death (if known) |__|__| / |__|__| / |__|__|__|__| [dd/mm/yyyy]
Discharge destination	|__|	Home
	|__|	Rehabilitation centre
	|__|	Ward
	|__|	Other ICU
	|__|	Long term care facility- high care
	|__|	Long term care facility- low care
	|__|	Other
	|__|	Unknown
Date and time oral intake was commenced		__|__| / |__|__| / |__|__|__|__| [dd/mm/yyyy]
	Time|__|__| - |__|__| [24 hr clock]	
PN status	|__|	Never started
	|__|	Never ceased
	|__|	Ceased:
	If ceased, Date |__|__| / |__|__| / |__|__|__|__| [dd/mm/yyyy]	
EN status	|__|	Never started
	|__|	Never ceased
	|__|	Ceased:
	If ceased, Date |__|__| / |__|__| / |__|__|__|__| [dd/mm/yyyy]	

EQ-5D-Hospital D/C		
Was QOL assessment performed	|__|	Yes
	|__|	No
	If you are unable to complete the assessment at hospital discharge, record why not: |__| Lost to follow up |__| Refused |__| Other	
Mobility	|__|	I have no problems with walking about
	|__|	I have some problems with walking about
	|__|	I am confined to bed
	|__|	Not answered
Personal Care	|__|	I have no problems with self care dressing
	|__|	I have some problems with washing or dressing myself
	|__|	I am unable to wash or dress myself
	|__|	Not answered
Usual activities	|__|	I have no problems with performing my usual duties
	|__|	I have some problems with performing my usual activities
	|__|	I am unable to perform my usual activities
	|__|	Not answered
Pain/Discomfort	|__|	I have no pain or discomfort
	|__|	I have moderate pain or discomfort
	|__|	I have extreme pain or discomfort
	|__|	Not answered
Anxiety/Depression	|__|	I am not anxious or depressed
	|__|	I am moderately anxious or depressed
	|__|	I am extremely anxious or depressed
	|__|	Not answered
Your own health state today	|__|__|__|	

DON'T FORGET: Functional/anthropometry outcomes at hospital discharge:

- ✓ Mid-arm muscle circumference
- ✓ Hand Grip Strength

PATIENT STUDY NUMBER |__|__|__|-|__|__|__|__|__|

PATIENT INITIALS |__|__|__|

Part 2: Hospital Discharge- ALL PATIENTS

Hospital Discharge		
Date and time of hospital discharge	|__|__|/|__|__|/|__|__|__|__| [dd/mm/yyyy] Time |__|__| - |__|__| (24 hr clock)
Survival status	|__| Alive
	|__| Deceased If deceased: Date of death (if known) |__|__|/|__|__|/|__|__|__|__| [dd/mm/yyyy]
Discharge destination	|__| Home
	|__| Rehabilitation centre
	|__| Ward
	|__| Other ICU
	|__| Long term care facility- high care
	|__| Long term care facility- low care
	|__| Other
	|__| Unknown
Date and time oral intake was commenced	|__|__|/|__|__|/|__|__|__|__| [dd/mm/yyyy] Time|__|__| - |__|__| [24 hr clock]
PN status	|__| Never started
	|__| Never ceased
	|__| Ceased: If ceased, Date |__|__|/|__|__|/|__|__|__|__| [dd/mm/yyyy]
EN status	|__| Never started
	|__| Never ceased
	|__| Ceased: If ceased, Date |__|__|/|__|__|/|__|__|__|__| [dd/mm/yyyy]

EQ-5D-Hospital D/C		
Was QOL assessment performed	|__| Yes |__| No If you are unable to complete the assessment at hospital discharge, record why not: |__| Lost to follow up |__| Refused |__| Other
Mobility	|__| I have no problems with walking about
	|__| I have some problems with walking about
	|__| I am confined to bed
	|__| Not answered
Personal Care	|__| I have no problems with self care dressing
	|__| I have some problems with washing or dressing myself
	|__| I am unable to wash or dress myself
	|__| Not answered
Usual activities	|__| I have no problems with performing my usual duties
	|__| I have some problems with performing my usual activities
	|__| I am unable to perform my usual activities
	|__| Not answered
Pain/Discomfort	|__| I have no pain or discomfort
	|__| I have moderate pain or discomfort
	|__| I have extreme pain or discomfort
	|__| Not answered
Anxiety/Depression	|__| I am not anxious or depressed
	|__| I am moderately anxious or depressed
	|__| I am extremely anxious or depressed
	|__| Not answered
Your own health state today	|__|__|__|	

DON'T FORGET: Functional/anthropometry outcomes at hospital discharge:

- ✓ Mid-arm muscle circumference
- ✓ Hand Grip Strength

PATIENT STUDY NUMBER |__| |__| |__|-|__| |__| |__| |__| |__|

PATIENT INITIALS |__| |__| |__|

Part 3: 3 and 6 month follow up- ALL PATIENTS

	3 months		6 months	
Date of follow up	|__| |__| / |__| |__| / |__| |__| |__| |__| [dd/mm/yyyy]		|__| |__| / |__| |__| / |__| |__| |__| |__| [dd/mm/yyyy]	
Survival status	|__|	Alive	|__|	Alive
	|__|	Deceased	|__|	Deceased
	If deceased: date of death if known (no further information required) |__| |__| / |__| |__| / |__| |__| |__| |__| [dd/mm/yyyy]		If deceased: date of death if known (no further information required) |__| |__| / |__| |__| / |__| |__| |__| |__| [dd/mm/yyyy]	
Current location	|__|	Home	|__|	Home
	|__|	Rehabilitation centre	|__|	Rehabilitation centre
	|__|	Other hospital- ward	|__|	Ward
	|__|	Other ICU	|__|	Other ICU
	|__|	Long term care facility- **high care**	|__|	Long term care facility- **high care**
	|__|	Long term care facility- **low care**	|__|	Long term care facility- **low care**
	|__|	Other: free text _____ _____	|__|	Other: free text _____ _____
	|__|	Unknown	|__|	Unknown
Where did you/ your relative go immediately after your acute care admission?	|__|	Home	|__|	Home
	|__|	Rehabilitation centre (determine length of admission in days below)	|__|	Rehabilitation centre (determine length of admission in days below)
	|__|	Other hospital- **ward** (determine length of admission in days below)	|__|	Other hospital- **ward** (determine length of admission in days below)
	|__|	Other **ICU** (determine length of admission in days below)	|__|	Other **ICU** (determine length of admission in days below)
	|__|	Long term care facility- **high care**	|__|	Long term care facility- **high care**
	|__|	Long term care facility- **low care**	|__|	Long term care facility- **low care**
	|__|	Other: free text _____ _____	|__|	Other: free text _____ _____
	|__|	Unknown	|__|	Unknown
	If yes was answered to **'Rehabilitation Centre'**, **'Other hospital- ward'** or **'Other ICU'** please determine how many days the patient/ the NOKs relative stayed? **Please be as accurate as possible** |__| |__| |__| days OR Date range: From: |__| |__| / |__| |__| / |__| |__| |__| |__| To: |__| |__| / |__| |__| / |__| |__| |__| |__|		If yes was answered to **'Rehabilitation Centre'**, **'Other hospital- ward'** or **'Other ICU'** please determine how many days the patient/ the NOKs relative stayed? **Please be as accurate as possible** |__| |__| |__| days OR Date range: From: |__| |__| / |__| |__| / |__| |__| |__| |__| To: |__| |__| / |__| |__| / |__| |__| |__| |__|	

PATIENT STUDY NUMBER |__| |__| |__|-|__| |__| |__| |__| |__|

PATIENT INITIALS |__| |__| |__|

Part 3: 3 and 6 month follow up- ALL PATIENTS CONTINUED

	3 months	6 months
Have you/your relative been readmitted to hospital?	|__| No |__| Yes **If yes please provide the following information and be as accurate as possible. Verify the data if possible from hospital records.** What was the admission for: _____ _____ _____ Please determine how many days the patient/ the NOKs relative stayed during their readmission? |__| |__| |__| days OR Date range: From: |__| |__| / |__| |__| / |__| |__| |__| |__| To: |__| |__| / |__| |__| / |__| |__| |__| |__|	|__| No |__| Yes **If yes please provide the following information and be as accurate as possible. Verify the data if possible from hospital records.** What was the admission for: _____ _____ _____ Please determine how many days the patient/ the NOKs relative stayed during their readmission? |__| |__| |__| days OR Date range: From: |__| |__| / |__| |__| / |__| |__| |__| |__| To: |__| |__| / |__| |__| / |__| |__| |__| |__|
Have you/your relative been readmitted to ICU?	|__| No |__| Yes **If yes please provide the following information and be as accurate as possible. Verify the data if possible from hospital records.** What was the admission for? _____ _____ _____ Please determine how many days the patient/ the NOKs relative stayed during their readmission? |__| |__| |__| days OR Date range: From: |__| |__| / |__| |__| / |__| |__| |__| |__| To: |__| |__| / |__| |__| / |__| |__| |__| |__|	|__| No |__| Yes **If yes please provide the following information and be as accurate as possible. Verify the data if possible from hospital records.** What was the admission for? _____ _____ _____ Please determine how many days the patient/ the NOKs relative stayed during their readmission? |__| |__| |__| days OR Date range: From: |__| |__| / |__| |__| / |__| |__| |__| |__| To: |__| |__| / |__| |__| / |__| |__| |__| |__|
Did you/your relative have any surgery in that readmission?	|__| No |__| Yes **If yes please provide the following information and be as accurate as possible. Verify the data if possible from hospital records.** What was the surgery for? _____ _____ _____	|__| No |__| Yes **If yes please provide the following information and be as accurate as possible. Verify the data if possible from hospital records.** What was the surgery for? _____ _____ _____

PATIENT STUDY NUMBER |__| |__| |__|-|__| |__| |__| |__| |__|

PATIENT INITIALS |__| |__| |__|

Part 3: 3 and 6 month follow up- ALL PATIENTS CONTINUED

EQ-5D				
	3 months		**6 months**	
Was a quality of life assessment performed?	|__| Yes |__| No If you are unable to complete the assessment at 3 months, record why not: |__| Lost to follow up |__| Refused |__| Other		|__| Yes |__| No If you are unable to complete the assessment at 3 months, record why not: |__| Lost to follow up |__| Refused |__| Other	
Mobility	|__|	I have no problems with walking about	|__|	I have no problems with walking about
	|__|	I have some problems with walking about	|__|	I have some problems with walking about
	|__|	I am confined to bed	|__|	I am confined to bed
	|__|	Not answered	|__|	Not answered
Personal Care	|__|	I have no problems with self care dressing	|__|	I have no problems with self care dressing
	|__|	I have some problems with washing or dressing myself	|__|	I have some problems with washing or dressing myself
	|__|	I am unable to wash or dress myself	|__|	I am unable to wash or dress myself
	|__|	Not answered	|__|	Not answered
Usual activities	|__|	I have no problems with performing my usual duties	|__|	I have no problems with performing my usual duties
	|__|	I have some problems with performing my usual activities	|__|	I have some problems with performing my usual activities
	|__|	I am unable to perform my usual activities	|__|	I am unable to perform my usual activities
	|__|	Not answered	|__|	Not answered
Pain/Discomfort	|__|	I have no pain or discomfort	|__|	I have no pain or discomfort
	|__|	I have moderate pain or discomfort	|__|	I have moderate pain or discomfort
	|__|	I have extreme pain or discomfort	|__|	I have extreme pain or discomfort
	|__|	Not answered	|__|	Not answered
Anxiety/Depression	|__|	I am not anxious or depressed	|__|	I am not anxious or depressed
	|__|	I am moderately anxious or depressed	|__|	I am moderately anxious or depressed
	|__|	I am extremely anxious or depressed	|__|	I am extremely anxious or depressed
	|__|	Not answered	|__|	Not answered
Your own health state today	|__|__|__|		|__|__|__|	

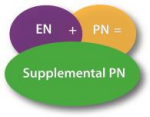
PATIENT STUDY NUMBER |__| |__| |__|- |__| |__| |__| |__| |__|

PATIENT INITIALS |__| |__| |__|

8 Protocol deviation record form

This paper form can be used to keep all information together. Please remember to enter this into the study website.

Deviation			
Date of deviation	|__| |__| / |__| |__| / |__| |__| |__| |__| [dd/mm/yyyy]	*Date discovered*	|__| |__| / |__| |__| / |__| |__| |__| |__| [dd/mm/yyyy]
Time of deviation	|__| |__| - |__| |__| (24 hr clock)	*Time discovered*	|__| |__| - |__| |__| (24 hr clock)
Patient randomised but not eligible	☐ Patient under 16 years ☐ Patient admitted more than 72 hours prior to enrolment ☐ Patient not mechanically ventilated or not expected to remain ventilated until at least the day after tomorrow ☐ No central venous access for PN ☐ Patient does not have organ failure ☐ EN and PN could not be delivered at enrolment ☐ Standard PN could not be delivered at enrolment ☐ Received PN prior to enrolment ☐ Death is imminent or deemed highly likely in the next 96 hours ☐ There is a current treatment limitation in place or the patient is unlikely to survive to 6 months due to underlying illness ☐ More than 80% of energy requirements have been satisfactorily delivered via the enteral route in the last 24 hours. ☐ The patient is pregnant ☐ The patient has previously been in the study		
Study PN not given when indicated (Supp PN group only)	☐ Abnormal blood work ☐ Held for a procedure ☐ No central access ☐ Refeeding syndrome ☐ Other, please specify_____ _____		
Study PN run at the incorrect rate	No other information needed- go to **'Consequence of the deviation'**		
Other types	☐ Did not receive study PN on the day of randomisation ☐ Dispensing/dosing error ☐ Unapproved procedure ☐ Other, please specify _____ _____ _____		
Consequence of the deviation			
☐ None ☐ Study PN permanently disabled ☐ Study PN missed/withheld ☐ Resulted in an AE ☐ Resulted in an SAE			



PATIENT STUDY NUMBER |__| |__| |__|- |__| |__| |__| |__| |__|

PATIENT INITIALS |__| |__| |__|

9 AE and SAE record form

This paper form can be used to keep all information together. Please remember to enter this into the study website.

AE			
Onset date	|__| |__| / |__| |__| /|__| |__| |__| |__| [dd/mm/yyyy]	*Onset time*	|__| |__| - |__| |__| (24 hr clock)
Event	☐ Allergic reaction ☐ Other: Describe:		
Action taken	☐ None ☐ Treatment temporally modified and discontinued ☐ Treatment permanently discontinued		
Outcome	☐ Unknown/lost to follow up ☐ Unresolved ☐ Resolved: If resolved: Date of resolution: |__| |__| / |__| |__| /|__| |__| |__| |__| [dd/mm/yyyy] Time of resolution: |__| |__| - |__| |__| (24 hr clock) ☐ Resolved with sequelae: If resolved with sequelae: Date of resolution: |__| |__| / |__| |__| /|__| |__| |__| |__| [dd/mm/yyyy] Time of resolution: |__| |__| - |__| |__| (24 hr clock) ☐ None of the above		
Related to the study	☐ Unrelated ☐ Possibly related ☐ Probably related ☐ Definitely related		

Name and signature of person submitting the AE:_____

PATIENT STUDY NUMBER |__| |__| |__|- |__| |__| |__| |__| |__|

PATIENT INITIALS |__| |__| |__|

All SAEs must have an AE recorded prior

SAE			
Onset date of SAE	|__| |__| / |__| |__| /|__| |__| |__| |__| [dd/mm/yyyy]	*Onset time of SAE*	|__| |__| - |__| |__| (24 hr clock)
Type of report	☐ Initial ☐ Follow-up ☐ Final		
SAE diagnosis	Describe:		
Type of SAE	☐ Death ☐ Life threatening event ☐ Congenital anomaly ☐ Prolongation of or rehospitalisation ☐ Permanently disabling ☐ Medically important		
SAE description			
Related to the study	☐ Unrelated ☐ Possibly related ☐ Probably related ☐ Definitely related		
Action taken	☐ None ☐ Treatment temporally modified and discontinued ☐ Treatment permanently discontinued		
Treatment of SAE			
Outcome	☐ Death ☐ Unknown/lost to follow up ☐ Unresolved ☐ Resolved: If resolved: Date of resolution: |__| |__| / |__| |__| /|__| |__| |__| |__| [dd/mm/yyyy] Time of resolution: |__| |__| - |__| |__| (24 hr clock) ☐ Resolved with sequelae: If resolved with sequelae: Date of resolution: |__| |__| / |__| |__| /|__| |__| |__| |__| [dd/mm/yyyy] Time of resolution: |__| |__| - |__| |__| (24 hr clock) ☐ None of the above		

Name and signature of person submitting the AE:_____

Chapter 6: Energy delivery throughout the whole hospital stay in critically ill patients

6.1 Chapter summary

This chapter describes a cohort study nested within the randomised trial described in Chapter 5. The primary aim of this observational study was to describe energy intake in the post-ICU period of hospitalization in critically ill adults. Secondary aims were to evaluate whether there was a difference between calculated and measured energy values and determine the feasibility of measuring energy expenditure with indirect calorimetry in the post-ICU period of hospitalization in critically ill adults. The work in this Chapter relates to thesis aim 3 and hypothesis 2.

6.2 Manuscript “What happens to nutrition intake in the post-ICU hospitalisation period? An observational cohort study in critically ill adults (under review, JPEN)”

What happens to nutrition intake in the post-ICU hospitalisation period? An observational cohort study in critically ill adults

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Clinical relevancy statement:

Little information exists regarding the progress of nutrition intake through the hospital admission in patients who have survived critical illness, with the majority of research focussed on the early period of illness. Furthermore, the later period of illness may be an important stage for nutrition rehabilitation, however nutrition interventions to date have not addressed this. We aimed to describe energy and protein intake and determine the feasibility of measuring energy requirements with indirect calorimetry in the post-ICU hospitalisation period in critically ill adults.

Statement of Authorship:

EJR, RP, ARD, SM, DJC equally contributed to the conception and design of the research;

ER, RP, ARD, MB, CH, AMD, SM and DJC contributed to the analysis and interpretation of the data; ER, ARD, CH, AMD and DJC drafted the manuscript; all authors critically revised the manuscript and agree to be fully accountable for the integrity and accuracy of the work. All authors have read and approved the final version of the manuscript.

Financial disclosure:

The primary randomised controlled trial was an investigator initiated study which included this pre-planned sub-study. The primary trial was funded by an unrestricted research grant from Baxter Healthcare Corporation. Baxter Healthcare Corporation was not involved in the original development of the trial concept, trial management, data collection, analysis or interpretation of the data. The final version of the study manuscript was reviewed by Baxter Healthcare Corporation prior to submission as per the funding agreement.

This work is part of PhD thesis and EJR has a National Health and Medical Research Council Postgraduate Scholarship for salary support.

CH is supported by a Future Leader Fellowship from the Heart Foundation of Australia.

Conflict of interest statement:

ARD is an employee of Baxter Healthcare Corporation, Australia. This position commenced in September 2015 which was after the primary trial had been designed and recruitment had begun. There are no conflicts of interest for any other authors.

Disclosure:

EJR has received unrestricted research funding for an independent investigator initiated study from Baxter Healthcare Corporation. RP, CH, AMD, SM and DJC are on the management committee for this study and MB is the study statistician (NCT03292237).

Acknowledgements:

Thank you to Baxter Healthcare Corporation for the funding associated with this study.

Thank you to the ICU research staff and Dietitians in the Cardiothoracic and Vascular Intensive Care Unit, the Nutrition and Dietetics Department at Auckland City Hospital, Auckland New Zealand and in the Intensive Care Unit and Nutrition Department at The Alfred Hospital, Melbourne, Australia for their support and efforts in this study.

Abstract:

Background: Little is currently known about nutrition intake and energy requirements in the post-intensive care unit (ICU) hospitalisation period in critically ill patients. We aimed to describe energy and protein intake and determine the feasibility of measuring energy expenditure during the post-ICU hospitalisation period in critically ill adults.

Methods: Nested cohort study within a randomised controlled trial in critically ill patients. After discharge from ICU, energy and protein intake was quantified periodically and indirect calorimetry attempted. Data are presented as n (%), mean (standard deviation (SD)) and median [inter quartile range (IQR)].

Results: Thirty-two patients were studied in the post-ICU hospitalisation period and 12 had indirect calorimetry. Mean age and BMI was 56 (18) years and 30 (8) kg/m^2 respectively, 75% were male and the median estimated energy and protein requirement 2000 [1650-2550] kcal and 112 [84-129] g, respectively. Over 227 total days in the post-ICU hospitalisation period, a median [IQR] of 1238 [869-1813] kcal and 60 [35-89.5] g of protein was received from nutrition therapy. Oral nutrition either alone (n=124 days, 55%) or in combination with EN (n=96 days, 42%) was the predominant mode. In the 12 patients who had indirect calorimetry, the median measured daily energy requirement was 1982 [1843-2345] kcal and daily energy deficit, -95 [-1050-347] kcal compared to the measured energy requirement.

Conclusion: Energy and protein intake in the post-ICU hospitalisation period was below estimated and measured energy requirements. Oral nutrition provided alone was the most common mode of nutrition therapy.

Introduction:

Randomised controlled trials (RCTs) comparing nutritional interventions in the critically ill have frequently failed to prove nutrition interventions positively benefit patients compared to usual care. One plausible explanation is that these trials have predominately focussed on interventions of short duration, applied early during critical illness, while patients are in the acute phase of illness and remain in the intensive care unit (ICU). This approach does not consider the dynamic metabolic response to critical illness and the potential role of nutrition delivery during different phases of hospital stay.

It is plausible that nutritional interventions administered during the post-ICU hospitalisation period may be even more important than those applied early. Early in critical illness, endogenous glucose supplies are high, meaning provision of artificial nutrition during this period may lead to relative overfeeding, which has been associated with deleterious consequences [1,2]. Later in the metabolic response to critical illness, endogenous glucose supplies have been utilised and anabolism takes over to facilitate recovery [2]. Accordingly, exogenous carbohydrate and protein may be even more important later than in the early phase of critical illness, as patients require and are capable of utilising the nutrition provided. However, in the few studies that have investigated nutrition intake in the post-ICU hospitalisation period, energy and protein deficits have been thought to continue, or even to accumulate for multiple reasons [3-5]. Additionally, there are no data available on energy requirements in critically ill patients during the post- ICU hospitalisation period.

Given the lack of data on nutrition intake and energy requirements in the post-ICU hospitalisation period in critically ill patients, we performed a cohort study nested within an RCT. Our primary aim was to describe energy and protein intake in the post-ICU hospitalisation period in critically ill adults. Secondary outcomes were to determine the feasibility of measuring energy expenditure with indirect calorimetry during this period and compare measured versus predicted estimates during this time.

Methods:

We performed a nested cohort study within a phase II, parallel group, open label RCT of a supplemental parenteral nutrition (PN) intervention compared to usual care, in critically ill patients [6,7]. In brief, 100 patients with at least 1 organ failure were randomized to a supplemental PN or usual care within 48-72 hours of ICU admission, with the intervention provided for 7 days. Consecutive patients from 2 participating sites were then eligible to participate in this nested study and included during the randomization process. Data collection for this cohort study commenced when the patient was transferred from the ICU to the hospital ward, or commenced oral intake in the ICU, whichever occurred first.

Estimated energy and protein requirements

Body weight was standardized in the primary trial at randomisation using 'calculated body weight' (CBW) according to the following schedule:

- CBW was the patient's actual weight if their BMI was deemed to be <25 kg/m^2
- CBW was set to the ideal weight at a BMI of 23 kg/m^2 if their BMI was ≥ 25 kg/m2

Once set, the CBW for all calculations was not changed. Energy requirements were determined daily in ICU using a fixed prescription method of 25 kcal/kg CBW or 30 kcal/kg CBW if the patient was receiving renal replacement therapy or extracorporeal membrane oxygenation on that day [8]. Once transferred to the ward, management of nutrition was as per the treating clinicians preference. For the purpose of this analysis, estimated energy and protein requirements were assumed to be constant and extrapolated from the last day of ICU stay.

Calculated Energy Expenditure

Indirect calorimetry was performed by trained staff using the FitMate for non-ventilated patients (manufactured by Cosmed, Rome, Italy). Measurements were attempted twice weekly if it was expected the patient could breathe through the mouthpiece for at least 10 minutes, using a nose clip supplied by Cosmed and censored at day 28 or hospital discharge. The quality of the test was monitored via the FitMate device, which provides an indication of variance during test conduct. When measurements could not be conducted, the explanation was recorded.

Nutritional intake

Nutrition intake data was censored at day 28 or hospital discharge. Intake was measured second daily (Monday-Friday) in the post-ICU hospitalisation period when there were study personnel available. Commencement of oral intake was defined as the commencement of food or fluid with the intent to provide nourishment (and excluded sips of fluid or tastes of food to assess ability to swallow or tolerate oral intake safely). The post-ICU hospitalisation period was defined as being from either the commencement of oral intake as per defined above (even if the patient remained

in ICU) or from the time of transfer from the ICU to a non-ICU hospital ward in the participating hospital, whichever occurred first. On the days assessment occurred, the mode of nutrition was recorded, with one of the following options allowed; EN, PN, oral, combined EN and PN, combined EN and oral or none. Food and oral supplements were both classed as 'oral' in mode, however the energy and protein contribution from food and oral supplements were collected separately. Assessment of oral nutrition intake was conducted using study food record charts (supplemental material, S1). Study dietitians and nursing staff used 24 hour recall methods, medical records, and the assistance of family and ward staff to record nutrition intake. Study dietitians with knowledge of their usual hospital foodservice estimated macronutrient intake.

Statistical analysis:

Categorical data are reported as numbers and percentages (%), continuous data as mean (standard deviation (SD)) where normally distributed or as median [interquartile range (IQR]] where not normally distributed. Baseline and outcome variables were compared using Chi-square tests for equal proportion, Student's t-test for normally distributed outcomes and Wilcoxon rank-sum tests otherwise. Bland-Altman analysis was performed between energy requirements measured by indirect calorimetry and the study predictive estimate to assess mean bias and limits of agreement. Mean bias was calculated as the mean difference between the measured energy requirement using indirect calorimetry and the energy requirement from the predictive estimate for each study day where both data points were available. The 95% limits of agreement were calculated as the mean bias ± 2 standard deviations. The Bland-Altman plots represent the mean of the measured and predicted energy requirement on the x-axis

and the difference between the 2 measurements on the Y-axis (measured minus the predicted energy requirement). Missing data was not imputed. Analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and Stata version 14.4 and a two-sided p-value of 0.05 was considered to be statistically significant.

Ethics approval

Ethics approval was obtained from The Alfred Hospital Research and Ethics committee and the Northern A Health and Disability Ethics Committee in New Zealand, as well as the Monash University Research and Ethics Committee. At the time of consent for the main trial, consent for the sub-study was also obtained. As participants were unable to provide consent themselves at the time of enrolment, the patient's legal surrogate, relative/friend or whanau member was approached for consent or agreement to participate in the study. Patients were approached at a later time if it was appropriate and they regained the capacity to provide consent to continue to participate.

Results:

Fifty-six patients were included in this sub-study; nutritional intake data during the post-ICU hospitalisation period were obtained in 32 patients and 12 patients had indirect calorimetry performed (Figure 1). Demographic data of the study population is provided in Table 1.

Overall in the 32 patients studied, there were 227 total study days in the post-ICU hospitalisation period. The median [IQR] predicted daily energy and protein

requirement for these patients was 2000 [1650-2550] kcal and 112 [84-129] g, respectively. A median of 1238 [869-1813] kcal and 60 [35-89.5] g of protein was received from all sources of nutrition therapy on the days assessed. The median overall nutrition adequacy using the predicted energy and protein estimate was 79% [41%-108%] and 73% [44-98%]. Oral nutrition alone was the most common mode of nutrition during this period (n=124 (55%) of study days), followed by oral nutrition in combination with EN (n=96 (42%)), EN alone (n=6 (3%)) and no nutrition (n=1 (0.5%)). PN provided alone, or in combination with EN, was not administered during the post-ICU hospitalisation period. The lowest median proportion of predicted energy and protein requirements was provided on the days oral intake was provided alone without oral supplements (37% [21%-67%] of energy and 48% [13%-63%] of protein requirements) and the highest on the days oral nutrition was combined with EN (104% [66%-132%] of energy and 99% [60%-127%] of protein requirements). Table 2 provides further details about the energy and protein contribution from nutrition sources and modes. Using the predictive energy and protein estimates, the median daily deficits were -442 [-1323-186] kcal/day for energy and -30 [-69- -1] g/day for protein during the post-ICU hospitalisation period.

In total there were 73 indirect calorimetry measurements attempted during the post ICU period. Of these, 50 (68%) could not be conducted, most commonly because the patient declined (n=13 (26%)) or they were considered confused by staff (n=11 (22%)) (Table 3). In those who had indirect calorimetry (n=12, 23 tests), the median measured energy requirement was 1982 [1843-2345] kcal compared to the median predicted energy requirement of 2000 [1725-2880] kcal in the same group. The median difference between the measured energy requirement on the days performed

and predictive study estimate was 16 [-307-520] kcal. In total, a median of 1890 [921-2348] kcal and 85 [35-121] g of protein was received from all sources of nutrition therapy on the days indirect calorimetry was performed. The median daily energy deficit was -161 [-886-150] kcal using a predictive equation and -95 [-1051-347] kcal using the measured requirement as the gold standard.

The mean bias between the measured estimate and the study predictive estimate (95% CI) was -58 kcal (CI -293 to 177) in the Bland-Altman analysis and the limits of agreement, -1.1e+03 to 1028 87 kcal. Bland-Altman plots are shown at Figure 2 and further details on indirect calorimetry measurements in Table 3.

Clinical outcomes are presented in Table 1.

Discussion

This is one of only a few published papers describing nutrition intake in the post-ICU hospitalisation period in critically ill survivors, and the largest in a mixed medical population. It is also the first study that has attempted to measure energy requirements with indirect calorimetry in a critically ill population after ICU stay. It provides important information which was previously unknown about the progress of nutrition intake and the feasibility of indirect calorimetry in critically ill survivors, after discharge from the ICU. Oral nutrition alone was the most common mode of nutrition delivery, and energy and protein intake with this mode was less than estimated and measured expenditure during the post-ICU hospitalisation period. The combination of EN and oral nutrition provided the greatest proportion of energy and protein delivery compared to estimated requirements. There was minimal difference between the

measured and predictive energy requirement however; the measurements could infrequently be conducted, and the limits of agreement were wide, indicating significant variability between the measured and predicted energy requirement.

There is limited literature describing nutrition intake in the post-ICU hospitalisation period following critical illness, however that which is available supports our findings; energy and protein intake was below predicted requirements [3-5]. A study conducted in 37 moderate traumatic brain injury patients suggested that energy and protein intake in ICU was lower than on the ward, however energy and protein intake was below predicted requirements during both periods. Additionally, those receiving oral intake had a much greater energy deficit than those receiving tube feeding, which we also observed [3]. In a study investigating oral nutrition intake 7 days post extubation in 50 critically ill patients, intake did not exceed 55% of predicted requirements on all 7 days assessed [5].

The reason poor nutrition intake occurs during the post-ICU hospitalisation period in patients who receive oral nutrition alone is likely to be multifactorial. One study followed 17 patients after their ICU admission and performed semi-structured interviews of patients to determine what was impacting on nutrition intake during this period. Factors such as appetite, viewpoint on food and eating, and physical ability to eat were all described [9]. Important system factors also appeared to be contributing, specifically; a culture of removing artificial feeding tubes with the view to promoting oral intake (even if oral intake was poor or the quantity not assessed by a dietitian) and the priority of nutrition therapy on the ward [4,9]. This was further supported by a second study that interviewed medical and nursing professionals working with patients with traumatic brain injury, also highlighting the competing healthcare-

related issues and priority of care for each patient and individual preference of and belief regarding the importance of nutrition [10].

Although measurements were few, we observed significant variation in metabolic rate measured by indirect calorimetry and a smaller daily energy requirement than when calculated by the study predictive estimate. The significant variability in measured energy requirements is not a new finding in critical illness and is the reason predictive equation estimates are considered to be at risk of error. [11] This study provides further evidence to support that variability in metabolic rate continues after ICU and although the mean bias was small in the Bland-Altman analysis, the limits of agreement observed were very wide and the mean difference between the measured estimate and the predictive study estimate highly variable. The wide limits of agreement are partially explained by a small sample size, however also support the significant individual variation observed in measured energy expenditure. It must also be noted that the choice of predictive energy equation may alter the observed agreement when compared to a measured energy estimate using indirect calorimetry, as each predictive equation has different accuracy rates, and these may change over the course of illness.

Implications for future practice and research

There are several important findings in this work that have implications for future nutrition practice and research. In these patients, oral nutrition was the primary mode of nutrition therapy provided, and energy and protein intake remained below both predicted and measured energy targets in the post-ICU hospitalisation period when oral intake was provided alone. Even with the combination of oral supplements, oral

nutrition alone may be insufficient to meet nutrition needs in this population. And importantly, when oral intake was combined with EN (occurring in almost half the patients (42%)), energy and protein intake was not deficient, but also frequently provided *more than* the estimated requirements. This may indicate that the combination of EN with oral nutrition may be the best way to meet nutrition needs in the post-ICU hospitalisation period. And in those who received more than their predicted energy and protein requirement with the combination of EN and oral nutrition, it can be hypothesised that perhaps the method or interval used to quantify nutrition intake was inaccurate, or that levels of staffing to review nutrition plans and tailor nutrition delivery may have been inadequate. Furthermore, it is unknown if a period of 'over-nutrition' following acute illness is beneficial or harmful in recovery. Indirect calorimetry could infrequently be conducted on the ward, most commonly because the patient refused. This has implications for the utility of this method in practice and research however this should be tested formally with dedicated staff. Therefore, research must now focus on understanding the barriers to adequate oral intake, accurate assessment of nutrition intake and the development of strategies to manage the associated issues in the post-ICU hospitalisation period.

Strengths and limitations:

This study is the largest study investigating nutrition provision in the post ICU hospitalisation period, and therefore provides valuable new information. The conduct within a RCT enabled rigorous data collection and study processes. There were however limitations to this work and these must be considered in the interpretation of our results. Firstly, this study was conducted at only 2 centres with a small cohort, and this limits some of the comparisons and conclusions that can be made. It was a sub-

study, and there were not always dedicated research staff at both sites on the post-ICU ward. Fifteen patients were included in the primary trial but who did not provide data for this nested cohort study. There may therefore have been selection bias. Furthermore, the hospital ward environment is unpredictable and not as controlled as in ICU. Despite best attempts by participating sites, this has affected data completeness for both assessment of oral intake and indirect calorimetry measurements. To reduce the burden of data collection with limited resources on the ward, nutrition intake assessment did not occur daily and there are well documented issues with the accuracy of using food record chats to assess oral intake [12]. To improve accuracy, dietitians with knowledge of the hospital menu were used to assist in recording and perform quantitative assessment of the food record charts. The energy deficit was small when energy intake was compared to measured energy requirements however it must be considered that the interval between nutrition intake and indirect calorimetry assessment, the method to quantify nutrition intake, as well as the limited number of indirect calorimetry measurements available may effect the accuracy of this result. No information was collected regarding why intake was limited, and while it has been reported that patients received oral nutrition as the greatest proportion, it is unknown if this mode of nutrition was the most appropriate mode for the patient, or what were the contributing issues when intake was inadequate. This is an area for future research. For the predictive energy and protein estimates, the last energy and protein requirement in ICU was extrapolated to the ward, and considered the ward requirement. This may not accurately reflect clinical practice and may have caused some inaccuracies. Lastly, this study has primarily focussed on energy intake. Macro and micronutrients provided by nutrition are likely to have a synergistic effect and energy is likely to be only one component which may benefit patients.

Conclusion

Energy and protein intake in the post-ICU hospitalisation period was less than both predicted and measured energy estimates and was most commonly provided by oral nutrition alone. Energy and protein intake was greatest in those who received EN in combination with oral nutrition, and lowest in those who received oral nutrition alone without oral supplements.. Indirect calorimetry measurements could infrequently be performed.

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Table 1: Baseline and outcome characteristics

Variable	Whole cohort (n=32)	Indirect calorimetry (n=12)	No indirect calorimetry (n=20)
Age, years, mean (SD)	56 (18)	59 (15)	53 (19)
Sex, male, n (%)	24 (75)	83 (10)	14 (70)
BMI, kg/m^2, mean (SD)	30 (8)	29.5 (6)	30 (9)
Weight, mean (SD)	90 (28)	88 (21)	91 (32)
Calculated body weight, mean (SD)	79 (17)	78.5 (12)	80 (19)
Energy requirement, kcal/kg actual weight, median [IQR]	24.5 [23-27]	23 [22-26]	25 [23-27]
Energy requirement, kcal/kg CBW, median [IQR]	25 [25-30]	25 [25-30]	25 [25-30]
Protein requirement, g/kg actual weight, median [IQR]	1.2 [1.1-1.3]	1.2 [1.1-1.3]	1.2 [1.1-1.4]
Protein requirement, g/kg CBW, median [IQR]	1.3 [1.3-1.5]	1.4 [1.2-1.5]	1.3 [1.3-1.5]
APACHE II score, mean (SD)	18 (7)	18 (8)	17 (5)
APACHE III diagnosis code, n (%)			
Cardiovascular	17 (53)	7 (53)	10 (50)
Trauma	7 (22)	5 (25)	2 (17)
Respiratory	2 (6)	1 (5)	1 (8)
Sepsis	3 (9)	3 (15)	0 (0)
Musculoskeletal	1 (3)	0 (0)	1 (8)
Time from ICU admission to oral intake commencement, days, median [IQR]	13 [4-16]	13 [4-16]	11 [5-15]
ICU LOS, days, mean (SD)	12[6-17]	12 [7-17]	12 [6-17]
Ward LOS, days, median [IQR]	10 [7-18]	13 [6-19]	9 [7-16]
Hospital LOS, days, mean (SD)	24 [18-33]	25 [21-33]	22 [17-34]
Survival, n (%)			
ICU D/C	100% (32)	100% (12)	100% (20)
Hospital D/C	100% (32)	100% (12)	100% (20)

APACHE: Acute Physiology and Chronic Health Evaluation II; BMI: Body mass index; CBW: Calculated body weight (see manuscript for definition); D/C: Discharge; ICU: Intensive care unit; IQR: Interquartile range; SD: Standard deviation

Table 2: Energy and protein intake in the post-ICU period on the days intake was assessed (n=227)

Variable	Result
Energy contribution by nutrition source on days assessed, median [IQR], kcal	
EN	893 [480-1996]
Food	648 [272-1207]
Oral supplements	250 [0-600]
Proportion of predictive study energy estimate, median [IQR], %	
EN	58 [21-93]
Food	35 [13-53]
Oral supplements	14 [0-29]
Protein contribution by nutrition source on days assessed, median [IQR], g	
EN	43 [24-84]
Food	31 [9-61]
Oral supplements	12 [0-24]
Proportion of predictive study protein estimate, median [IQR], %	
EN	55 [20.5-88]
Food	31 [9-56]
Oral supplements	11 [0-25]
Energy contribution by combination of nutrition on days assessed, median [IQR], kcal	
EN alone	962 [469-1685]
Oral nutrition	1443 [803-1923]
Oral nutrition (food only, no oral supplements provided)	894 [406-1473]
Oral nutrition (food and supplements provided)	1562 [1099-1992
EN and oral nutrition combined	1921 [1215-2627]
Protein contribution by combination of nutrition on days assessed, median [IQR], g	
EN alone	48.5 [24-84]
Oral nutrition alone	68.5 [40-94.5]
Oral nutrition (food only, no oral supplements provided)	50 [13.5-73.5]
Oral nutrition (food and supplements provided)	76 [52-100]
EN and oral nutrition combined	90 [51-123]
Proportion of predictive study energy estimate provided by combination of nutrition on days assessed, median [IQR], %	
EN alone	62 [21-96]
Oral nutrition alone	66 [38-89]
Oral nutrition (food only, no oral supplements provided)	37 [21-66]
Oral nutrition (food and supplements provided)	73 [51-94]
EN and oral nutrition combined	104 [66-132]
Proportion of predictive study protein estimate provided by combination of nutrition on days assessed, median [IQR], %	
EN alone	59 [20.5-97]
Oral nutrition alone	60 [37-83]
Oral nutrition (food only, no oral supplements provided)	48 [13-63]
Oral nutrition (food and supplements provided)	68 [49-84]
EN and oral nutrition combined	99 [60-127]

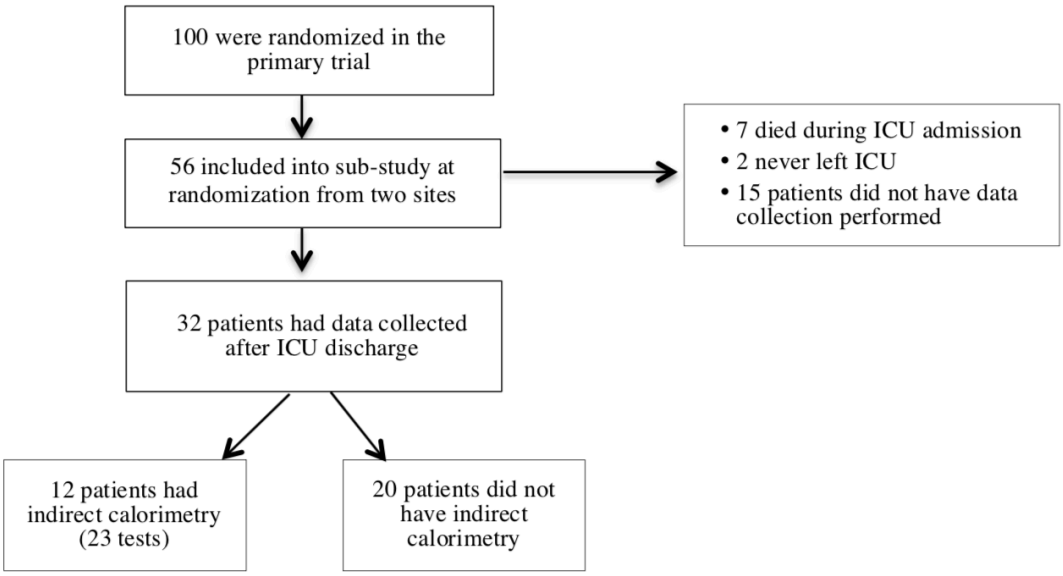
EN: Enteral nutrition; IQR: Interquartile range;

Table 3: Indirect calorimetry results

Variable	**Result (n=23)**	**Min**	**Max**
Measured RMR, kcal, median [IQR]	1982 [1843-2345]	1705	3306
VO2, ml/L, median [IQR]	284 [264.5-313]	245	475
Test length, mins, median [IQR]	7 [5-9]	1	11
Indirect calorimetry could not be performed, n (%)	50 (60)		
Reason, n (%)			
Patient declined	13 (26)	n/a	n/a
Agitated/confused	11 (22)		
Patient unsuitable	9 (18)		
Nasal oxygen	4 (8)		
Other	3 (6)		
Clinician unavailable	1 (2)		
Patient unavailable	1 (2)		

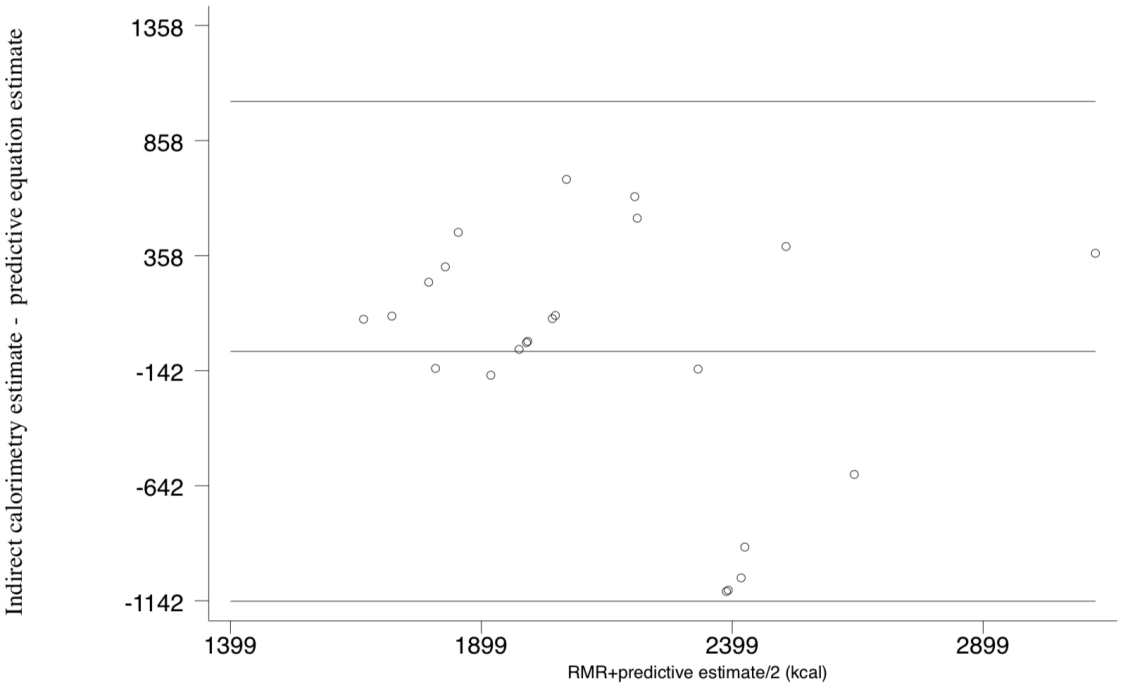
IQR: Interquartile range; RMR: Resting metabolic rate

Figure 1: Patient flow diagram



ICU: Intensive care unit

Figure 2: Bland-Altman analysis of agreement between measured energy estimates using indirect calorimetry and the study predictive equation estimate in the post-ICU hospitalisation period.



X axis: Mean energy requirement obtained with indirect calorimetry and the predictive study estimate; Y axis: difference between measured energy requirement and predictive equation estimate. The upper and lower lines represent the 95% limits of agreement

RMR: Resting metabolic rate

6.3 Case report forms

PATIENT STUDY NUMBER ___ ___ ___ - ___ ___ ___ ___ ___

PATIENT INITIALS ___ ___ ___

Ward nutrition intake record form

IMPORTANT NOTES:

- When the patient is in ICU please complete PART 4 OF THE DAILY DATA FORM DAILY
- When the patient is discharged to the ward, fill out this form second daily, Monday to Friday until hospital D/C or D 28).
- Fill out PART 1 if the patient received EN, PN or NO nutrition. You do not need to fill out PART 2.
- Fill out PART 2 instead of PART 1 if the patient received any oral nutrition and/or any PN/EN

Study Day	___ ___	___ ___	___ ___	___ ___	___ ___	___ ___
Date	___ ___ / ___ ___ / ___ ___ ___ ___ [dd/mm/yyyy]	___ ___ / ___ ___ / ___ ___ ___ ___ [dd/mm/yyyy]	___ ___ / ___ ___ / ___ ___ ___ ___ [dd/mm/yyyy]	___ ___ / ___ ___ / ___ ___ ___ ___ [dd/mm/yyyy]	___ ___ / ___ ___ / ___ ___ ___ ___ [dd/mm/yyyy]	___ ___ / ___ ___ / ___ ___ ___ ___ [dd/mm/yyyy]
Mode of nutrition received today?	☐ EN ☐ PN ☐ Oral ☐ Combined EN and PN ☐ Combined EN and oral ☐ None	☐ EN ☐ PN ☐ Oral ☐ Combined EN and PN ☐ Combined EN and oral ☐ None	☐ EN ☐ PN ☐ Oral ☐ Combined EN and PN ☐ Combined EN and oral ☐ None	☐ EN ☐ PN ☐ Oral ☐ Combined EN and PN ☐ Combined EN and oral ☐ None	☐ EN ☐ PN ☐ Oral ☐ Combined EN and PN ☐ Combined EN and oral ☐ None	☐ EN ☐ PN ☐ Oral ☐ Combined EN and PN ☐ Combined EN and oral ☐ None
PART 1						
Total energy intake	___ ___ ___ ___ kcal	___ ___ ___ ___ kcal	___ ___ ___ ___ kcal	___ ___ ___ ___ kcal	___ ___ ___ ___ kcal	___ ___ ___ ___ kcal
Total protein intake	___ ___ ___ g/day	___ ___ ___ g/day	___ ___ ___ g/day	___ ___ ___ g/day	___ ___ ___ g/day	___ ___ ___ g/day
PART 2						
Energy intake from nutrition supplements	___ ___ ___ ___ kcal	___ ___ ___ ___ kcal	___ ___ ___ ___ kcal	___ ___ ___ ___ kcal	___ ___ ___ ___ kcal	___ ___ ___ ___ kcal
Protein intake from nutrition supplements	___ ___ ___ g/day	___ ___ ___ g/day	___ ___ ___ g/day	___ ___ ___ g/day	___ ___ ___ g/day	___ ___ ___ g/day
Energy intake from food	___ ___ ___ ___ kcal	___ ___ ___ ___ kcal	___ ___ ___ ___ kcal	___ ___ ___ ___ kcal	___ ___ ___ ___ kcal	___ ___ ___ ___ kcal
Protein intake from food	___ ___ ___ g/day	___ ___ ___ g/day	___ ___ ___ g/day	___ ___ ___ g/day	___ ___ ___ g/day	___ ___ ___ g/day
Total energy intake	___ ___ ___ ___ kcal	___ ___ ___ ___ kcal	___ ___ ___ ___ kcal	___ ___ ___ ___ kcal	___ ___ ___ ___ kcal	___ ___ ___ ___ kcal
Total protein intake	___ ___ ___ g/day	___ ___ ___ g/day	___ ___ ___ g/day	___ ___ ___ g/day	___ ___ ___ g/day	___ ___ ___ g/day

Ward nutrition_Paper CRF V2 01 08 14 Page 1 of 2

PATIENT STUDY NUMBER __ __ __ - __ __ __ __ __

PATIENT INITIALS __ __ __

Ward nutrition intake record form

Study Day	__ __	__ __	__ __	__ __	__ __	__ __
Date	__ __ / __ __ / __ __ __ __ [dd/mm/yyyy]	__ __ / __ __ / __ __ __ __ [dd/mm/yyyy]	__ __ / __ __ / __ __ __ __ [dd/mm/yyyy]	__ __ / __ __ / __ __ __ __ [dd/mm/yyyy]	__ __ / __ __ / __ __ __ __ [dd/mm/yyyy]	__ __ / __ __ / __ __ __ __ [dd/mm/yyyy]
Mode of nutrition received today?	☐ EN ☐ PN ☐ Oral ☐ Combined EN and PN ☐ Combined EN and oral ☐ None	☐ EN ☐ PN ☐ Oral ☐ Combined EN and PN ☐ Combined EN and oral ☐ None	☐ EN ☐ PN ☐ Oral ☐ Combined EN and PN ☐ Combined EN and oral ☐ None	☐ EN ☐ PN ☐ Oral ☐ Combined EN and PN ☐ Combined EN and oral ☐ None	☐ EN ☐ PN ☐ Oral ☐ Combined EN and PN ☐ Combined EN and oral ☐ None	☐ EN ☐ PN ☐ Oral ☐ Combined EN and PN ☐ Combined EN and oral ☐ None
PART 1						
Total energy intake	__ __ __ __ kcal	__ __ __ __ kcal	__ __ __ __ kcal	__ __ __ __ kcal	__ __ __ __ kcal	__ __ __ __ kcal
Total protein intake	__ __ __ g/day	__ __ __ g/day	__ __ __ g/day	__ __ __ g/day	__ __ __ g/day	__ __ __ g/day
PART 2						
Energy intake from nutrition supplements	__ __ __ __ kcal	__ __ __ __ kcal	__ __ __ __ kcal	__ __ __ __ kcal	__ __ __ __ kcal	__ __ __ __ kcal
Protein intake from nutrition supplements	__ __ __ g/day	__ __ __ g/day	__ __ __ g/day	__ __ __ g/day	__ __ __ g/day	__ __ __ g/day
Energy intake from food	__ __ __ __ kcal	__ __ __ __ kcal	__ __ __ __ kcal	__ __ __ __ kcal	__ __ __ __ kcal	__ __ __ __ kcal
Protein intake from food	__ __ __ g/day	__ __ __ g/day	__ __ __ g/day	__ __ __ g/day	__ __ __ g/day	__ __ __ g/day
Total energy intake	__ __ __ __ kcal	__ __ __ __ kcal	__ __ __ __ kcal	__ __ __ __ kcal	__ __ __ __ kcal	__ __ __ __ kcal
Total protein intake	__ __ __ g/day	__ __ __ g/day	__ __ __ g/day	__ __ __ g/day	__ __ __ g/day	__ __ __ g/day

6.4 Study food record chart

Version 2 010814

FOOD RECORD CHART

Participant Study No |__| |__| |__| - |__| |__| |__|__| |__|

Study Day: |__| |__| Date:

Diet Code: Supplements Prescribed (if applicable):

Dietitian/Research Coordinator name: Pager:

Instructions for use:
- Tick amount consumed of each item
- If patient has received additional/alternative menu items please describe item e.g. scrambled eggs, yoghurt, meal brought in by family (with description) and tick amount consumed
- Please indicate if item is smaller/greater than 1 serve e.g. 2 pieces of bread; meal on bread and butter plate etc.

		Amount Consumed					For Dietitian/ Researcher	
Meals	**Food**	**None**	**¼**	**½**	**¾**	**All**	**Energy**	**Protein**
B-fast	Juice							
	Cereal							
	Milk							
	Toast/bread							
	Fruit							
	Supplement Drink Name:							
	Other							
	Other							
	Other							
Mid-morning	Supplement Drink Name:							
	Other							
	Other							
Lunch	Soup &/or bread (circle)							
	Salad &/or sandwich (circle)							
	Main- meat							
	Main – vegetables							
	Dessert (1 or 2)							
	Supplement Drink Name:							
	Other							
	Other							
	Other							
Mid-afternoon	Supplement Drink Name:							
	Other							
	Other							
Dinner	Soup &/or bread (circle)							
	Salad &/or sandwich (circle)							
	Main- meat							
	Main – vegetables							
	Dessert (1 or 2)							
	Supplement Drink Name:							
	Other							
	Other							
	Other							
Supper	Supplement Drink Name:							
	Other							
	Other							

Name:_____ Designation:_____Signature:_____
Date:_____

Supp PN FOOD RECORD CHART Instructions

1. A Food Record Chart is to be completed for each participant, second daily (Monday to Friday) post commencement of oral diet for 28 Days or until discharge.
2. Provide as much detail regarding food items as possible i.e. specify meal size; if patient has received additional/alternative menu items or meal brought in by family, describe item and estimate size (if required – gather further information by asking patient/nursing staff). Add a new line for each additional food item.
3. Tick amount consumed of each food item.
4. Validate with patient that they consumed all food items and amounts ticked (if able).
5. Utilise hospital ready reckoner/Food Works (if required) to estimate amount of energy and protein consumed each day.
6. Record amount of protein and energy consumed on study forms for each day.
7. Remove all Food Record Charts each day post completion and keep in original in Study Folder.

Chapter 7: Integrated discussion and conclusion

7.1 Chapter summary

This chapter summarises the key findings and research outcomes from the work presented in this thesis, provides context for future directions in critical care nutrition practice and research, and acknowledges the strengths and limitations of the research program.

7.2 Thesis outputs and key findings

This thesis describes the conduct and outcomes of a coordinated research program, including a systematic review and meta-analysis (Chapter 3); an observational study of nutrition practice in Australian and New Zealand ICUs (Chapter 4); a pilot RCT of optimised energy delivery in critically ill patients (Chapter 5); and a nested cohort study within a large randomised trial (Chapter 6).

The most substantial contribution to the literature arising from this program was the conduct of the bi-national multi-centre RCT of 100 critically ill patients to evaluate the use of a supplemental PN strategy. The intervention resulted in the delivery of significantly more energy during ICU stay than standard care. This novel strategy was designed to minimise the risk of overfeeding during the acute phase of critical illness, an important feature which distinguished this strategy from previous work. This pilot trial established the feasibility of a future research program and larger multicentre RCT, which the author will lead during her postdoctoral period. This work was discussed in detail in Chapter 5.

Additional contributions to the literature include a systematic review and meta-analysis (Chapter 3) that evaluated the association of energy delivery with clinical outcomes in critical illness, an important and unanswered clinical question. Whilst no association between clinical outcomes and energy delivery was observed, this review clearly identified that the quality of the literature currently guiding energy delivery in critical illness is very low. Most of the research in the literature was observational, and the few existing RCTs suffered from substantial methodological limitations, including small patient numbers and inadequate power to evaluate important clinical outcomes. Furthermore, there were problems with the heterogeneity of study participants and in the application of nutrition therapy interventions within trials. Lastly, there was considerable variation both in the outcome measures used and in the quality of reporting. These factors reduce comparability of studies and complicate interpretation.

A further contribution of the research program was the largest description to date of nutrition practice within Australia and New Zealand ICUs (Chapter 4). This work showed that nutrition therapy practices in Australia and New Zealand are similar to international practice. This finding confirms the generalisability of international nutritional research to Australia and New Zealand and vice versa. Nevertheless, some important differences were noted: Australian and New Zealand ICUs are more likely to report following nutrition guidelines than international ICUs, and the contents of these guidelines differed considerably between international and ANZ ICUs. The variability of guidelines reflects the low quality of evidence and lack of definitive RCTs in the area of critical care nutrition. Consistent with work over many years across several locations and populations, this observational study highlighted a significant practice and research gap in Australia and New Zealand with respect to the phenomenon of the

delivery of energy and protein to critically ill patients being markedly less than these patients are predicted to require. Several patient and service factors contribute to the inadequate delivery of energy and protein, but it may also be that clinicians have ceased their efforts to optimise delivery beyond standard care until better evidence is available. Finally, it was found that in Australia and New Zealand a significant proportion of patients also received oral nutrition during their ICU stay, either alone or with EN.

The final contribution of this research to the literature was the nested cohort study within an RCT (Chapter 6). This observaional work is significant due to the scarcity of data about nutrition delivery throughout a patient's hospitalisation, from admission to ICU through to the hospital wards to hospital discharge. This work highlighted that energy intake in the post-ICU period remained below predicted and measured energy requirements and that oral nutrition was the dominant mode of nutrition therapy in the post-ICU hospitalization period. Further, in the few indirect calorimetry measurements which were conducted, metabolic rate was highly variable and the agreement between predictive energy estimates and measured requirements was poor.

7.3 Implications for clinical practice and research

There is uncertainty as to the optimal amount of energy that should be provided to patients during critical illness. Nevertheless, clinical practice guidelines recommend that 100% of energy expenditure, estimated using standard equations, be delivered [9-12]. However, aside from one novel EN strategy, which was definitively tested in a large RCT in Australia and New Zealand and will be published in 2018 (the author is a co-investigator on this trial, which is registered at ClinicalTrials.gov, NCT02306746), supplemental PN is the only established methodology which has been able to achieve

these estimated energy requirements in critically ill patients [37, 60, 70, 71]. A central piece of work described in this thesis established the feasibility of a safe and successful method to reduce energy deficits early in the ICU stay, while at the same time protecting patients against overfeeding. The clinical implications of these observations will be determined in the student's postdoctoral work. Secondly, the work in this thesis identified that oral nutrition is an increasingly common additional mode of nutrition therapy in critical illness, both acutely but also during recovery. This has significant implications for clinical practice, as provision of adequate nutrition with this mode alone or in combination with other modes is challenging [44-46].

To further inform clinical practice in critically ill patients, future researchers should strive to improve research methodology in the field of critical care nutrition. Ideally, this should include larger and adequately powered trials, with clinical outcomes that are important to patients and that are likely to be affected by nutritional interventions. Ideally, this would include the development of key outcome sets for ICU nutrition trials, as well as rigorous design and reporting of trials using standard guidelines such as the Consolidated Standards of Reporting Trials (CONSORT), and the inclusion of important clinical information which relates to the provision of nutrition in critical care [72]. This would allow easy comparison of data across studies and populations.

Future research should also consider whether optimised energy delivery in the post-ICU period improves patient-centred outcomes. The complete and complementary body of work contained in this thesis has informed the methodology of a larger randomised controlled phase II trial that the author will conduct during her postdoctoral period and that will begin to address this idea. This 240 patient study will address the research

question “Does an intensive nutrition intervention provided during the whole hospital admission deliver increased amounts of energy to critically ill adults compared to standard nutrition care?”. This trial is the first to attempt a whole hospital nutrition intervention in critically ill adults and will use the supplemental PN strategy tested in the research contained in Chapter 5 but extend the delivery period to the whole ICU stay. For the post-ICU period, a new nutrition intervention will be devised and the feasibility tested. This trial is significant as it will provide valuable information about standard care nutrition delivery post critical care, and the feasibility of a post-ICU nutrition intervention in critical illness; it will have the potential to be applied to other populations once tested.

7.4 Strengths and limitations

The work described in this thesis identified key gaps within the field of critical care nutrition practice, and in the reporting of the literature in critical care nutrition. A strength of the program of work is the variety of included methodologies – an observational study, a systematic review and meta-analysis, a multi-centre bi-national RCT and a nested cohort study.

One limitation of the research is the fact that energy is only one of several important macronutrients required during critical illness. Other macronutrients and micronutrients are important and indeed are synergistic to optimal nutritional response during illness. It should be acknowledged, however, that nutrients may need to be investigated separately to understand their individual roles before considering their probable synergistic effects. A second limitation, and a key finding of this thesis, was that the quality of research currently being used to guide nutrition therapy in critical illness is of

varying and often low quality, and could be markedly improved. This has implications for the work conducted for this thesis, because this thesis itself is also subject to these limitations.

7.5 Conclusions

The program of research that contributed to this thesis established the feasibility of a novel technique (supplemental PN) to improve energy delivery in critical care settings. The method appears to be safe and will be evaluated further during postdoctoral work in a larger RCT. This program also identified that adequately powered trials, with standardised study processes and outcomes which are intuitive to nutrition, are required to better inform clinical practice decisions about nutrition delivery for critically ill patients.

Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning

\- *Winston Churchill*

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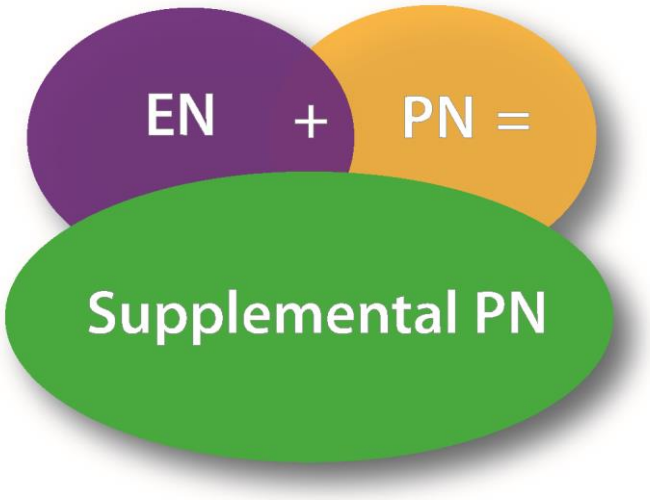
Thesis appendices

Study documents for the randomized trial (Chapter 5): *"Supplemental parenteral nutrition versus usual care in critically ill adults: a pilot randomized controlled study"*

a) Data dictionary

b) Standard Operating Procedure

Supplemental Parenteral Nutrition: A Pilot Randomised Controlled Trial



Website Instructions and Data Dictionary

Protocol AD003 Version 8 10 07 14

Data Dictionary Version 2 01 08 14

anzic research centre

Table of Contents

Summary of changes between V1 and V2

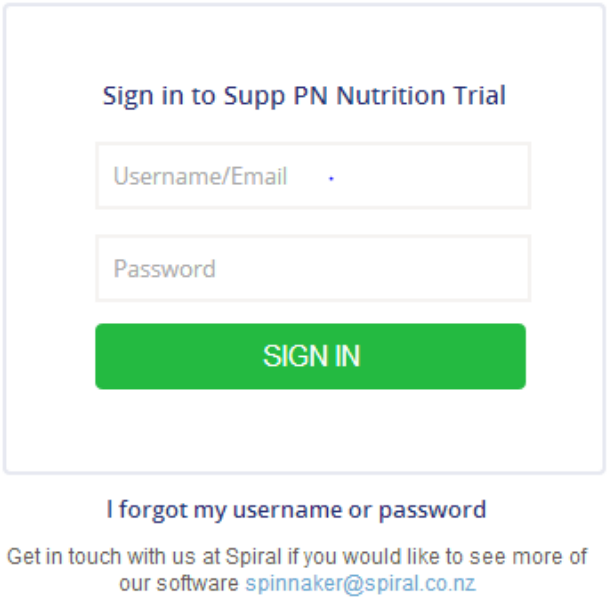
- Changes to inclusion critiera:
  - ✓ Change of PaO2/FiO2 to ≤300 mmHg
  - ✓ Addition of extracorporeal membrane oxygenation and currently has a ventricular assist device as organ failures
- Greater explanation of some of the data points based on feedback from the sites
- There is a 48 hour window for ICU and hosptial outcome data to allow for weekends/ missed discharges
- Changes to the Hospital, 3 and 6 month outcome processes to allow for economic analysis

Access to the website

- To access the website go to:

http://nutrition.spinnakersoftware.com/Login/

- You will be provided with log on access by the project manager.
- Your user name is your email address.
- Your password will be set as 'password'. Please change it the first time you log in.
- If you forget your password use the **'I forgot my username or password'** function.



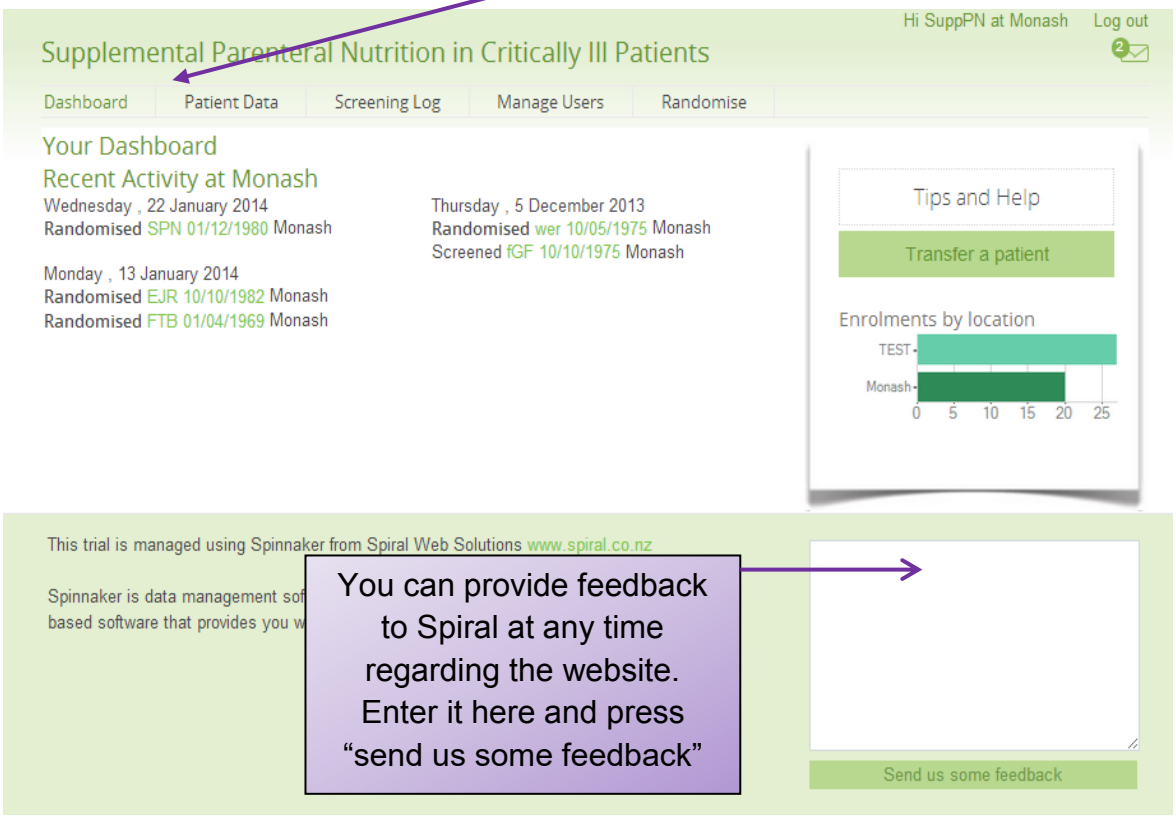
Changing your password:

- If you need to change your password, log into the website and then go to the 'manage users' tab of the website.
- Find your name and select 'edit user'

You will see your password in the 'password' field of the screen. Change this to your chosen password and select 'update user' at the bottom of the screen.

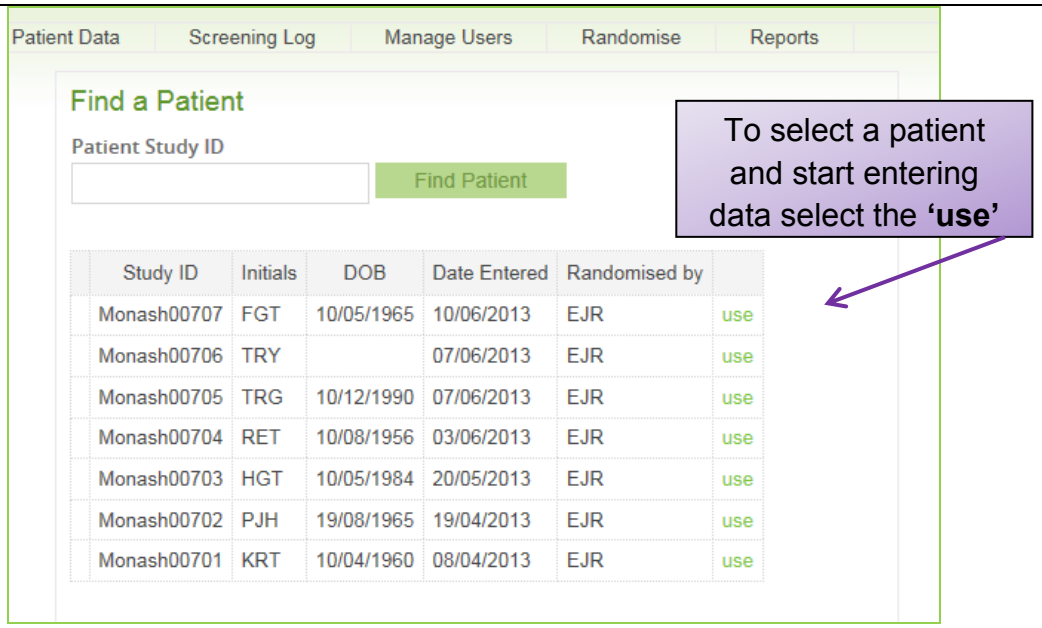
Dashboard

- After log on you will be directed to the **'dashboard'** of the web-site.



Patient Data

- The **'patient data'** tab will display all the patients that have been randomised at your site.

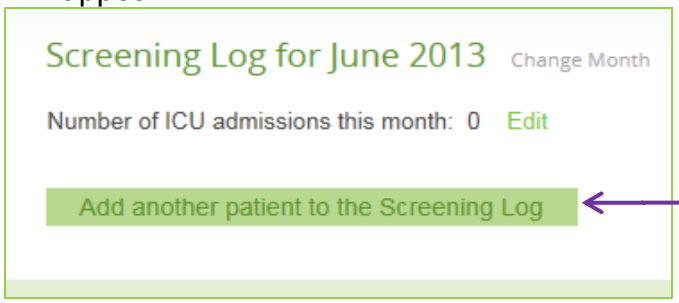


- You will then be taken to the **'patient summary'** where you can proceed to enter data.

Introduction to Study Website and eCRF

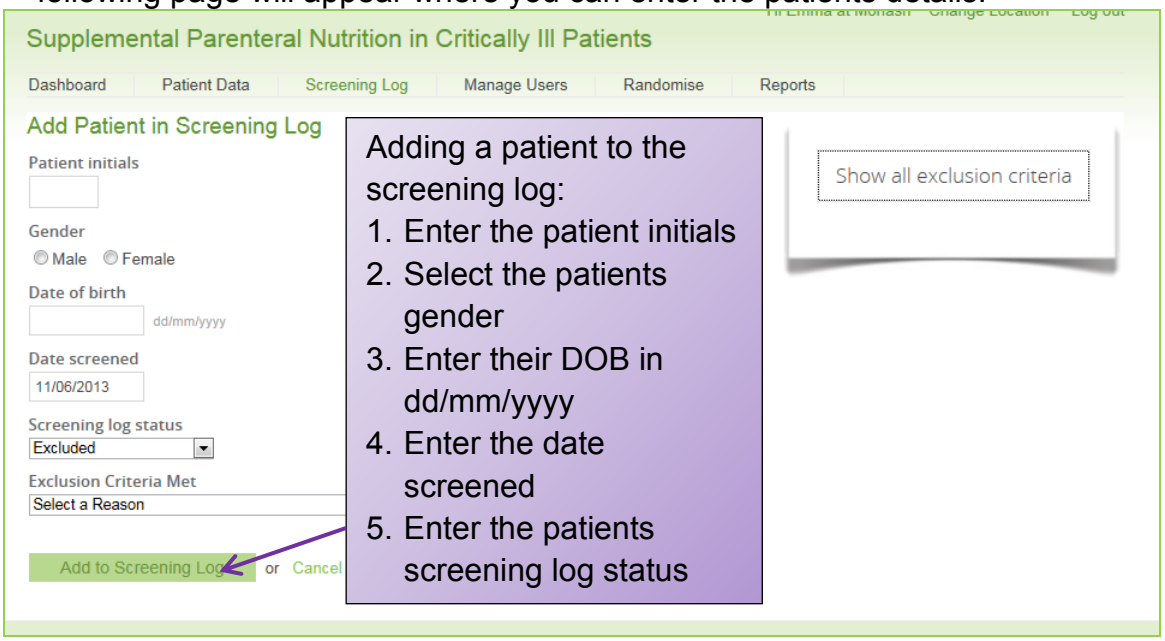
Screening log

- As this study is a pilot study, screening information is very important for planning of a larger trial.
- Select the **'screening log'** tab to enter a new entry. The following page will appear.



Please add the number of ICU admissions each month. This helps us with recruitment rates for the pilot study.
To add a patient onto the screening log select the **"Add another patient to the Screening Log"** button found here.

- Once you have selected **"Add another patient to the Screening Log"** the following page will appear where you can enter the patients details.



Adding a patient to the screening log:
1. Enter the patient initials
2. Select the patients gender
3. Enter their DOB in dd/mm/yyyy
4. Enter the date screened
5. Enter the patients screening log status

If the patient is excluded, select the exclusion criteria that was met. The options are:

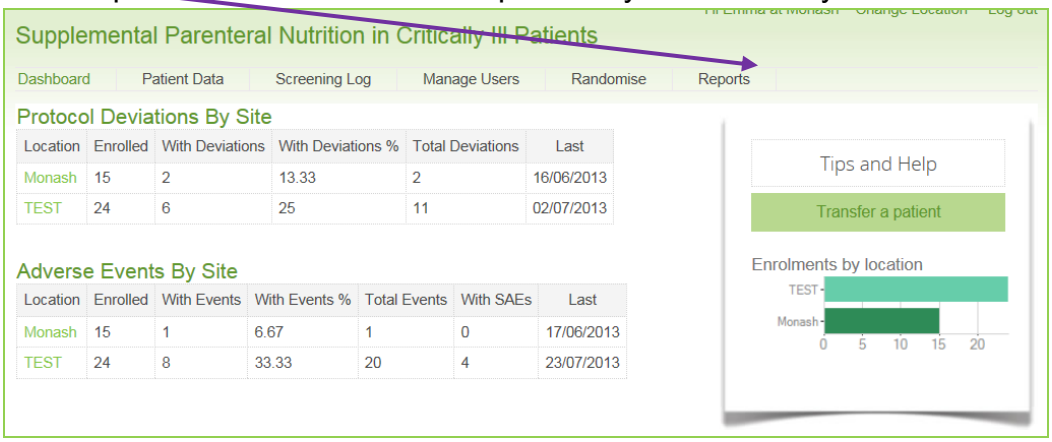
- Excluded: please enter the exclusion criteria that was met
- Failed an inclusion criteria: please select the criteria that was failed
  The following additional options are also available under the **"Failed an inclusion criteria"**:
  - ✓ Missed, did not consent and other with a free text option.
- If the option **"treating clinician does not believe the study is in the patients best interest"** is chosen, please enter the reason why this is the case.

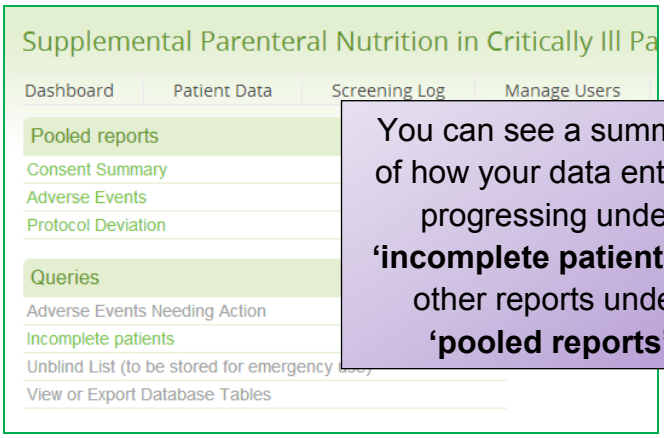
Time out function

- There is a timeout function on the website. If there is no activity on the webpage a message will appear warning the user of the time-out period.Select 'OK' to stay
  logged in.

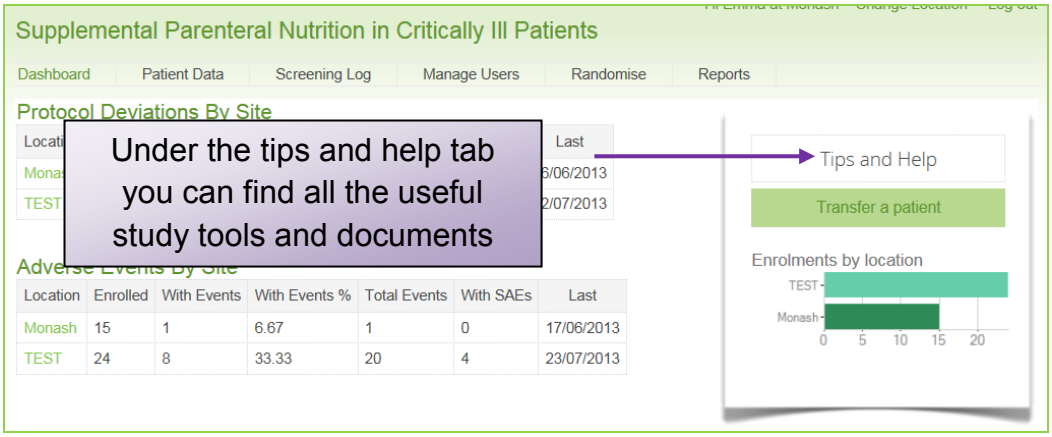
Reports

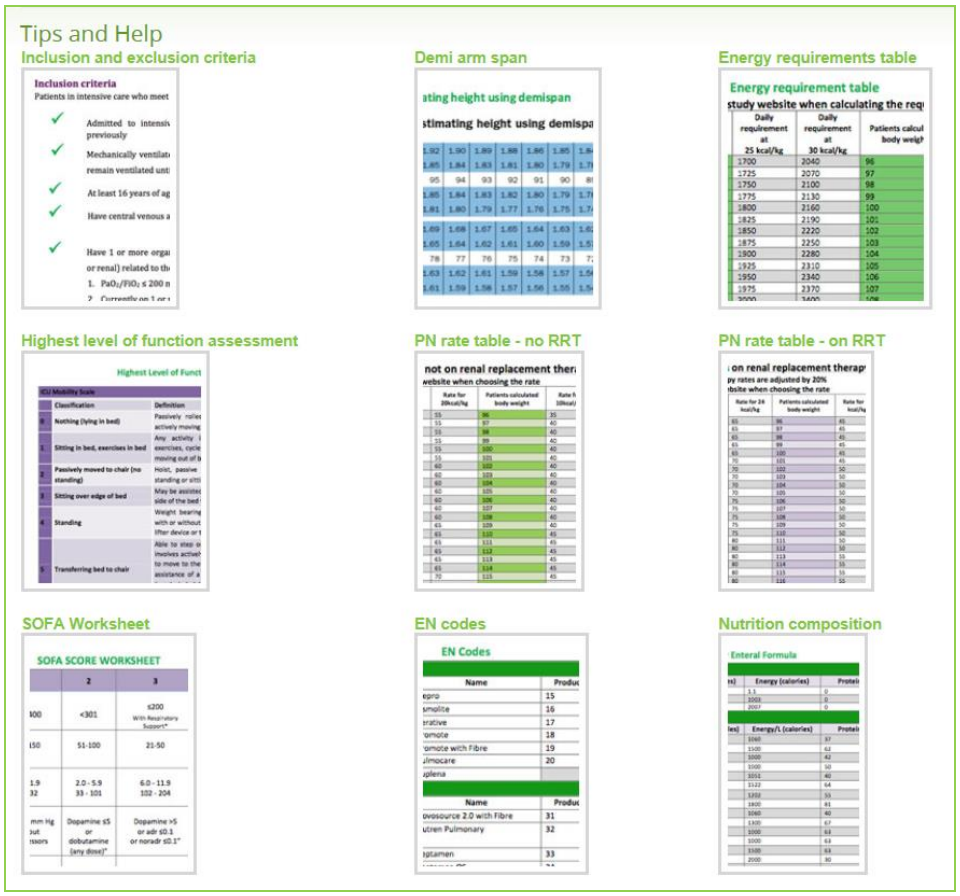
- The reports tab houses various reports on your data entry.





Tips and Help





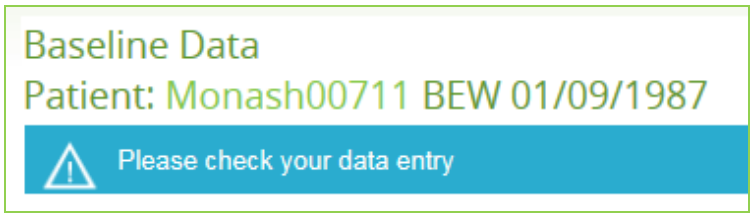
Error Messages

- There are several error messages that will appear as you try to enter data. The main messages you will see are:
  - ✓ a **'required'** message
  - ✓ a **'check your data entry'** message and
  - ✓ a **'range'** check message.

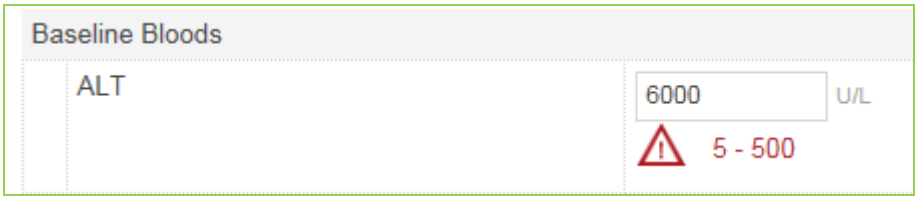
- Where **'required'** displays it indicates that the field is mandatory before the form can be submitted.

- Some options have a **'not measured'** box that can be selected if you are not aware of the answer at the time you are submitting data.
- **Please remember to re-enter the correct value at a later time if you select this option.**

- This entry means that there is likely a date error.



- This error message is for an out of range entry. The expected range is shown for you.

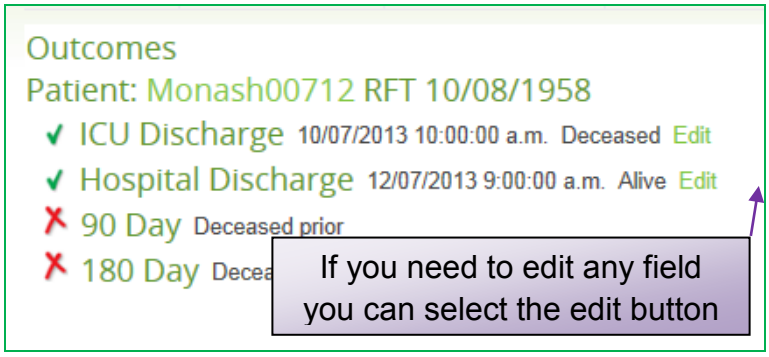


Required fields

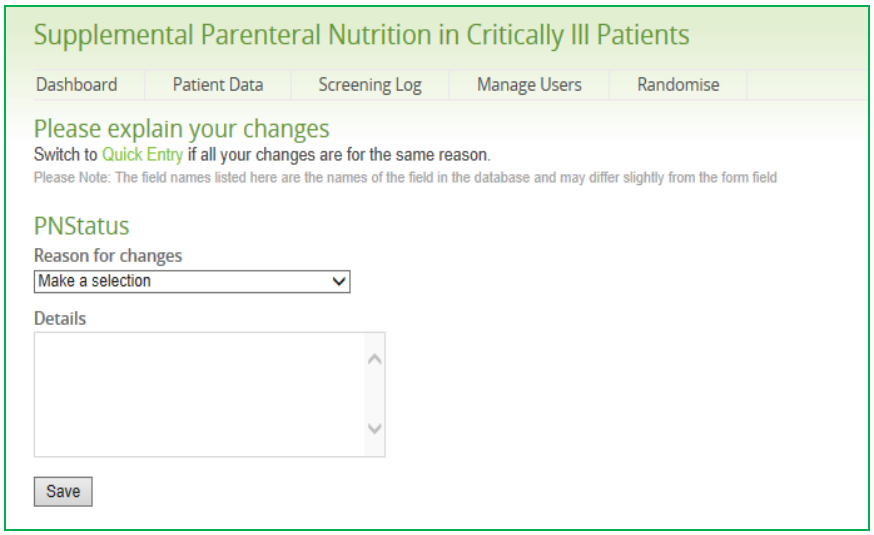
- Below is a summary of the **'required fields'.**

	Form submission	Form status indicators
Randomisation	All fields must be entered before form will submit data to database.	No status indicator. Immediately after randomisation and before any data is input all the patient status indicators are ✗
Baseline	All fields are required to save the form. "Not measured" checkboxes can be used if test results are not available.	✗ when no data entered ✓ when all data entered ? when some data entered
Daily Data	All fields (except witnessed complications) are required to save the form. "Not measured" checkboxes can be used if test results are not available at the time of data entry.	✗ when no data entered for any day ✓ when all days have been entered (to date) ? when some days have been entered but its not up-to-date Shows the number of daily data records, in brackets, that have been entered in the database.
Nutrition Intake	All fields must be entered before form will submit data to database.	✗ when no data entered for any day ✓ when all days have been entered (to date). We expect NI for all days between ICU discharge and hospital discharge. ? when some days have been entered
Consent	All fields must be entered before form will submit data to database.	✗ when no consent present ✓ when any consent has been obtained even if later withdrawn ? not used
Indirect Calorimetry	All fields must be entered before form will submit data to database.	Status box displays the number of Indirect Calorimetry records entered in the database
Protocol Dev	All fields must be entered before form will submit data to database.	Status box displays the number of protocol deviations
Adverse Event	All fields must be entered before form will submit data to database.	Status box displays the number of Adverse Events that have occurred. Does not count SAE's
Outcome forms • ICU discharge • Hosp d/c • 3 months • 6 months	Most fields must be entered before form will submit data to database.	✗ when no outcomes have been entered ✓ when all outcomes are in place ? when some outcomes have been entered

Changing data after it has been entered (editing)

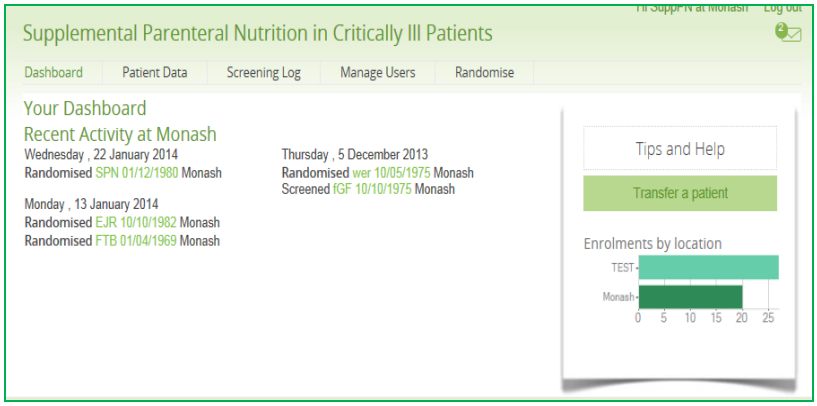


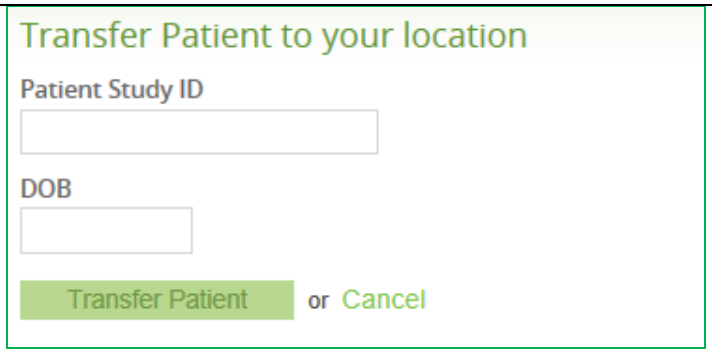
- After you have edited the relevant data the following screen will appear where you should enter the reason you have changed the data and any relevant details.



Transferring a patient

- If a patient is transferred between Supplemental PN sites, you can select the **'transfer a patient'** option on the website from the **'dashboard'** screen.





The patient and relevant data will be transferred to your site.

Reminder function

- Reminders will be provided by email for follow up items.
- Each Monday an email will be sent listing which patient follow ups are due in the coming week and any follow ups that are waiting for data.
- The Project Manager can also set these for each user.
- Supp PN users can opt out of receiving these reminders through their profile page in the "Manage Users" section of the website. We would prefer however that users receive the reminders.

Study days

- Study Day 1 is from randomisation up to the end of the calendar day. E.g. If the patient is randomised at 16:00 hours and then Day 1 is from 16:00 hours to 23:59 hours.
- All other study days start at 00:00 until 23:59

Printing

- To print any form on the website, select print on your browser and print the page as you usually would.

Using paper data forms:

- The best functionality will occur from entering data directly onto the website
- Paper forms have been provided if you prefer to collect data this way. **Please review which fields are required daily and what fields are required on specific days (detailed in this data dictionary and at appendix 4 OR 5.**
- The forms that are provided as paper are:
  1. Baseline data
  2. Daily forms for all nutrition intake options
  3. Physical measurement log to record all physical measurements
  4. SOFA record form
  5. Blood test record form
  6. Consent record form
  7. Outcomes record form
  8. Protocol deviation record form

9. Adverse events and serious adverse events record form

And for those at The Alfred and Auckland City doing the additional items:

10. Nutrition intake forms
11. Indirect calorimetry and oral intake record log

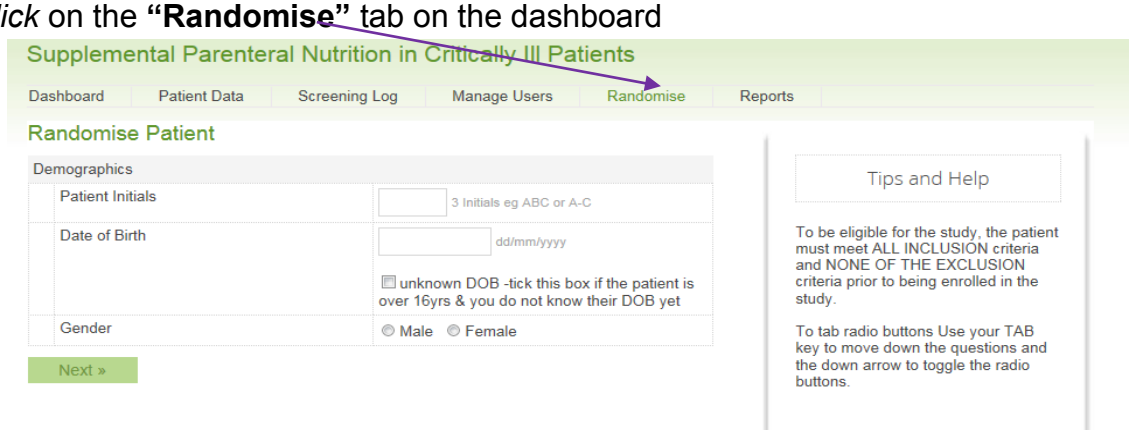
Randomisation

Notes:

- **If there is any doubt about the eligibility of a patient – DO NOT randomise the patient.** Every patient that is randomised has to be included in the data analysis (using the intention to treat principle) – therefore we must avoid including ineligible patients. It is better to miss a patient than to enroll an ineligible one.
- All patients must meet all the inclusion criteria and none of the exclusion criteria to be eligible.
- All eligibility questions and all data fields must be answered.

Log into the website.

Click on the **"Randomise"** tab on the dashboard



1. Enter 1st letter of given name, 1st letter of middle name (if exists) and 1st letter of surname. eg John Harry Bloggs would be JHB If there is no middle name, use a dash to replace this eg J-H.

2. Enter their DOB in the dd/mm/yyyy format. If DOB is unknown, select the **"unknown"** option. **Please ensure the patient is over 16 years prior to randomisation. If the age is unknown and there is any doubt about whether or not the patient is older than 16 years, DO NOT randomise the patient (to avoid a potential protocol violation).**

3. Select the patients gender

4. Select **"Next"**

You will be taken to the **"inclusion/exclusion"** screen of the randomisation page.	
Inclusion Criteria **If No is selected to any of the criteria, the patient is <u>NOT</u> eligible**	
Is the patient over 16 years old?	**At the time of randomisation the patient must be ≥ 16 years old.** If the age is unknown and there is any doubt about whether or not the patient is older than 16 years, **DO NOT randomise the patient (to avoid a potential protocol violation).**
Was the patient admitted to intensive care between 48-72 hours previously?	**At the time of randomisation the patient must have been admitted to an intensive care between 48-72 hours prior.**  **<u>This includes time in other units if the patient was transferred from another ICU- please ensure you check this prior to randomisation.</u>** If a patient was admitted before this window please rescreen the following day.
Is the patient mechanically ventilated and expected to remain so until at least the day after tomorrow?	**At the time of randomisation the patient must be receiving invasive mechanical ventilation and the treating clinician must believe they will remain so until the day after tomorrow.** Invasive ventilation is defined as any form of positive pressure ventilation administered via an endotracheal tube or tracheostomy tube.
Does the patient have central venous access suitable for PN administration?	**At the time of randomisation the patient must have central venous access that is suitable for PN administration.** This includes a central line, PICC line or Hickmann's. **A peripheral line is not a suitable line for delivery of PN.**
Does the patient have 1 or more organ system failures?	**At the time of randomisation the patient must <u>have 1 or more organ system failures</u> defined by the criteria listed.** PaO2/FiO2 ≤300 mmHg Currently on 1 or more continuous vasopressor infusion which were started at least 4 hours ago at a minimum dose of: ✓ Dopamine > 5 mcg/kg/min ✓ Noradrenaline ≥ 0.1mcg/kg/min ✓ Adrenaline ≥ 0.1 mcg/kg/min

	✓ Any dose of vasopressin ✓ Milrinone >0.25mcg/kg/min Renal dysfunction defined as: **<u>In patients without documented renal disease</u>** ✓ Serum creatinine > 171 mmol/l **OR** ✓ Currently receiving/scheduled to receive renal replacement therapy **<u>In patients with a documented history of chronic renal disease</u>** ✓ An absolute increase of > 50% in creatinine from baseline **OR** ✓ Currently receiving/scheduled to receive renal replacement therapy Currently has an intracranial pressure monitor or ventricular drain Currently receiving extracorporeal membrane oxygenation Currently has a ventricular assist device Refer to the Study SOP for further instructions regarding inclusion criteria and any associated calculations.
Exclusion Criteria **If YES is selected to any of the criteria the patient is <u>NOT</u> eligible**	
EN and PN cannot be delivered at enrolment	**Select "yes" if the patient has a true contraindication to EN.** This is defined as a non-functioning gastro-intestinal tract or inability to obtain EN access or if the treating clinician feels that EN **can not be safely delivered at any rate.** **Delivery of trophic EN is acceptable.** If the patient does not have central venous access for PN delivery or the treating clinician feels that PN is contraindicated then **"yes"** should be selected.
Standard PN cannot be delivered at enrolment.	**Select "yes" if the treating clinician feels that a standard PN solution** (one with lipids, carbohydrate, protein, vitamins and electrolytes, but without glutamine) **is not in the patients best interest**.
Currently receiving PN	**Select "yes" if the patient is already receiving or has previously received PN at any stage in their**

	hospital admission.
There is a current treatment limitation in place or the patient is unlikely to survive 6 months due to underlying illness	**Select "yes" If the patient has a terminal condition that will likely lead to death in the next 6 months.**
Death is imminent or deemed highly likely in the next 96 hours	**Select "yes" if death is anticipated in the next 96 hours** and the treating physician is not committed to full supportive care.
More than 80% of energy requirements have been delivered via the enteral route in the last 24 hours	**Select "yes" if more than 80% of energy requirements have been delivered via the enteral route in the last 24 hours.** • **An excel calculation tool is provided to assist you with this (Supp PN eligibility and energy calculation tool V2_01082014).** Refer to the SOP and study tools provided for additional assistance.
Are known to be pregnant	**Select "yes" if it is documented in the medical file that the patient is pregnant.**
The treating clinician does not believe the study to be in the best interest of the patient	**Select "yes" if it is the treating clinician's decision not to enrol the patient.** Please enter the reason why on the screening log.
Randomisation • If you have completed the inclusion and exclusion criteria satisfactorily then proceed to enter the following information	
Person Randomising	**Enter your full name.** Alice Wood would be entered as Alice Wood. This helps us to identify study personnel if needed.
Is this patient included in the sub-study **THE ALFRED AND AUCKLAND CITY HOSPITALS ONLY**	**Other sites please select no.** Select **"yes"** if the patient is going to be included in the sub-study.
Is the patient currently on renal replacement therapy and/or ECMO?	**Mark "yes" if the patient is receiving or is expected to receive renal replacement therapy (RRT), hemofiltration or extracorporeal membrane oxygenation (ECMO) today**. This includes continuous or intermittent dialysis.
Height	**Enter the patients demi-arms span in cm.** Refer to the study SOP for instructions.

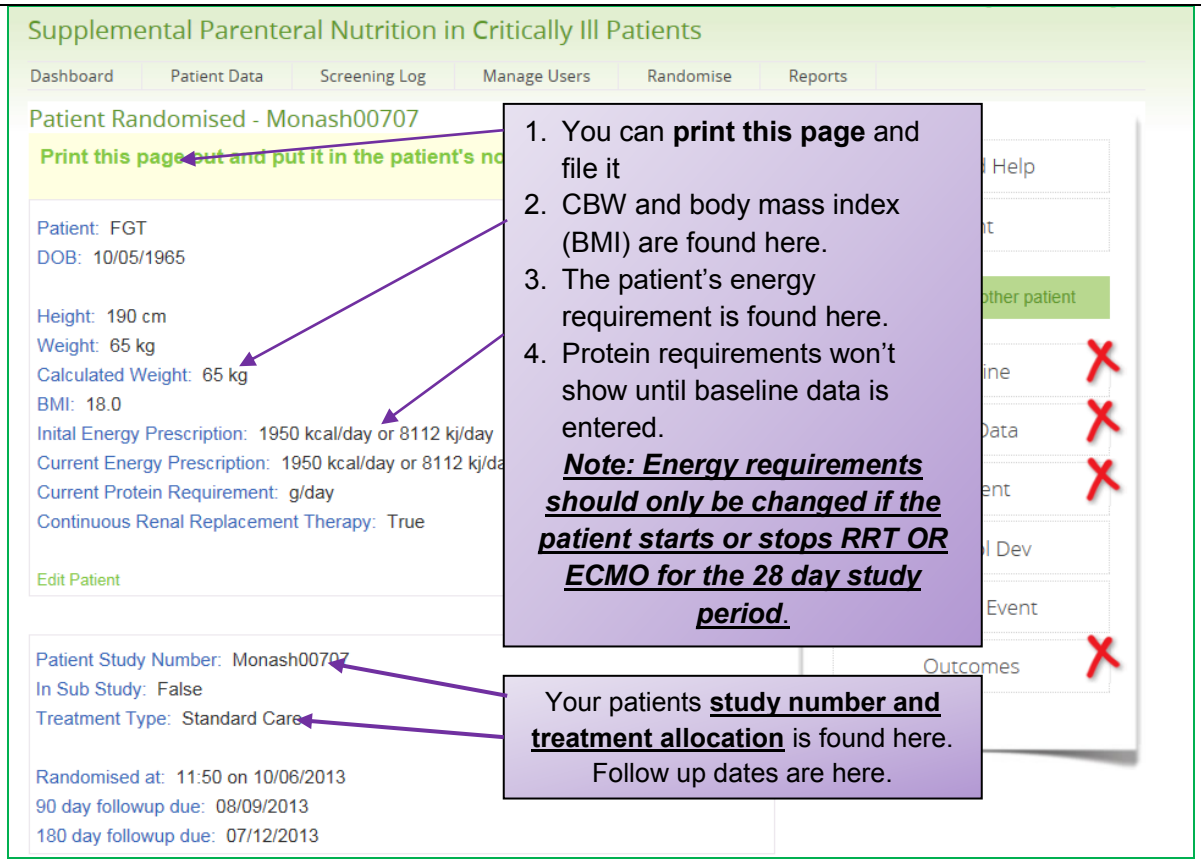
	In the event that you can not complete the demi-arm span assessment, please estimate the patients height and work backwards on the table to get the corresponding demi-arm span for entry into the website.
Weight	**Enter the patients actual weight in Kilograms (kgs) as per the following preferred hierarchy:** a) Actual body weight if it has been recorded in the previous 6 weeks b) Estimated dry weight if actual weight is not known. If estimated, please record the Dietitian's estimation as first preference followed by any other method of estimation. The website will then determine the patients calculated body weight (CBW) for the purposes of estimating nutrition requirements. Refer to the SOP for instruction on how the website calculates this.

Once all the fields have been entered select the "randomise" tab.

- If any of the responses to questions are missing, a message will appear prompting completion of the appropriate question(s).
- If the responses to any of the eligibility questions result in the patient being ineligible for the study, a message will appear stating the patient is not eligible to be randomised. The option to either exit the randomisation procedure or return to the randomisation form for correction is displayed.

Patient randomised

Once you have randomised your patient you will be taken to the following screen

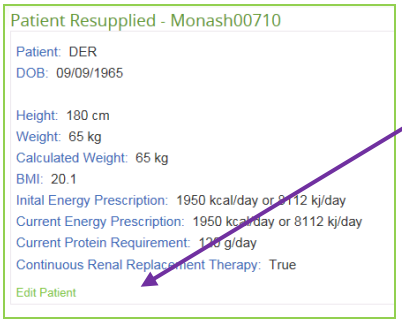


- The patients study number is generated by the website.

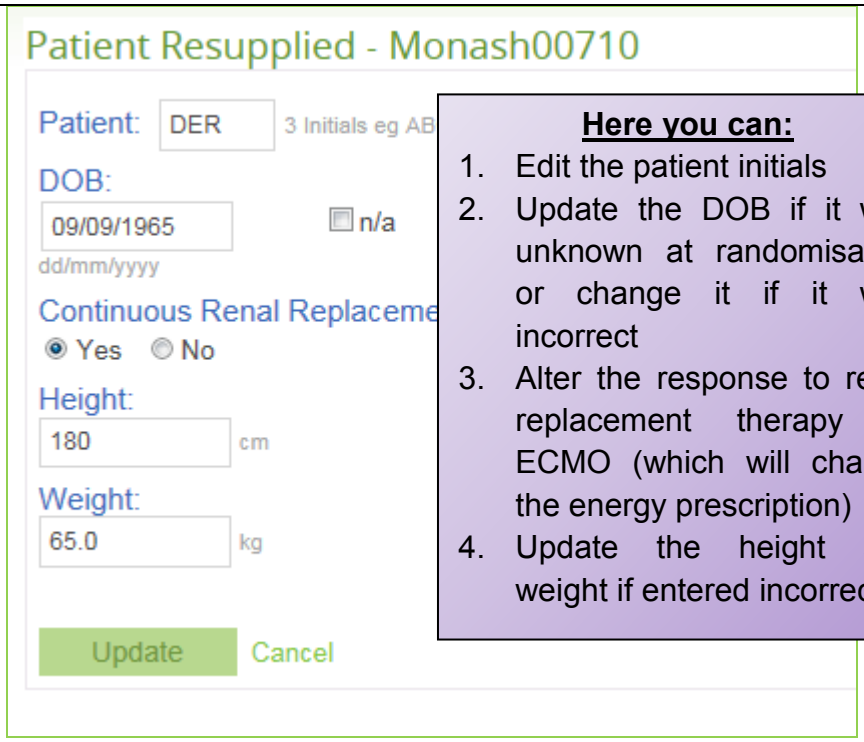
- The Patients initials and DOB should appear as you entered them in the initial randomisation screen.

Edit patient

- If you need to edit the details of a patient after randomisation, select the **'edit patient'** option.



- You will be taken to the following screen.



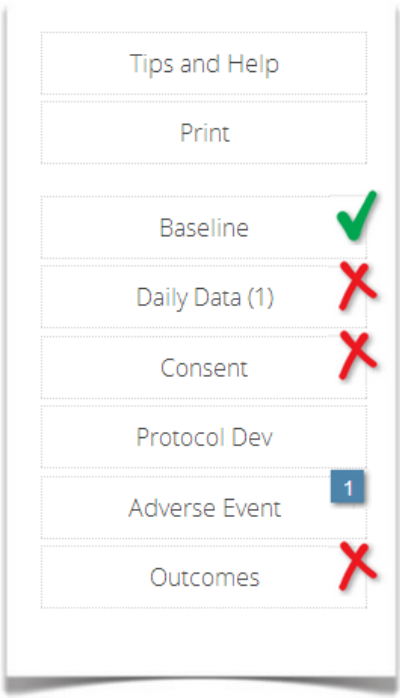
Here you can:

1. Edit the patient initials
2. Update the DOB if it was unknown at randomisation or change it if it was incorrect
3. Alter the response to renal replacement therapy or ECMO (which will change the energy prescription)
4. Update the height and weight if entered incorrectly.

- If the date of birth was initially unknown and the entered D.O.B corresponds to the patient being aged less than 16 years at the time of randomisation you will need to complete a protocol deviation form.

Entering patient data

- To enter patient data select the tabs on the side of the website.



- As data is entered, numbers will appear on some tabs showing you how many

events/days have been entered.

Baseline data

Notes:

- For this form, all fields must be entered before you can submit all data. If you do not have all data, you can select the 'unknown box'. Please remember to go back and update this data.
- Baseline data should be taken within the 24 hours prior to randomisation. If multiple values are available please choose the most deranged value in the time period.
- The corresponding paper form is number '1'- Baseline data form.
- Refer to the study SOP for further information and instructions

Where was the patient before this ICU admission?	**Select the location of the patient prior to admission to ICU.** ✓ **Emergency Department** = the Emergency at your hospital. ✓ **Hospital Ward =** any WARD in your hospital, including day care facilities but not including an ICU, CCU, HDU in your hospital (if care is provided by an intensive care specialist in that ICU, CCU or HDU) . ✓ **Transfer from other ICU** = any other ICU or HDU from within your hospital where care is provided by intensive care specialists OR an ICU from another hospital ✓ **Transfer from another hospital** = transfer from any area in another hospital EXCEPT an ICU. ✓ **Operating theatre following EMERGENCY surgery or Operating theatre following ELECTIVE surgery.** In considering whether a patient has been admitted after elective or emergency surgery, 'elective' is defined as not involving a medical emergency and able to be done at the convenience of the patient or medical staff. Any surgery that is performed for the purposes of source control of known or suspected infection, whether acute or chronic, is defined as emergency surgery for the purposes of this definition. This includes surgery for a perforated viscus, irrespective of whether infection is clearly established or not.

Date and time of first hospital admission	**Enter the date of hospital admission using the online calendar.** If the patient was transferred from another hospital or ICU you should enter the date they were admitted to that hospital. Use the hospital database or ICU observation chart (whatever is applicable at your site) but be consistent with the source. Use this full date format 01/02/2011 for 1st February 2011 Enter the time of hospital admission using 24 hour format: 03:15 for quarter past 3 in the morning.
Date and time of first ICU admission	**Enter the date of ICU admission using the online calendar.** **<u>If the patient was transferred from another ICU you should enter the date they were admitted to that ICU.</u>** Use the hospital database or ICU observation chart (whatever is applicable at your site) but be consistent with the source. Use this full date format 01/02/2011 for 1st February 2011 Enter the time of ICU admission using 24 hour format: 03:15 for quarter past 3 in the morning.
Date and time mechanical ventilation was commenced	**Enter the date the patient commenced mechanical ventilation (MV) using the online calendar.** **<u>If the patient was transferred from another ICU you should enter the date that MV was commenced in that ICU.</u>** Use the hospital database or ICU observation chart (whatever is applicable at your site) but be consistent with the source. At the time of randomisation the patient must be receiving invasive ventilation. Invasive ventilation is defined as any form of positive pressure ventilation administered via an endotracheal tube or tracheostomy.

	Use this full date format 01/02/2011 for 1st February 2011 Enter the time MV using 24 hour format: 03:15 for quarter past 3 in the morning.
Apache	
Apache III Diagnosis	**Select the APACHE III diagnosis code at the time of admission to ICU.** The codes are provided as a link on the web site or as Appendix 1.
Apache II Score	**Record the APACHE II Score derived from data collected from the 24 hours prior to the time of randomisation.** Enter the exact score a leading zero is not required. ✓ The APACHE II Worksheet is provided as a link on the website and in Appendix 2. ✓ If APACHE II is calculated using the worksheet manually (not on the website), please follow the following instructions. ✓ The APACHE II score is the sum of 3 parts: Part A – Acute Physiology Score, Part B – Age Points, Part C – Chronic Health Points ✓ To complete Part A - Acute Physiology Score, for each of the 12 physiological variables, select the most deranged value up to (but not including) the time of randomisation. For example, if the temperature from the time of admission to randomisation has been as high as 40°C and as low as 33°C, tick the box in the column that assigns 3 points in the 'high abnormal range' column because 40°C attracts 3 points but 33°C, whilst still abnormal, only attracts 2 points. When necessary round data up or down to the nearest integer (whole number). For data 0.5 or above always round upwards. E.g., 44 years and 3 months is rounded down to ≤ 44 years and assigned 0 points; a calculated MAP of 129.7 is rounded up to 130 and assigned 3 points. This must be followed for every patient to ensure consistency. Below is further information to guide you in the completion of APACHE II PART A: ✓ Temperature – this should be a core temperature measurement (rectal, tympanic, oesophageal or via PAC). Where this is not possible, add 0.5°C to the

	oral or axillary temperature. ✓ If mean arterial pressure (MAP) is not calculated by the monitoring equipment, use the systolic and diastolic measurement to obtain MAP using this equation MAP = [(DBP x 2) + SBP] ÷ 3. Use the converter tool to derive the MAP value. ✓ If the patient has an atrial arrhythmia, measure the ventricular response rate (R waves) only to record the heart rate. ✓ A – aDO2 is the difference between the calculated alveolar oxygen tension and the arterial oxygen tension. The alveolar oxygen tension is calculated by this equation: AO2 = 713 x FiO2 – PaCO2 x 1.25. The FiO2 here is expressed as a proportion of a unit. E.g. 100% FiO2 = 1 and 60% equals 0.6. If the FiO2 (inhaled oxygen concentration) is greater than 50%, APACHE II records the most deranged value from the time of injury up to randomisation for the A – aDO2. If the FIO2 is less than 50% APACHE II records only the PaO2 (arterial oxygen pressure). All measurements are in mmHg. A – aDO2 calculation is [(FiO2 (713)-(PaCO2/0.8)]-PaO2 If arterial blood gases have not been performed or are unavailable, choose the most deranged value for the serum venous bicarbonate (HCO3) in place of the arterial pH ✓ Acute renal failure: "If abnormal serum creatinine values reflect acute renal failure as opposed to chronic renal failure then the points assigned to the creatinine values should be doubled. Acute renal failure is defined as any creatinine value that is not within the normal range designated by the APACHE II system." Thus for the purposes of this study if your patient has any points for an increased creatinine and they are not documented to have chronic renal failure then the creatinine points should be doubled. ✓ To obtain a score for the Glasgow Coma Scale (GCS) use the GCS worksheets provided (for TBI patients use the GCS from the head injury observation chart or ambulance notes where possible) and subtract the GCS score from 15 to arrive at a score on the APACHE II worksheet. Use

	the lowest GCS collected prior to intubation, prior to administration of sedative agents and if possible post fluid volume administration to obtain the true neurological GCS. ✓ Whenever possible, make an attempt to obtain a score for each physiological variable. If one of the 12 variables is not available, assign 0 points and make a note of this absence on the APACHE II worksheet. The assumption being made is that a test or measurement was not ordered because the status of the patient did not warrant investigation, rather than the data was missing. To complete PART B – assign points to the age range that the patient fits in to. E.g., a 48 year old patient would be assigned 2 points. To complete PART C – first decide if the patient meets any of the criteria provided on the worksheet for a history of severe organ insufficiency or immune-compromised. If there is no history, assign 0 points. If there is a history, assign points depending on whether the patient is a non-operative emergency admission or an emergency post-operative admission (5 points) OR a post-operative admission following elective / planned surgery (2 points). **Finally, add the points recorded for each of the 3 parts and enter this total score.** The minimum score is 0 and the maximum score is 71. Keep the completed APACHE II worksheet in the Patient CRF Worksheet File for this patient.

SOFA	
A SOFA worksheet is provided on the study website and in Appendix 3 The corresponding paper form is number '1'- Baseline data form and '4'- SOFA Record Form	
Cardiovascular	**Enter the one digit SOFA score for the cardiovascular system. Use data within the 24 hours prior to randomisation. Use the value that derives the worst score.** If the value is unknown select the 'not measured' option. Do not use data from after randomisation.
Respiratory	**Enter the one digit SOFA score for the respiratory system. Use data within 24 hours prior to randomisation. Use the value that derives the worst score.** If the value is unknown select the 'not measured' option. Do not use data from after randomisation.
Liver	**Enter the one digit SOFA score for the liver. Use data within 24 hours prior to randomisation. Use the value that derives the worst score.** If the value is unknown select the 'not measured' option. Do not use data from after randomisation.
Renal	**Enter the one digit SOFA score for the renal system. Use data within 24 hours prior to randomisation. Use the value that derives the worst score.** If the value is unknown select the 'not measured' option. Do not use data from after randomisation.
Coagulation	**Enter the one digit SOFA score for coagulation. Use data within 24 hours prior to randomisation. Use the value that derives the worst score.** If the value is unknown select the 'not measured' option. Do not use data from after randomisation.

Baseline bloods	
Notes: • Baseline bloods should be measured on the same day as randomisation. Choose the value closest to randomisation but within the previous 24 hours. • If bloods are not previously ordered, please order them at the time of randomisation but do not delay randomisation. Enter the baseline bloods once they have returned from the lab. • The corresponding paper form is number '1'- Baseline data form.	
Alanine aminotransferase (ALT)	**Enter the serum ALT level in U/L.** If no ALT is available and could not be ordered on the same day as randomisation, enter not measured to indicate the data was unavailable at baseline. If the test has been ordered and you are waiting for the result, select **'not measured'** and enter the data once it has been returned from the lab. Alternatively, wait to enter the baseline data until all tests are available or are truly **'not measured'.**
Gamma glutamyl transferase (GGT)	**Enter the serum GGT level in U/L.** If no GGT is available and could not be ordered on the same day as randomisation, enter not measured to indicate the data was unavailable at baseline. If the test has been ordered and you are waiting for the result, select **'not measured'** and enter the data once it has been returned from the lab. Alternatively, wait to enter the baseline data until all tests are available or are truly **'not measured'.**
Alkaline phosphatase (ALP)	**Enter the serum ALP level in U/L.** If no ALP is available and could not be ordered on the same day as randomisation, enter not measured to indicate the data was unavailable at baseline. If the test has been ordered and you are waiting for the result, select **'not measured'** and enter the data once it has been returned from the lab. Alternatively, wait to enter the baseline data until all tests are available or are truly **'not measured'.**
Bilirubin	**Enter the serum bilirubin in µmol/L.** If no bilirubin is available and could not be ordered on the same day as randomisation, enter not measured to indicate the data was unavailable at baseline. If the test has been ordered and you are waiting for the result, select **'not measured'** and enter the data once it

	has been returned from the lab. Alternatively, wait to enter the baseline data until all tests are available or are truly **'not measured'.**
White Cell Count (WCC)	**Enter the WCC in 10^9/L.** If no WCC is available and could not be ordered on the same day as randomisation, enter not measured to indicate the data was unavailable at baseline. If the test has been ordered and you are waiting for the result, select **'not measured'** and enter the data once it has been returned from the lab. Alternatively, wait to enter the baseline data until all tests are available or are truly **'not measured'.**
Triglycerides (TG)	**Enter the TG level in mmol/L. Please order before the study PN is commenced (if so allocated).** If no TG is available and could not be ordered on the same day as randomisation, enter not measured to indicate the data was unavailable at baseline. If the test has been ordered and you are waiting for the result, select **'not measured'** and enter the data once it has been returned from the lab. Alternatively, wait to enter the baseline data until all tests are available or are truly **'not measured'.**
C-Reactive Protein (CRP)	**Enter the CRP in 'mg'.** If no CRP is available and could not be ordered on the same day as randomisation, enter not measured to indicate the data was unavailable at baseline. If the test has been ordered and you are waiting for the result, select **'not measured'** and enter the data once it has been returned from the lab. Alternatively, wait to enter the baseline data until all tests are available or are truly **'not measured'.**
Baseline Nutrition Assessment	
Total Protein Requirements	**Enter the daily protein requirements as determined by the dietitian in the nutrition assessment in grams (g) per day. This estimation is at the dietitian's discretion** If a range is estimated enter the middle value of the range. If a nutrition assessment has not been conducted at the time of randomisation then estimate the protein requirements using 1.2g/kg of CBW for patients who are not receiving renal replacement therapy or 1.5g/kg

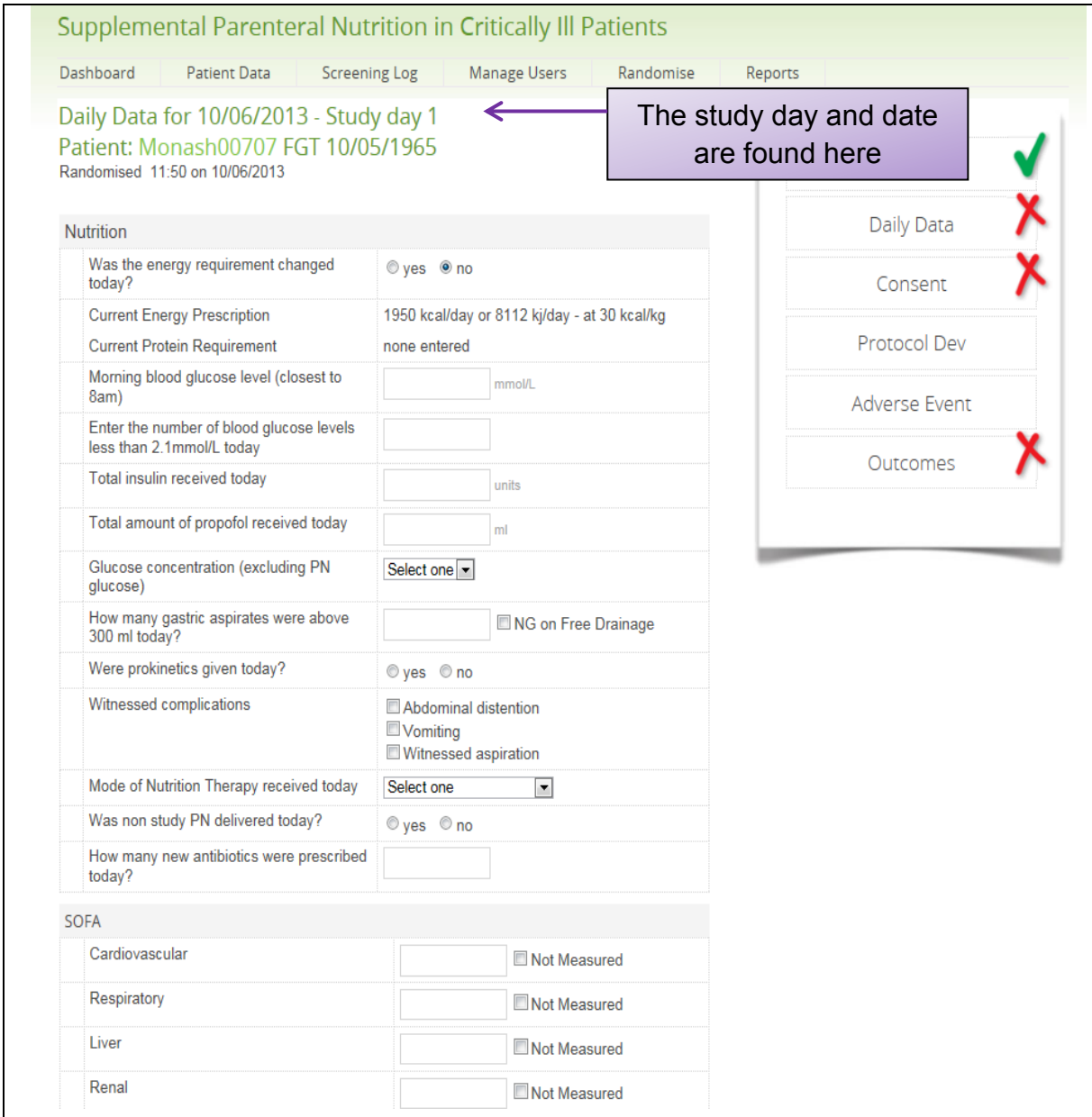
	for patients who are receiving RRT and/or ECMO and then update the data when the assessment is completed.
Was EN commenced prior to enrolment into the study	**Select "yes" if enteral nutrition was commenced prior to randomisation for any time period.**
How much energy from all sources was received prior to enrolment into the study?	**Enter the energy contributions from all sources in whole numbers from hospital admission to randomisation in kcal.** **An excel calculation tool is provided to assist you with this (Supp PN eligibility and energy calculation tool V2_01082014).** Only include 25 and 50% dextrose in your considerations for glucose contributions. Enter '0' if there is not any energy provided from a particular source. For example, if a patient received 1000ml of a 1cal/ml enteral feed, no glucose and 400ml of propofol enter 1000, 0 and 440 respectively (NB: 1ml of propofol equals 1.1kcal). Refer to the study SOP for further information on calculating energy contributions.
Mid Arm Muscle Circumference	**Enter the patients mid arm muscle circumference in cm.** If it is unable to be obtained select the "not measured" option. Refer to the study SOP for instructions on how to measure mid arm muscle circumference. This can be recorded on paper form '3'- Physical measurement log.
Sub-study only	
Nitrogen Loss	Nitrogen loss will be calculated based on the 6 hour urinary nitrogen study that is conducted. Remember to multiply the result by 4 if a 24 hour nitrogen balance estimate is not provided by the laboratory. Enter this value into the website in g/day.
Nitrogen intake	Enter the total nitrogen intake on the study day. Refer to the study SOP for instructions on how to calculate this.
Once all fields are completed select the *"add baseline data".* Once you select "add baseline data" you will be taken back to the following screen.	

To enter daily data, select the **"daily data tab"**

Daily Data

Notes:

- Please complete this form for all randomised patients.
- Complete this form each day during the ICU admission up to Day 28, ICU discharge or death, whichever occurs first.
- **For patients at The Alfred or Auckland City Hospital, please continue data collection as per the requirements for the additional part of the study.**
- Study Day 1 is from randomisation up to the end of the calendar day. E.g. If the patient is randomised at 16:00 hours and then Day 1 is from 16:00 hours to 23:59 hours.
- All other study days start at 00:00 until 23:59
- If the patient is readmitted to ICU during the current hospital stay daily data will not be collected.
- The corresponding paper form is number '2'- Daily data form.



Nutrition

Notes:

- **The following questions are required to be answered for all patients every day of the study period.**
- **For the first 7 days of the study, where PN is used it is to be the <u>'study PN'</u> provided by Baxter in both the supplemental PN group and the standard care arm (if needed).**
- **After Day 7, PN may still be used if indicated, but it is to be the hospitals usual formula, referred to as 'non-study PN'.**

Was the energy requirement changed	**This question should only be answered 'yes' if RRT and/or ECMO was commenced or ceased up until**

today?	**day 28, ICU or hospital discharge (in the case of the patients having additional data collection). This includes continuous or intermittent dialysis.** **If you are using the paper collection form remember to review this manually.** Otherwise the requirement should not change. If you select **"yes"** a drop down option will appear and you should select "25" if it is expected that the patient is not going to be on RRT and/or ECMO in the next 24 hours or **"30"** if the patient is expected to receive RRT and/or ECMO in the next 24 hours. This includes continuous or intermittent dialysis. The website will automatically calculate the patients' energy requirements for the following 24 hour period. For those in the supplemental PN group, this requirement should be used when assessing how much energy the patient has received to determine if the PN rate. If the protein requirement also changed enter the new number in g/day. This is at the discretion of the dietitian. Refer to the SOP manual for further instructions on determining the energy provision daily.
Morning blood glucose	**Record the first blood sugar reading taken closest to 08:00 hrs.** The result can be either a blood serum or finger prick capillary result.
Enter the number of blood glucose levels less than 2.1mmol/L today	**Enter the number of blood glucose levels less than 2.1mmol/L documented in the study day period.**
Total insulin received today	**Enter the total number of units of insulin administered over the 24 hr period.** If the patient is receiving 2 different types of insulin add the number of units together to provide the total amount of insulin. If the patient did not receive insulin enter '0'.
Total amount of propofol received today	**Enter the total amount of propofol provided today in mls.**
Glucose concentration (excluding PN Glucose)	**Enter the concentration of glucose that was provided today (only 25 or 50%).** Once you have selected the concentration that was provided enter the volume in mls. If none was provided, select **'none'**.
How many gastric	**Enter the number of gastric aspirates that were**

aspirates were above 300 ml today	**above 300ml today. If there were no aspirates above 300ml then enter '0'.** Alternatively, if the gastric tube was on free drainage then select **'NG on free drainage'**.
Were prokinetics given today	**Select 'yes' if Metoclopramide and/or Erythromycin were provided today. Select 'no' if they were not. This includes if they were charted but not given.** If you select **'yes'** you then need to select the prokinetic agent and **enter the dose that was provided in the 24 hour period.** For example if Metoclopramide was provided 4 times and the dose was 10mg per time you would enter 40mg as the daily total. If only one prokinetic agent is given select the **'none given box'** for the alternate prokinetic.
Witnessed complications	**Select the box relating to the witnessed complication if you observe the complication yourself or it is documented in the patients file.** This includes the medical history and other relevant history such as the nursing chart. Do not select this option unless you observe the episode yourself or there is documentation in the patients medical file relating to the episode.
Mode of nutrition therapy received today	**Select the mode of nutrition therapy that was received on the study day.**
Mode of nutrition therapy received today: *EN*	**Select EN if the patient received enteral nutrition via any route.** • **Select up to three product codes from the list provided. Select 'n/a' for the other option is only 1 or 2 are provided.** • **Enter the total volume of EN actually received by the patient for each formula.** • **The volume received should not include gastric aspirates that were discarded.** For example, if the infusion was turned off for 4 hours during a procedure the volume received would be 65mls x 20 hrs = 1300mls. You would enter 1300mls. For example, if the patient received 65 x 20 hrs of EN (1300mls) but had 2 x 200 ml aspirates and 100ml was discarded the volume received will be 1300-100= 1200ml. If the patient receives more than one type of EN during the 24 hour period determine the volume of each

	formula received and enter the corresponding code. Enter the location of the feeding tube. If the location of the tube changes throughout the day enter only one mode. Choose the mode that was used for the majority of the time during this feeding day. Post-pyloric = the tube is located past the pyloric sphincter in either the duodenum or jejunum.
Mode of nutrition therapy received today: *PN*	**This only refers to study PN delivered on its own, not in combination with EN. If other hospital PN is delivered please enter it under 'Non Study PN'.** If study PN was delivered today, enter the volume received in mls.
Mode of nutrition Therapy received today: *Oral*	Select **'oral'** nutrition if oral diet or nourishing fluids were taken (excluding water) with the intent to provide nutrition.
Mode of nutrition Therapy received today: *Combined EN and PN*	**Select combined EN and PN if both EN and PN were delivered today.** **This should be selected for patients randomised to the Supplemental PN arm who are still receiving EN.** **This will also include patients in the standard care arm who receive PN if required and EN is continued.** • **Select up to three product codes from the list provided. Select 'n/a' for the other option is only 1 or 2 are provided.** • **Enter the total volume of EN actually received by the patient for each formula.** • **The volume received should not include gastric aspirates that were discarded.** For example, if the infusion was turned off for 4 hours during a procedure the volume received would be 65mls x 20 hrs = 1300mls. You would enter 1300mls. The volume received should not include gastric aspirates that were discarded. For example, if the patient received 65 x 20 hrs of EN (1300mls) but had 2 x 200 ml aspirates and 100ml was discarded the volume received will be 1300-100= 1200ml. If the patient receives more than one type of EN during the 24 hour period determine the volume of each formula received and enter the corresponding code.

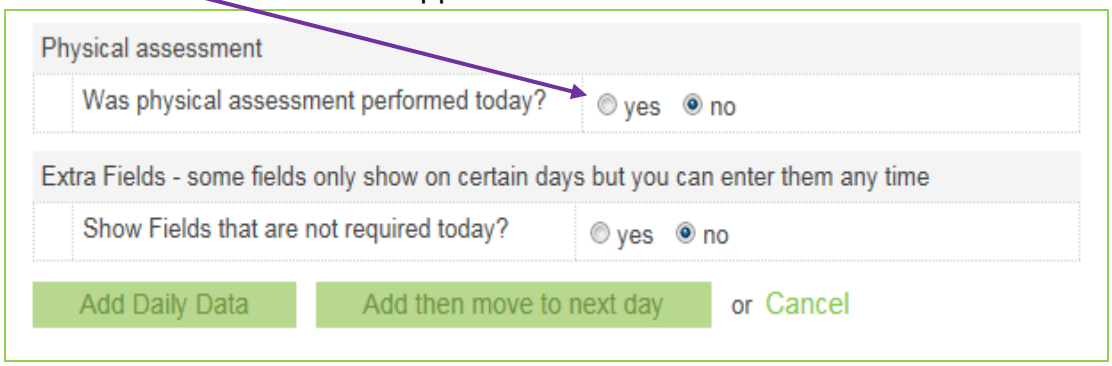
	Enter the location of the feeding tube. If the location of the tube changes throughout the day enter only one mode. Choose the mode that was used for the majority of the time during this feeding day. Post-pyloric = the tube is located past the pyloric sphincter in either the duodenum or jejunum. Enter the volume of Study PN received today. If non-study PN was delivered enter as per below in 'non study PN delivered today'.
Was non study PN delivered today?	**If non study PN was delivered today (ie the hospitals standard formula), select 'yes' and enter the following information:** ✓ **Lipid percentage:** Enter the percentage of lipid that is the PN bag being delivered. ✓ **Lipid volume in PN bag:** Enter the volume of lipid that is in the bag being delivered. ✓ **Glucose concentration:** Enter the percentage of glucose that is the PN bag being delivered. ✓ **Glucose volume in bag:** Enter the volume of lipid that is in the bag being delivered. ✓ **Protein:** Enter the grams of protein found in the total volume of PN being delivered to the patient. ✓ **Enter the total volume** of non-study PN that was provided to the patient.
How many new antibiotics were prescribed today	**Enter the number of new antibiotics prescribed today on the medication chart.** For example, if the patient had 2 antibiotics yesterday and a new one is prescribed today, enter '1' as the number of new antibiotics administered on the study day.

SOFA	
Notes: • SOFA Score will only appear on specific days. • SOFA Score needs to be completed on study Days 1-3, 7, 14, 21, 28 (unless discharged from ICU) • On other days it will not appear on the daily data collection. • Use data from the 24 hour period of the specified study day. • The corresponding paper form is number '4'- SOFA Record form. • A SOFA worksheet is available at appendix 3 and on the website.	
Cardiovascular	**Enter the one digit SOFA score for the cardiovascular system. Use data within the 24 hours prior to randomisation. Use the value that derives the worst score.** If the value is unknown select the **'not measured'** option.
Respiratory	**Enter the one digit SOFA score for the respiratory system. Use data within 24 hours prior to randomisation. Use the value that derives the worst score.** If the value is unknown select the **'not measured'** option.
Liver	**Enter the one digit SOFA score for the liver. Use data within 24 hours prior to randomisation. Use the value that derives the worst score.** If the value is unknown select the **'not measured'** option.
Renal	**Enter the one digit SOFA score for the renal system. Use data within 24 hours prior to randomisation. Use the value that derives the worst score.** If the value is unknown select the **'not measured'** option.
Coagulation	**Enter the one digit SOFA score for coagulation. Use data within 24 hours prior to randomisation. Use the value that derives the worst score.** If the value is unknown select the **'not measured'** option.

Physical Assessment

Notes:

- Physical assessment only needs to be completed **once the patient is ready for ICU discharge.**
- This information needs to entered as part of the 'daily data' for the last day in ICU. Select 'yes' under 'physical assessment' when you are ready to enter this information and the fields will appear.

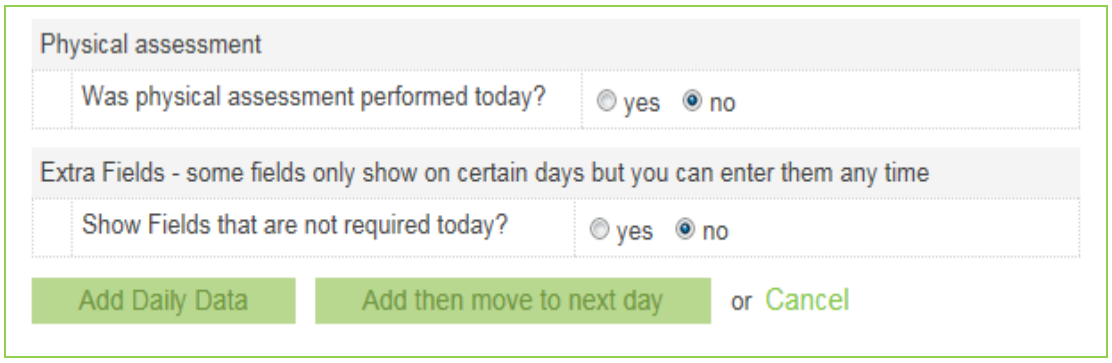


- **Only select *'yes'* when the treating team deems that the patient is ready for ICU discharge and enter the information.** If the patient is ready for discharge but can not be discharged due to 'bed block' please complete the assessment as soon as the patient is deemed 'ready' to go.
- The corresponding paper form is number '3'- Physical measurement log

Mid Arm Muscle Circumference	**Enter the patients mid arm muscle circumference in cm. If it is unable to be obtained select the "not measured" option and enter the reason why this could not be obtained.** Refer to the study SOP for instructions on how to measure mid arm muscle circumference.
Hand Grip Strength	**Enter the patients hand grip strength in kg. If it is unable to be obtained select the "not measured" option and enter the reason why this could not be obtained.** Refer to the study SOP for instructions on how to measure hand grip strength.

Extra Fields

Notes:



- **Please carefully review the schedule of events to ensure bloods are ordered if not routinely completed on the relevant study days (see appendix 4 and 5).**

Study Day	1	2	3	4	5	6	7	14	21	28
LFTs and WCC	If collected as routine care please enter the value						x	x	x	X
TG			x				x	x		
CRP							x	x		X

- Data within this field is only required to be collected on specific study days
- If you select **'yes'** to **'extra fields'** additional fields will appear in the daily data form
- These include:
  - ✓ Blood tests: Please ensure that the bloods are completed according to the following schedule (unless discharged from the ICU) and remember that if collected as part of routine care we would like to collect this information. If multiple values are available please collect the most deranged value for that day.
  - ✓ Note this does not include baseline bloods, refer to the full table of events at appendix 4 and 5 for full study requirements.
  - ✓ Nitrogen Loss and Intake for the sub study only

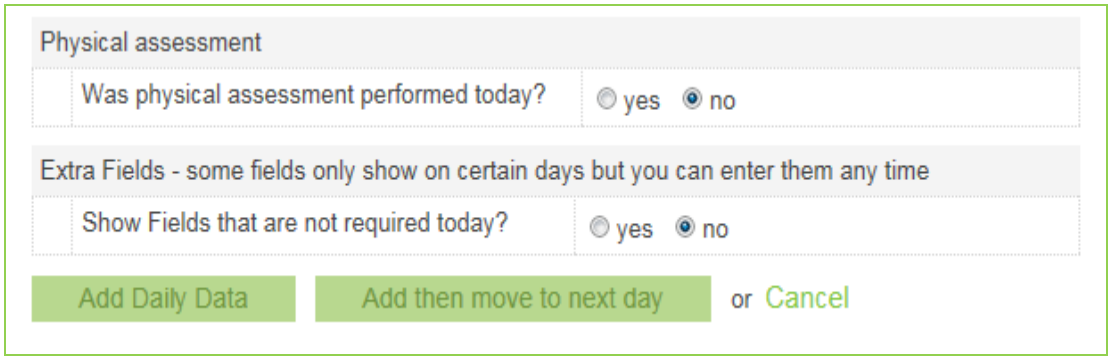
X denotes blood test required. If not already completed, please request the blood test on this study day (ONLY if the patient remains in ICU).

C-Reactive Protein (CRP)	**Enter the CRP in 'mg'.** If no CRP is available and could not be ordered, enter not measured to indicate the data was unavailable. If the test has been ordered and you are waiting for the result, select **'not measured'** and enter the data once it has been returned from the lab. Alternatively, wait to enter the data until all tests are available or are truly

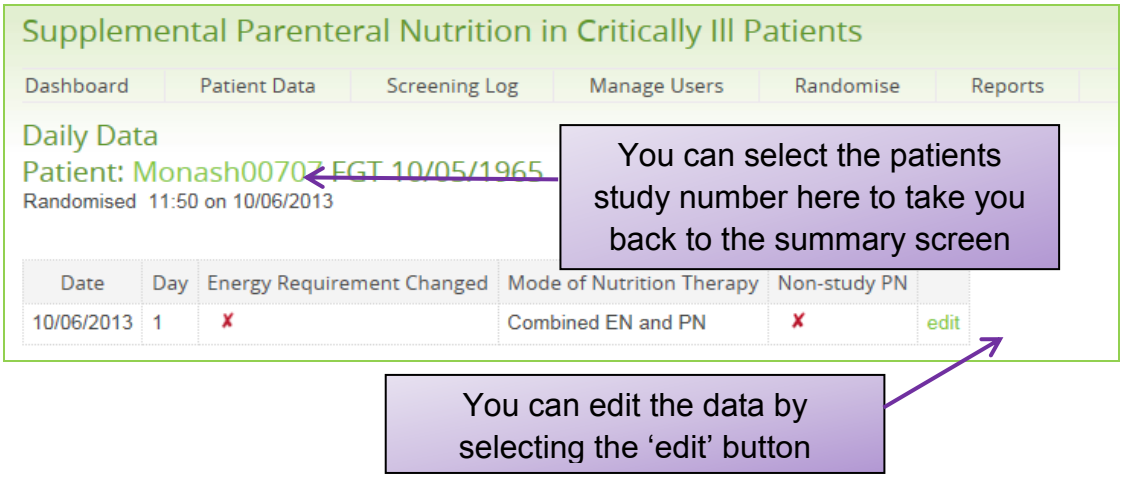
	'not measured'.
Triglycerides (TG)	**Enter the TG level in mmol/L. If PN is running please ensure the level is not taken from the same lumen as the PN.** If no TG is available and could not be ordered, enter not measured to indicate the data was unavailable. If the test has been ordered and you are waiting for the result, select **'not measured'** and enter the data once it has been returned from the lab. Alternatively, wait to enter the baseline data until all tests are available or are truly **'not measured'.**
Alanine aminotransferase (ALT)	**Enter the serum ALT level in U/L.** If no ALT is available and could not be ordered, enter not measured to indicate the data was unavailable. If the test has been ordered and you are waiting for the result, select **'not measured'** and enter the data once it has been returned from the lab. Alternatively, wait to enter the baseline data until all tests are available or are truly **'not measured'.**
Gamma glutamyl transferase (GGT)	**Enter the serum GGT level in U/L.** If no GGT is available and could not be ordered, enter not measured to indicate the data was unavailable. If the test has been ordered and you are waiting for the result, select **'not measured'** and enter the data once it has been returned from the lab. Alternatively, wait to enter the baseline data until all tests are available or are truly **'not measured'.**
Alkaline phosphatase (ALP)	**Enter the serum ALP level in U/L.** If no ALP is available and could not be ordered, enter not measured to indicate the data was unavailable. If the test has been ordered and you are waiting for the result, select **'not measured'** and enter the data once it has been returned from the lab. Alternatively, wait to enter the baseline data until all tests are available or are truly **'not measured'.**
Bilirubin	**Enter the serum bilirubin in µmol/L.** If no bilirubin is available and could not be ordered, enter not measured to indicate the data was unavailable. If the test has been ordered and you are waiting for the result, select **'not measured'** and enter the data once it has been returned from the lab. Alternatively, wait to enter the baseline data until all tests are available or

	are truly **'not measured'.**
White Cell Count (WCC)	**Enter the WCC in 10^9/L.** If no WCC is available and could not be ordered, enter not measured to indicate the data was unavailable. If the test has been ordered and you are waiting for the result, select **'not measured'** and enter the data once it has been returned from the lab. Alternatively, wait to enter the baseline data until all tests are available or are truly **'not measured'.**
Sub-Study only	
Nitrogen Loss	Nitrogen loss will be calculated based on the 6 hour urinary nitrogen study that is conducted. Remember to multiply the result by 4 if a 24 hour nitrogen balance estimate is not provided by the laboratory. Enter this value into the website in g/day.
Nitrogen intake	Enter the total nitrogen intake on the study day. Refer to the study SOP for instructions on how to calculate this.

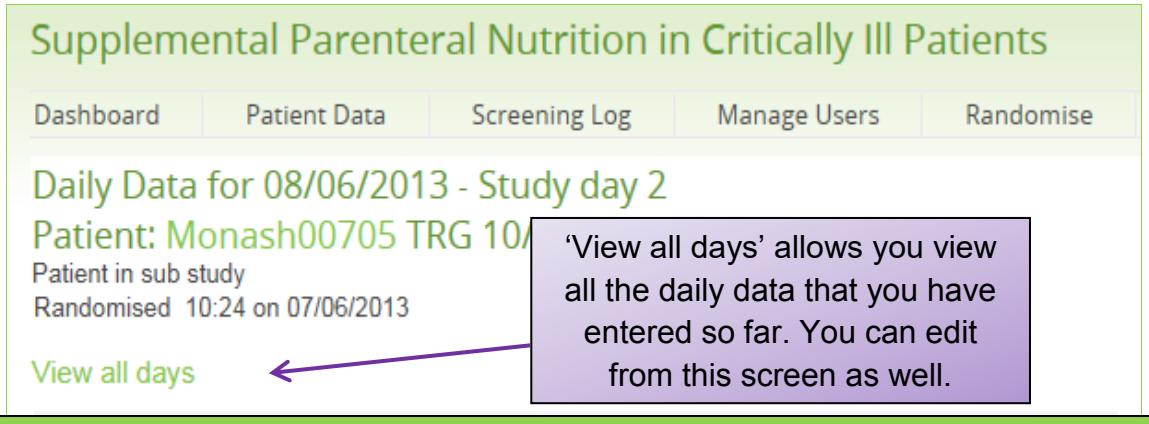
Once you have finished data collection, select ***"add daily data"*** or ***"Add then move to the next day"***



If you select "Add daily data" you will be taken to the following screen.



From the daily data entry page you can select ***"view all days"*** which will take you back to the previous summary screen.



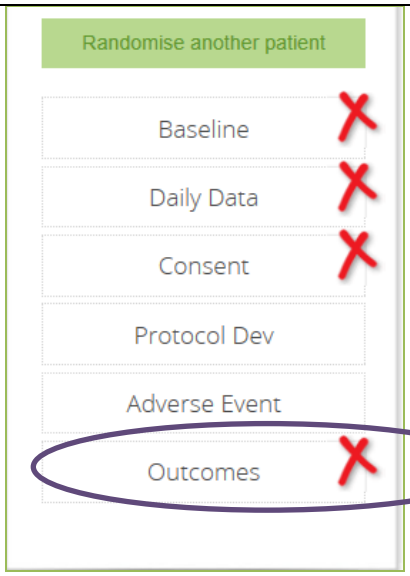
Outcomes

Notes:

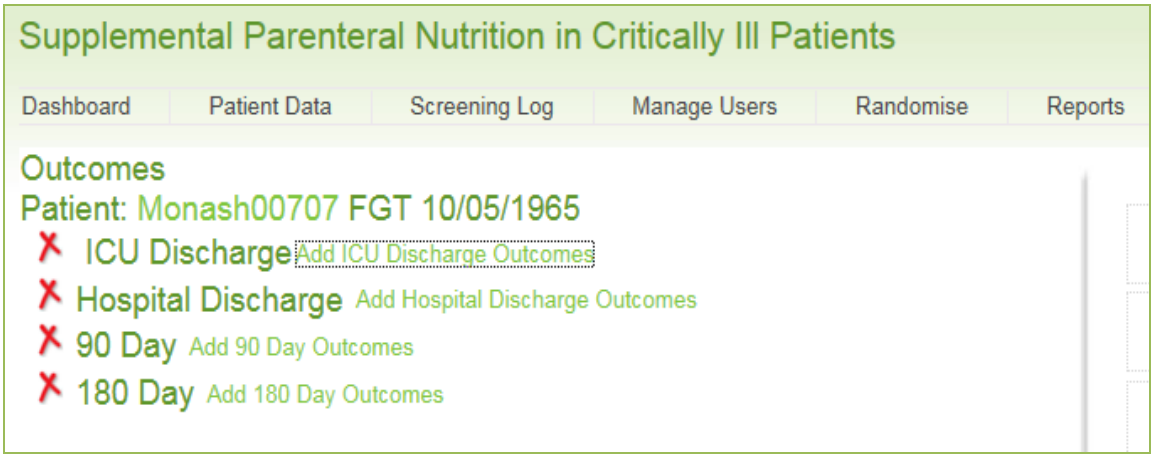
- ICU and Hospital outcome data should be obtained at the time the patient is discharged from ICU or hospital.
- There is a 48 hour window to allow you to get this data 48 hours prior or 48 hours after the relevant discharge.
- This means data can be done prior if it is likely that the patient will be discharged over the weekend.
- If you do not collect this data please record the reason why not.
- If a patient is discharged from your facility but to another facility, the discharge date is the date of discharge from your facility. Please then select the
- The corresponding paper form is number '7'- Outcomes record form.
- A suggested 'outcomes' script has been provided (Supp PN_outcome script and instruction V1 01 08 14)

ICU Discharge

Select the ***"Outcomes"*** Box to enter the patients' outcome data.



You will then be taken to the following screen.



ICU Discharge	
Date and time of ICU Discharge	**Enter the date of ICU discharge using the online calendar.** Use this full date format 01/02/2011 for 1st February 2011. Enter the time of ICU discharge using 24 hour format: 03:15 for quarter past 3 in the morning.
Survival status	**Select *'alive'* if the patient was not deceased in ICU.** **Select *'deceased'* if the patient was deceased in ICU.** **If you select '*deceased*' enter the date of death.** Use this full date format 01/02/2011 for 1st February 2011.
Date and time mechanical ventilation was ceased	**Enter the date and time mechanical ventilation was ceased using the online calendar.** Use this full date format 01/02/2011 for 1st February 2011. Enter the time using 24 hour format: 03:15 for quarter past 3 in the morning.

Discharge destination	Select from the following based on where you expect the patient to be discharged to. Please confirm the discharge destination via official documentation where possible: ✓ **Home:** discharged to their own home **or to a similar facility to where they were residing prior to their acute admission** – e.g. if the patient was a nursing home resident and discharged back to a nursing home, then select **"home"** rather than long term care facility. ✓ **Rehabilitation Centre:** discharged to a rehabilitation facility. ✓ **Ward:** discharged to another hospital or acute care facility, including regional ongoing acute care (ward only). ✓ **Other ICU:** discharged to another ICU within your hospital OR at an ICU at a different facility. ✓ **Long term care facility- high care:** discharged to a nursing home. ✓ **Long term care facility- low care**: discharged to a hostel/ supported accommodation or low level nursing home ✓ **Unknown:** Select this option if you are unable to determine where the patient has been/will be discharged to. ✓ **Other**: Free text option
PN Status	Select ***'Never Started'*** if the patient never received PN during the ICU admission. Select ***'Never ceased'*** if at ICU discharge the PN is continuing at any rate and for any period of time. PN refers to lipids, protein and carbohydrate infused together. Select ***'ceased'*** if the patient received PN during the ICU admission but it is now ceased. Please enter the date that it was ceased in dd/mm/yyyy.
EN Status	Select ***'Never Started'*** if the patient never received EN during the ICU admission Select ***'Never ceased'*** if at ICU discharge the EN is continuing at any rate and for any period of time. Select ***'ceased'*** if the patient received EN during the ICU admission but it is now ceased. Please enter the date that it was ceased in dd/mm/yyyy.

Hospital Discharge	
Date and time of Hospital Discharge	**Enter the time and date of hospital discharge using the online calendar.** Use this full date format 01/02/2011 for 1st February 2011. Enter the time using 24 hour format: 03:15 for quarter past 3 in the morning.
Survival status	Select ***'alive'*** if the patient was not deceased at hospital discharge. If the patient is deceased at hospital discharge then please enter the data of death using this full date format 01/02/2011 for 1st February 2011. If deceased was selected at ICU discharge, this will be pre-populated with the date and deceased tab.
Discharge destination	Select from the following based on where you expect the patient to be discharged to. Please confirm the discharge destination via official documentation where possible: ✓ **Home:** discharged to their own home **or to a similar facility to where they were residing prior to their acute admission** – e.g. if the patient was a nursing home resident and discharged back to a nursing home, then select **"home"** rather than long term care facility. ✓ **Rehabilitation Centre:** discharged to a rehabilitation facility. ✓ **Ward:** discharged to another hospital or acute care facility, including regional ongoing acute care (ward only). ✓ **Other ICU:** discharged to another ICU within your hospital OR at an ICU at a different facility. ✓ **Long term care facility- high care:** discharged to a nursing home. ✓ **Long term care facility- low care**: discharged to a hostel/ supported accommodation or low level nursing home ✓ **Unknown:** Select this option if you are unable to determine where the patient has been/will be discharged to. ✓ **Other**: Free text option
Oral Intake Commenced	**Enter the date and time oral intake commenced using the online calendar.** **An approximate time is acceptable.**

	Use this full date format 01/02/2011 for 1st February 2011. Enter the time using 24 hour format: 03:15 for quarter past 3 in the morning.
6 minute walk test	**Enter the time taken to complete the 6-minute walk test in minutes**. **If the 6MWT could not be conducted please select the reason why from the drop down options.** They are: ✓ Clinician unavailable ✓ Patient discharged prior ✓ Patient unable to complete assessment ✓ Other: Please specify reason Refer to the study SOP for instructions and the pre-prepared script regarding the 6-minute walk test.
Highest level of functional assessment	**Select a response for the highest level of functional assessment.** Unknown- If you were unable to complete the assessment please enter the reason why. The options are: ✓ Clinician unavailable ✓ Patient discharged prior ✓ Patient unable to complete assessment ✓ Other: Please specify reason The options for the function scale are: 0. nothing (lying in bed) - passively rolled by staff but not actively moving 1. sitting in bed, exercises in bed - any activity in bed including rolling, bridging, active exercises, cycle ergometer, active assisted exercises . Not moving out of bed or over the edge of the bed 2. passively moved to chair (no standing) – hoist, passive lift or slide transfer to the chair (no standing or sitting on the edge of the bed) 3. sitting over edge of bed – may be assisted by staff but involves actively sitting over the side of the bed with some trunk control 4. standing – weight bearing through the feet in the standing position with or without assistance. This may include a standing lifter 5. transferring bed to chair – able to step or shuffle through standing to the chair. This involves actively transferring weight from one leg to another to move to the chair. If the patient has been stood with a

	machine they must step to the chair (<u>not</u> included if the patient is wheeled in a standing lifter) 6. marching on spot (at bedside) – able to walk on the spot by lifting alternate feet (must be able to step at least 4 times = 2 one each foot) with or without assistance 7. walking with assistance of 2 or more people – walking away from the bed/chair by at least 5 metres assisted by 2 or more people 8. walking with assistance of 1 person – walking away from the bed/chair by at least 5 metres assisted by 1 person 9. walking independently with a gait aid – walking away from the bed/chair by at least 5 metres with a gait aid but no assistance from another person. In a wheelchair bound person this includes wheeling the chair independently 5m away from the bed/chair. 10. walking independently without a gait aid – walking away from the bed/chair by at least 5 metres without assistance from a person or a gait aid
Hand Grip Strength	Enter the patients hand grip strength in kg. Refer to the study SOP for instructions regarding hand grip strength test. If the test could not be conducted please enter the reason why. They are: ✓ Clinician unavailable ✓ Patient discharged prior ✓ Patient unable to complete assessment ✓ Other: Please specify reason
PN Status	Select '**Never Started'** if the patient never received PN during the hospital admission Select ***'Never ceased'*** if at hospital discharge the PN is continuing at any rate and for any period of time. PN refers to lipids, protein and carbohydrate infused together. Select ***'ceased'*** if the patient received PN during the hospital admission but it is now ceased. Please enter the date that it was ceased in dd/mm/yyyy.
EN Status	Select ***'Never Started'*** if the patient never received EN during the hospital admission Select ***'Never ceased'*** if at hospital discharge the EN is continuing at any rate and for any period of time. Select ***'ceased'*** if the patient received EN during the

	hospital admission but it is now ceased. Please enter the date that it was ceased in dd/mm/yyyy.
EQ-5D (Quality of Life Assessment)	**Select 'yes' if the EQ-5D was completed at hospital discharge. More fields will appear.** Refer to the study SOP and the provided document EQ-5D-3L_UserGuide_2013_v5.0_October_2013 for instructions about completion of the EQ-5D. ✓ Enter the relation of the person who answered the questions. - If it was the patient, enter **'patient'.** - If it was a relative or NOK enter **'relative/NOK'.** ✓ Select a response for Mobility, Personal Care, Usual Activities, Pain/Discomfort and Anxiety/Depression. ✓ Enter a response from 0-100 regarding the patients' health state. **If 'no' is selected, enter the reason why the EQ-5D was not completed.**
90 and 180 day outcomes	
Notes: • The dates for follow up can be found on the patient **'summary'** screen on the website. • Please attempt the follow up on the date and continue to attempt for up to 14 days after the date. Do not attempt before the date. • If the patient is deceased at ICU or hospital follow-up, **'deceased'** will be pre-populated at 90 and 180 day follow up nothing additional needs to be added. • A suggested 'outcomes' script has been provided (Supp PN_outcome script and instruction V1 01 08 14)	
Date	**Enter the date using the online calendar.** Use this full date format 01/02/2011 for 1st February 2011. Enter the time using 24 hour format: 03:15 for quarter past 3 in the morning.
Survival status	Select ***'alive'*** if the patient was not deceased.
Current Location	**Ask the patient or NOK where they are currently residing.** Select from the following: ✓ **Home:** discharged to their own home **or to a similar facility to where they were residing prior to their acute admission** – e.g. if the patient was a nursing home resident and discharged back to a nursing home, then select **"home"** rather than

	long term care facility. ✓ **Rehabilitation Centre:** discharged to a rehabilitation facility. ✓ **Ward:** discharged to another hospital or acute care facility, including regional ongoing acute care (ward only). ✓ **Other ICU:** discharged to another ICU within your hospital OR at an ICU at a different facility. ✓ **Long term care facility- high care:** discharged to a nursing home. ✓ **Long term care facility- low care**: discharged to a hostel/ supported accommodation or low level nursing home ✓ **Unknown:** Select this option if you are unable to determine where the patient has been/will be discharged to. ✓ **Other**: Free text option
Where did you/ your relative go immediately after your acute care admission? ***(90 day follow up only)***	**Ask the patient or NOK where they went immediately after their acute hospital admission ie. Their first place of discharge after the acute admission that led to them being enrolled in the study.** Select from the following: ✓ **Home:** discharged to their own home **or to a similar facility to where they were residing prior to their acute admission** – e.g. if the patient was a nursing home resident and discharged back to a nursing home, then select **"home"** rather than long term care facility. ✓ **Rehabilitation Centre:** discharged to a rehabilitation facility. ✓ **Other hospital- ward:** discharged to another hospital or acute care facility, including regional ongoing acute care. ✓ **Other ICU:** discharged to another ICU within your hospital OR at a different facility. 💧 **NB:** If **'yes'** is selected for either **'other hospital-ward', 'other ICU'** or **'rehabilitation centre'** **please ask how many days the patient stayed for and enter this answer. If the other centre is within your health network and you can verify**

	the admission dates easily please attempt to do this. ✓ **Other:** Free text ✓ **Long term care facility- HIGH CARE:** :Nursing home or at home with significant care needs/full time care. ✓ **Long term care facility- LOW CARE:** Hostel/ supported accommodation or low level nursing home **.** ✓ **Unknown:** Select this option if the person providing the responses is unsure or if you feel the answer provided is not reliable.
Have you/your relative been readmitted to hospital?	✓ Select **'yes'** if the patient has been readmitted to a hospital ward (not ICU) since their 1st acute admission. Any period over 24 hours after discharge from their acute admission should be considered a new admission/readmission. Admission back to hospital within 24 hours of discharge should be considered the same admission. ● If **'yes'** is selected then please: 1. **Determine what the admission was for (free text). Be as specific as possible. If the other centre is within your health network and you can verify the admission reason please attempt to do this.** 2. **Determine how many days the patient stayed in the hospital and enter this answer. If the other centre is within your health network and you can verify the admission dates easily please attempt to do this.** ✓ **Unknown:** Select this option if the person providing the responses is unsure or if you feel the answer provided is not reliable. **The website can only allow 1 readmission in the current format. If the patient has been readmitted more than once, please enter this information in the free text box provided. Please ensure you have entered all the correct information as requested.**
Have you/your relative been readmitted to ICU?	Select **'yes'** if the patient has been readmitted to an ICU since their 1st acute admission. Any period greater than 24 hours after their first discharge from ICU should classify as a new admission/readmission. Admission

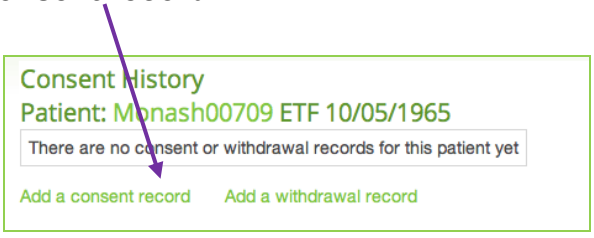
	back into ICU within 24 hours of discharge should be considered the same admission. 💧 If **'yes'** is selected then please: 1. **<u>Determine what the admission was for (free text). Be as specific as possible. If the other centre is within your health network and you can verify the admission reason please attempt to do this.</u>** 2. **<u>Determine how many days the patient stayed in the ICU and enter this answer. If the other centre is within your health network and you can verify the admission dates easily please attempt to do this.</u>** ✓ **Unknown:** Select this option if the person providing the responses is unsure or if you feel the answer provided is not reliable.
Did you/your relative have any surgery?	Ask the patient if they have had any surgery during their readmission. If **'yes'** is selected then please: 1. **<u>Determine what the surgery was for (free text). Be as specific as possible. If the other centre is within your health network and you can verify the admission reason please attempt to do this.</u>** ✓ **Unknown:** Select this option if the person providing the responses is unsure or if you feel the answer provided is not reliable.
EQ-5D (Quality of Life Assessment)	Select 'yes' if the EQ-5D was completed 90 day follow-up. More fields will appear. Refer to the study SOP and the provided documents for instructions about completion of the EQ-5D. ✓ Enter the relation of the person who answered the questions. - If it was the patient, enter **'patient'.** - If it was a relative or NOK enter **'relative/NOK'.** ✓ Select a response for Mobility, Personal Care, Usual Activities, Pain/Discomfort and Anxiety/Depression. ✓ Enter a response from 0-100 regarding the patients' health state. **If 'no' is selected, enter the reason why the EQ-5D was not completed.**
Consent	
Notes: 💧 Select each type of consent or assent (acknowledgement) obtained for each	

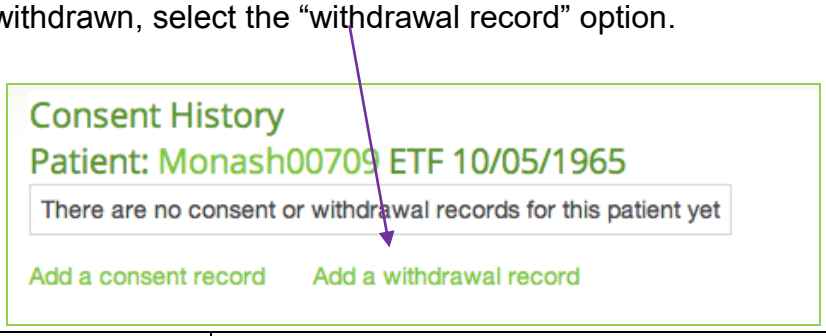
patient.

- There may be up to 3 consent processes e.g. prior telephone consent from the person responsible, written consent following telephone consent, then if the patient regains competency, delayed consent from the patient (if follow up consent from the patient is applicable at your site).
- The person who can provide consent for the patient is the "person responsible" or "Next of Kin" (NOK) or "legal surrogate" or "relative/friend/ whanau member" or "parent or guardian".
- For the purposes of this eCRF the term **"person responsible"** has been used to cover all of the terms above.
- Procedural Authorisation is applicable to Victorian sites only.
- Prior consent is required for this study (telephone or written), delayed consent by the person responsible is not permitted. Procedural Authorisation is not consent but patient enrolment is permitted by Victorian legislation if criteria are met (as outlined in the Section 42T SOP).
- Delayed consent from relative/friend/ whanau member is permitted in New Zealand, but every attempt should be made to contact and speak to the relative/friend/ whanau member prior to study enrolment.
- The corresponding paper form is number '6'- Consent record form.

To enter a consent record select **"Consent"**

Then select **"add a consent record"**

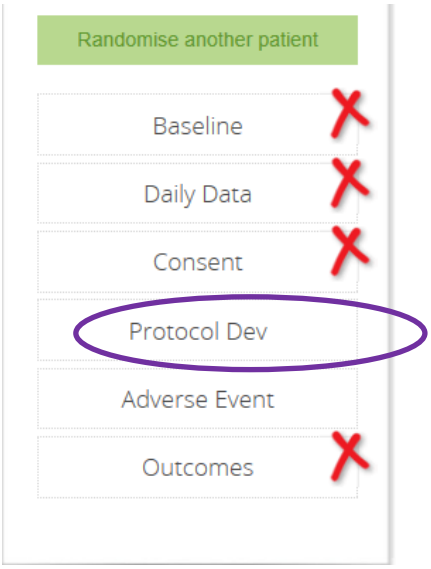


Add a consent record	
Date consent given	Enter the date (using the online calendar) and time (using 24 hour format) verbal consent was granted.
Prior consent from patient	Select this option for prior patient consent.
Delayed consent from patient	**This question is related to sites where delayed consent or "consent to continue" from the patient who has regained competency is required.** For the purposes of this study assessment of patient competency is only required during the current hospital admission.
Prior consent from 'person responsible' relative or friend	**Select this option for prior consent from any one who is the 'person responsible'.** This definition includes relatives or friends that are allowed to give consent as per your HREC or HDRC and parent or guardian consent for sites that have HREC approval to enrol patients who are minors (less than 16 or 18 years of age).
Delayed consent from person responsible (after procedural authorisation)	**This is for Victorian sites only.** Following enrolment by Procedural Authorisation, if the person responsible is found seek written delayed consent or "consent to continue".
Patient died before consent could be obtained, permission to keep data from ethics	Select this option if the patient died prior to consent being obtained and your ethics committee has allowed you to keep data in this circumstance.
Withdrawal record	
If consent is withdrawn, select the "withdrawal record" option.  	
Who withdrew consent	Enter the following information: ✓ **Person responsible withdrew consent** –The person responsible withdrew consent or acknowledgement. Select this option if the person responsible did not consent to continue after Procedural Authorisation (Victorian sites only). ✓ **Patient withdrew consent** – The patient regained competency and refused consent to continue (i.e.

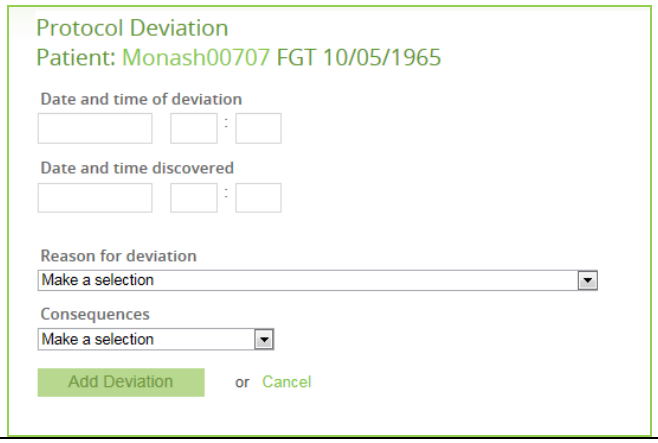
	written revocation or verbal communication). ✓ **Patient withdrawn by physician** – In the treating physician's opinion, the patient should be permanently withdrawn from the study. No further doses will be administered; daily data will be collected.
Date consent withdrawn	Enter the date of withdrawal using the online calendar.
Has the patient agreed to ongoing follow-up	If ***No*** follow up will not be conducted. If ***Yes*** is selected it means that data can be used or it can mean that ongoing data can be collected. It is important to ascertain what the person responsible or the patient has refused consent for.
Has the patient agreed to the use of the data already collected	If ***No*** is selected the data will not be included in the final analysis. If ***Yes*** is selected it means that data can be used or it can mean that ongoing data can be collected. It is important to ascertain what the person responsible or the patient has refused consent for.

Protocol Deviation

To enter a protocol deviation select '**protocol dev'.**



You will be taken to the following screen.



Notes:

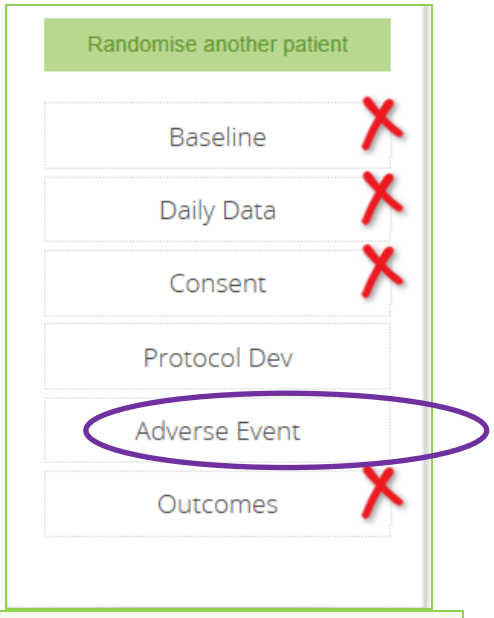
- Complete this form for all randomised patients where a managed or accidental protocol deviation occurs.
- Contact the Chief Investigator on +[redacted] or project manager on [redacted] if you wish to discuss protocol deviation reporting.
- Protocol deviations will be reported via the study website only.
- For the purposes of this study the term ***'protocol deviation'*** is used consistently throughout the protocol and study materials. Protocol Deviation has the same meaning as 'protocol violation'. We have elected to use one consistent term for deliberate or accidental deviations from protocol.
- For each protocol deviation complete a new form.

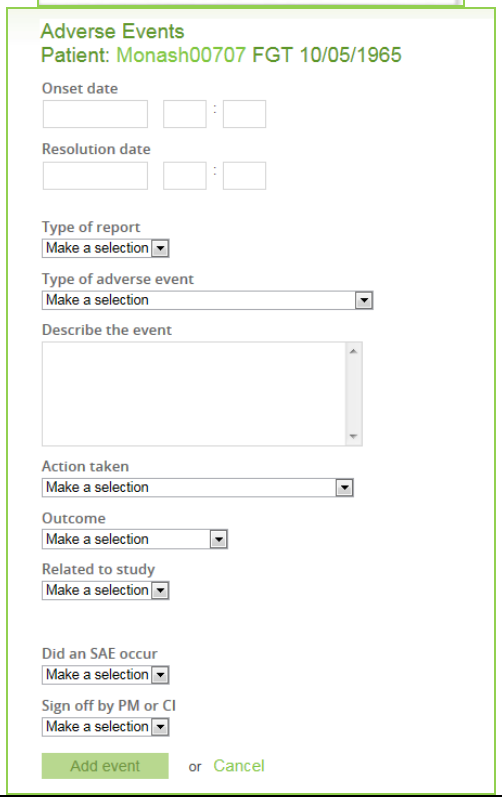
- Only report protocol deviations to the HREC/HDRC if this is the requirement at your site.
- The corresponding paper for is number '8'- Protocol deviation record form'

Date and time of deviation	**Record the date the protocol deviation occurred using the online calendar.** This is the date that the activity should (e.g. PN not provided) or should not (e.g. ineligible patient randomised) occur.
Date and time discovered	**Record the date the protocol deviation occurred using the online calendar.** This is the date and time that you were first made aware of the deviation.
Reason for deviation	Select the deviation: ✓ **Patient randomised but not eligible:** Select the reason that the patient was not eligible from the drop down list of exclusions ✓ **Study PN not given when indicated** - Abnormal blood work - Held for a procedure - No central access - Refeeding syndrome - Other, please specify. Enter into free text box ✓ **Study PN run at the incorrect rate:** (ie. Turned off when it should have continued, run at 10kcal/kg instead of 20kcal/kg). ✓ **Other types:** - Did not receive study PN on the day of randomisation - Dispensing dosing error - Unapproved procedure - Other- free text
Consequences	Select one from the following list: ✓ **None** – There were no consequences of the protocol deviation. ✓ **Study PN permanently disabled** – Study drug is ceased **because of** the protocol deviation. ✓ **Study PN withheld / missed dose** – Study PN was not provided when it was indicated. PN is withheld or missed for one day but the patient will be assessed again daily for recommencement as

	per the study schedule. ✓ **Resulted in SAE** – Select this option if a serious adverse event occurred because of the protocol deviation. ✓ **Resulted in AE** – Select this option if an adverse event occurred because of the protocol deviation.

Adverse Events





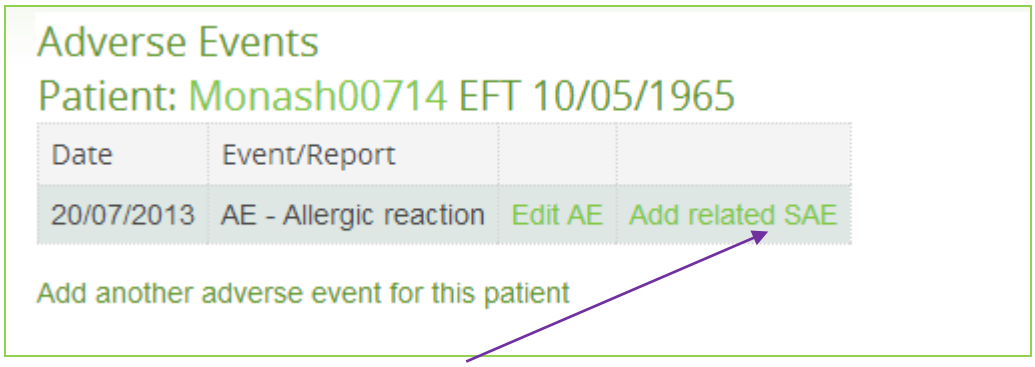
Notes

- Complete this form for all randomised patients who experience an adverse event.
- Adverse events include all unexpected untoward medical events experienced by the patient which are not anticipated in the study population and in the opinion of the investigator are related to the study.
- **Adverse events will be collected from randomisation up study day 180.**
- **The corresponding paper record form is number '9'- AE and SAE form**

Onset Date	Enter the date the AE first developed using the online calendar.
Resolution Date	If ***"Resolved"*** or ***"Resolved with sequelae"*** is selected in the Outcome section enter the date the AE resolved using the online calendar. If any other option is selected from the Outcome section the date of resolution will be disabled.
Event	The 2 options are: ✓ Allergic Reaction and ✓ Other: If you select other you are required to enter more explanation in the free text box provided.
Action taken	**This is the action taken with the study PN.** ✓ **None:** The patient continues to be given study PN or at the time of the event no further study PN is a possibility (i.e. the patient is discharged from the ICU or the patient has already pasted the 7 day intervention period so the decision not to provide study PN was made before this event occurred). ✓ **Treatment modified or temporarily discontinued**: Study PN is missed because of the event and there is an intention to assess the patient again tomorrow for the next provision of study PN. ✓ **Treatment permanently discontinued**: The patient will not be given any further study PN as a result of this event (e.g. anaphylactic reaction) however the need for further study PN is a possibility.
Outcome	Select one of the following options: ✓ **Unknown/ lost to follow up:** The patient was not contactable at the 90 and or 180 day follow up and it is not known if the event resolved or not. This assumes the patient was alive at the end of the

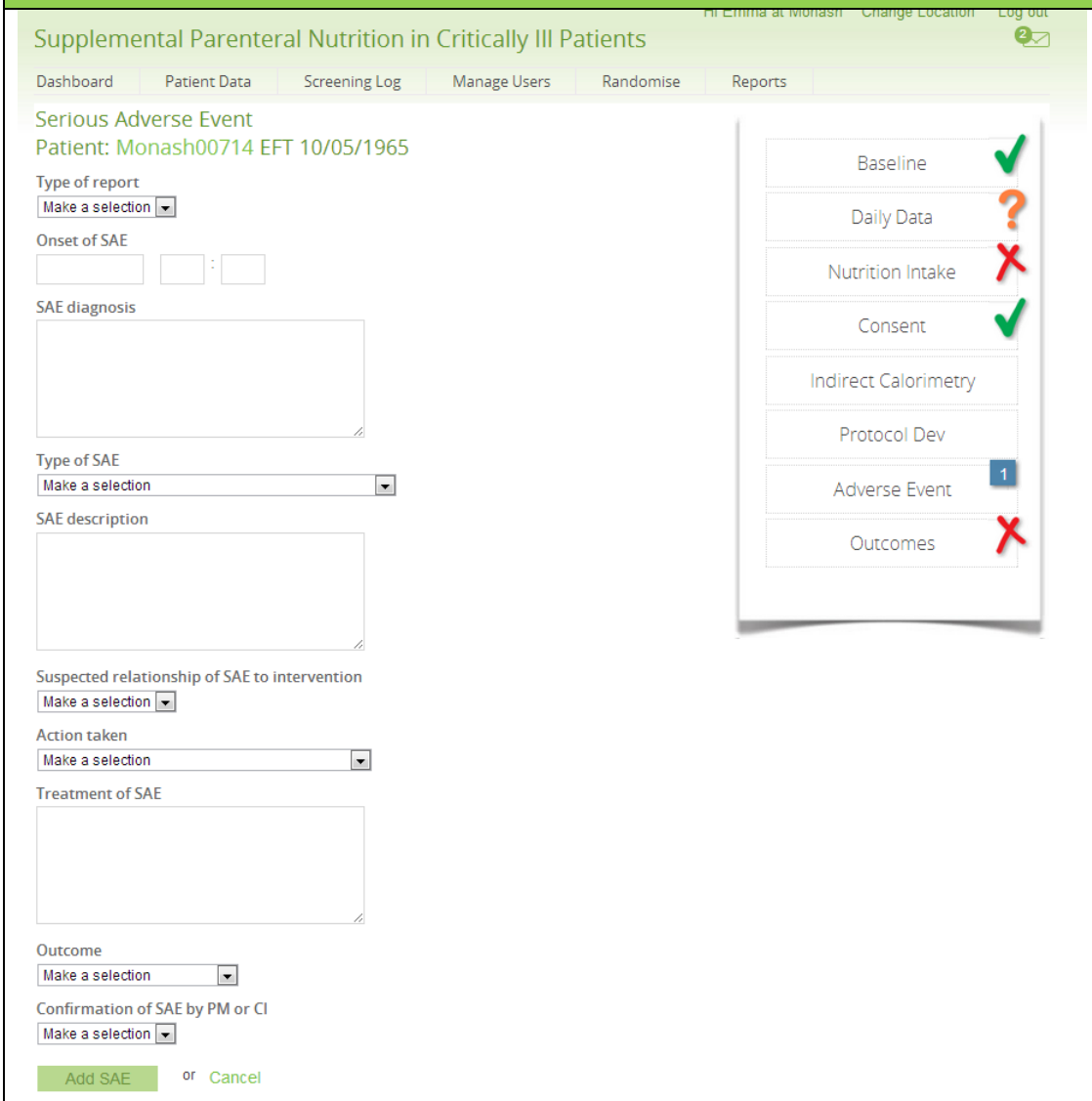
	study. ✓ **Unresolved:** In the investigators opinion, the event is unresolved. ✓ **Resolved:** In the investigators opinion, the event is resolved. ✓ **Resolved with sequelae** – In the investigators opinion, the event is resolved but the patient continues to have sequelae from the event.
Related to study	Select one of the following options: The definitions are provided for the investigator to determine causality of the event. ✓ **Unrelated**: The investigator determines that study PN had no effect on this event. ✓ **Possibly**: The investigator determines that study PN contributed to the event, but may not be the prime cause. There is another contributing factor such as a co-morbid condition which has more likely caused the event. ✓ **Probably**: The investigator determines that the study PN has more likely caused the event than another factor. ✓ **Definitely:** The investigator determines that study PN caused the event and there are no other factors which could have contributed. This would ordinarily include a strong temporal relationship.
Sign off on the event	Select **yes** if the PI at the site is aware of the event

- Once you have finished entering the event, select **"add event"**
- You will be taken to the following screen



To enter an SAE select ***"add related SAE".*** All SAEs should have a prior AE entered.

Serious Adverse Events (SAEs)



Notes:

- **Complete one SAE form for each serious adverse event.**
- SAEs are defined in accordance with the Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95) (July 2000) as any untoward medical occurrence which may or may not have a causal relationship with the study treatment that:
  - ✓ Results in death
  - ✓ Is life-threatening
  - ✓ Requires inpatient hospitalisation or prolongation of existing hospitalisation
  - ✓ Results in persistent or significant disability/incapacity
  - ✓ Is a congenital anomaly/birth defect
- Report SAE to ANZIC-RC within 1 working day (24 hours) of the event

becoming known to study staff.

- Report the event online via eCRF
- A confirmation email will be sent to the project manager, the site principal investigator and research coordinator/s that the submission of the SAE Form has been successful.
- Do not wait for complete information (e.g. resolution date) before reporting.
- Additional information can be added at a later date on the same form by entering the information and selecting “Follow up report” or “Final report”
- SAEs will be reported from randomisation up to 180 days (after randomisation).
- The person who enters the data using their secure log-in will be indentified on the SAE confirmation email and this person will be identified as being responsible for the collection of data. Assessment of causality is the responsibility of the site principal investigator.
- File the SAE confirmation email in the Investigator Site File.
- For Ethics Committee submission, print the online SAE form and submit. If the principal investigator is required to sign the form for the submission then sign and date the bottom of the form.
- Only serious adverse events **unexpected in the population** or **possibly/probably/definitely related to study treatment** will be reported. For example, in a young patient with an isolated TBI, if the patient developed VAP which resulted in severe sepsis with multi-organ failure this should be reported as an SAE because multi-organ failure is unexpected in the TBI population.
- **Only deaths expected to be related to the study intervention should be reported as SAEs from randomisation until the end of follow up (Day 180).**
- Supporting evidence, such as laboratory results, radiological diagnostic reports, if applicable should be scanned and emailed to the project manager or fax on +61 3 9903 0071.
- **The corresponding paper record form is number ‘9’- AE and SAE form**

Type of report	✓ **Initial** – The first report will always be labeled “Initial”. ✓ **Follow up** – If subsequent reports are required before the final report then select “Follow up” ✓ **Final** – The final report for this event and no

	further information is required e.g. an autopsy report is available and sent to the coordinating centre.
Onset of SAE	**Enter the date the SAE first developed using the online calendar.**
SAE Diagnosis	**Provide the diagnostic name of the SAE. Do not list the symptoms**
Type of SAE	Select the most appropriate SAE (only one). ✓ **Death** ✓ **Prolongation of (current) hospitalisation or re-hospitalisation –** Re-hospitalisation is defined as an admission to an acute hospital for at least 24 hours. Presentation to an Emergency Department is not classified as re-hospitalisation nor is a procedure performed at a Day Surgical Unit. ✓ **Life-threatening –** The term "life threatening" in the definition of serious refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. ✓ **Permanently disabling** – This SAE type will be determined by the treating physician because it is very difficult to determine if the permanent disability is due to the SAE or the traumatic brain injury. ✓ **Congenital anomaly** ✓ **Medically important**
SAE description	**Please provide as much detail as possible and include any results of relevant supportive laboratory data, other investigations and a cause of death if death was the SAE.**
Suspected relationship of SAE to intervention	Select one of the following options: The definitions are provided for the investigator to determine causality of the event. ✓ **Unrelated**: The investigator determines that study PN had no effect on this event. ✓ **Possibly**: The investigator determines that study PN contributed to the event, but may not be the prime cause. There is another contributing factor such as a co-morbid condition which has more likely caused the event.

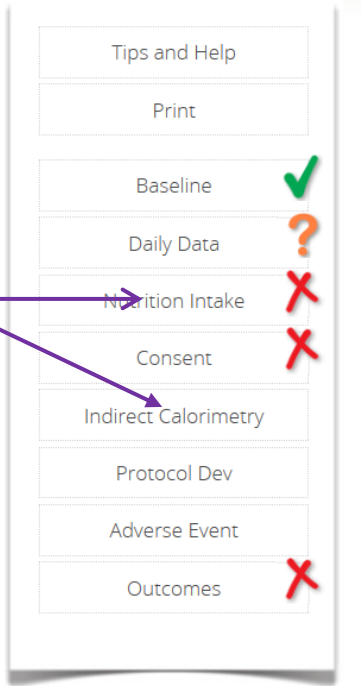
	✓ **Probably**: The investigator determines that the study PN has more likely caused the event than another factor. ✓ **Definitely:** The investigator determines that study PN caused the event and there are no other factors which could have contributed. This would ordinarily include a strong temporal relationship.
Action Taken	**This is the action taken with the study PN.** ✓ **None:** The patient continues to be given study PN or at the time of the event no further study PN is a possibility (i.e. the patient is discharged from the ICU or the patient has already pasted the 7 day intervention period so the decision not to provide study PN was made before this event occurred). ✓ **Treatment modified or temporarily discontinued**: Study PN is missed because of the event and there is an intention to assess the patient again tomorrow for the next provision of study PN. ✓ **Treatment permanently discontinued**: The patient will not be given any further study PN as a result of this event (e.g. anaphylactic reaction) however the need for further study PN is a possibility.
Treatment of SAE	**Describe the treatment of the specific SAE**. Do not include all treatment the patient is receiving just the treatment of SAE.
Outcome	Select one of the following options: ✓ **Unknown/lost to follow up:** The patient was not contactable at the 90 and or 180 day follow up and it is not known if the event resolved or not. This assumes the patient was alive at the end of the study. ✓ **Unresolved:** In the investigators opinion, the event is unresolved. ✓ **Resolved:** In the investigators opinion, the event is resolved. ✓ **Resolved with sequelae** – In the investigators opinion, the event is resolved but the patient continues to have sequelae from the event. ✓ **Death**

Confirmation of SAE by PM or CI	Select: ***"Confirm SAE"*** or "***Not yet"*** depending on the status of the SAE at the time of reporting.

Sub-study

- This section is only relevant for patients enrolled at The Alfred and at Auckland City Hospital (CVICU and DCCM).
- At randomisation select ***"yes"*** for sub-study to enable the additional data items
- Patients in the sub-study will have data collected as per the usual processes. **They have additional data** which is outlined here.
- The corresponding paper forms are number '10' and '11'- Indirect calorimetry log and Ward data collection. There are also additional fields on the daily data filed that need to be completed if oral intake commences in ICU.

When your patient is in the sub-study you will notice some different tabs.
All data should be entered as per the previous instructions however there are additional fields to be entered.



Nutrition intake

Notes:

- The nutrition intake tab should be used once the patient commences oral intake.
- Oral intake is considered to be oral diet or nourishing fluids were taken (excluding water) with the intent to provide nutrition.
- Nutrition intake should be assessed **daily whilst the patient is in ICU** and **second daily on the ward** (excluding weekends).

- If a patient commences oral intake in ICU please follow the following processes:
  - ✓ Fill out the usual 'daily data' paper form for the day
  - ✓ ALSO Complete PART 4 of the daily form.
  - ✓ To enter this data into the website, the daily data gets entered as per usual processes
  - ✓ The oral intake information is entered under 'nutrition intake'. Select the 'oral' option and enter the relevant data regarding oral intake. **DO NOT SELECT ANY PN OR EN OPTIONS AS YOU HAVE ENTERED THIS UNDER THE DAILY DATA IN ICU**
- Once the patient is discharged to the ward use paper form '11- Ward data collection'.
- Refer to the Study SOP for further instructions about assessing nutrition intake and use the provided study food record chart.

Date	Enter the date using the online calendar.
Mode of nutrition Therapy received today	Select the mode of nutrition therapy that was received on the study day.
Mode of nutrition Therapy received today: EN (alone or in combination with oral nutrition)	**Select EN if the patient received enteral nutrition via any route.** Enter the total amount of energy and protein received via the EN route. **The volume used to calculate this energy and protein intake should not include gastric aspirates that were discarded.**
Mode of nutrition Therapy received today: PN	**Select PN if the patient received parenteral nutrition.**
Mode of nutrition Therapy received today: Oral (alone or in combination with EN)	Select **'oral'** nutrition if oral diet or nourishing fluids were taken (excluding water) with the intent to provide nutrition.
Mode of nutrition Therapy received today: Combined EN and PN	**Select combined EN and PN if both EN and PN were delivered today.**
Energy Intake	

Notes:

- When EN, PN or Combined EN and PN is selected, only **Total Energy Intake and Total Protein Intake** will appear
- When Oral intake is selected on its own or in combination with EN additional

fields will appear	
Energy intake from nutrition supplements	Enter the energy that is provided from oral nutrition supplements in kcal.
Protein intake from nutrition supplements	Enter the protein that is provided from oral nutrition supplements in g.
Energy intake from food	Enter the energy that is provided from food in kcal (excluding supplements).
Protein intake from food	Enter the protein that is provided from food in g (excluding supplements).
Total energy intake	Enter the total energy received by the patient on the study day in kcal from all sources. **This includes EN, PN and oral intake.**
Total protein intake	Enter the total protein received by the patient on the study day in g from all sources. **This includes EN, PN and oral intake.**
Indirect calorimetry	
Notes: • IC should be performed at baseline (within 48 hours of randomisation) and then twice weekly thereafter. • In ICU this will be with the Quark RMR and on the ward, with the FitMate. Some of the fields can not be completed with tests from the FitMate so please select the ***'none'*** option where applicable. • **Nutrition management is not to be changed according to the measurement.** • **If possible keep treating Dietitian blinded.**	
Date	Enter the date that IC **was or was supposed to be performed** using the online calendar.
Was IC performed	Select **'yes'** if IC was performed on the indicated study day and complete the fields that appear. **If IC was not performed please select a response indicating why it was not performed.** Available responses are: ✓ **Patient Unstable:** in the opinion of the medical team the patient is too medically unwell for an IC measurement ✓ **Patient is on RRT:** The patient is receiving renal replacement therapy. The measurement can be done if the RRT is intermittent, but should be done when the patient is not receiving RRT. ✓ **Patient agitation:** IC should not be performed if

	the patient is significantly agitated. ✓ **Ventilator settings changed in the past hour:** Ideally ventilation settings should be stable for 1 hour prior to IC. ✓ **Patient unavailable:** At the time of the test the patient was not in the bedspace or was having another procedure/care that prevented the measurement ✓ **Clinician unavailable:** The clinician was unavailable to complete the test ✓ **FiO_2>0.60:** FiO_2 is greater than 60% at the time the test was due. ✓ **PEEP>12cmH_2O:** PEEP is greater than 12 at the time the test was due. ✓ **Other:** Free text entry
Test Length	Enter the length of the test in mm:ss.
Temperature	**Enter the patients most recent temperature at the time of IC measurement**
$Fi0_2$ (Quark RMR only)	**Enter the FiO_2 the patient is receiving during the test as a fraction** ie 40% $Fi0_2$ is entered as 0.40.
PEEP (Quark RMR only)	**Enter the positive end expiratory pressure that the patient is receiving at the start of the IC measurement.** Use a leading 0 if needed ie 6 cmH_2O of PEEP would be entered as 06.0
Mean VO_2	**Enter the mean measurement of oxygen consumption as per the IC device during the test period**
Mean VCO_2 (Quark RMR only)	**Enter the mean measurement of carbon dioxide production as per the indirect calorimeter information during the test period**
Mean RQ (Quark RMR only)	**Enter the mean Respiratory Quotient during the testing period from the indirect calorimeter information**
Measured RMR	Enter the patients resting metabolic rate measured by IC in **kilocalories.**

Appendix 1 Apache III codes

Appendix 1 : APACHE III Diagnosis Codes

Non-operative

Cardiovascular

- 101 Cardiogenic shock
- 102 Cardiac arrest
- 103 Aortic aneurysm
- 104 Congestive heart failure
- 105 Peripheral vascular disease
- 106 Rhythm disturbance
- 107 Acute myocardial infarction
- 108 Hypertension
- 109 Other cardiovascular disease
- 110 Cardiomyopathy
- 111 Unstable angina

Respiratory

- 201 Aspiration pneumonia
- 202 Respiratory neoplasm
- 203 Respiratory arrest
- 204 Pulmonary oedema (non-cardiac)
- 206 COPD
- 207 Pulmonary embolism
- 208 Mechanical airway obstruction
- 209 Asthma
- 210 Parasitic Pneumonia
- 211 Other Respiratory Disease
- 212 Bacterial Pneumonia
- 213 Viral Pneumonia

Gastrointestinal

- 301 Hepatic Failure
- 303 GI Bleeding - Varices
- 305 GI Bleeding - Ulcer/lacerat.
- 306 GI Bleeding - Diverticulosis
- 307 Other GI Disease
- 308 GI Perforation
- 309 GI Obstruction
- 310 GI Vascular Insufficiency
- 311 Pancreatitis
- 312 GI Cancer
- 313 Other GI Inflammatory Disease

Neurological

- 401 Intracerebral Haemorrhage
- 402 Subarachnoid Haemorrhage
- 403 Stroke Neurologic Infection
- 405 Neurologic Neoplasm
- 406 Neuromuscular Disease
- 407 Seizure
- 408 Other Neurologic Disease
- 409 Epidural haematoma
- 410 Coma

Sepsis

- 501 Sepsis (other than Urinary)
- 502 Sepsis of Urinary Tract Origin
- 503 Sepsis with Shock (not urinary)
- 504 Sepsis - UT Origin with Shock

Trauma

- 601 Head Trauma +/- Multi Trauma
- 602 Multiple Trauma excl. Head
- 603 Burns
- 604 Multi. Trauma – Spin. Cord Inj.
- 605 Isolated Cervical Cord Injury

Metabolic

- 701 Metabolic Coma
- 702 Diabetic Ketoacidosis
- 703 Drug Overdose
- 704 Other Metabolic Diseases

Non-operative (cont)

Haematological

801	Coagulop./Neutro./Thromb.
802	Other Haem. Diseases
101	Genitourinary
901	Renal Diseases
902	Pre-eclampsia
903	Haemorrhage, post partum

Other Musculoskeletal/skin

1101	Musculoskeletal/skin Disease
1102	Cellulitis/soft tissue infection

Other

1002	Other medical diseases (Use only if 'Other Diseases' in specific organ system is inappropriate)

Post-Operative

Cardiovascular

1202	Periph. Vascular Dis. – no Graft
1203	Periph. Artery Bypass Graft eg Fempop
1204	Elective AA Surgery
1205	Carotid Endarterectomy
1206	Valvular Heart Surgery
1207	Coronary Artery Bypass Graft
1208	Other Cardiovascular Diseases
1209	Dissecting Aortic Aneurysm
1210	Ruptured Aortic Aneurysm
1211	Aorto-femoral bypass Graft
1212	CABG with Valve repair replacement
1213	Endoluminal Aortic Repair

Respiratory

1301	Respiratory Infection
1302	Respiratory Neoplasm – Lung
1303	Neopl.Mouth/larynx/sinus/trach
1304	Other Respiratory Disease

Gastrointestinal

1401	GI Perforation/Rupture
1403	GI Bleeding
1404	GI Obstruction
1405	GI Neoplasm
1406	Cholecystitis/cholangitis
1407	Liver Transplant
1408	Other GI Disease
1409	Fistula/Abscess surgery
1410	GI Vascular ischemia resection surgery
1411	Pancreatitis
1412	Peritonitis
1413	Other GI Inflammatory Disease

Appendix 2 – APACHE II Severity of Disease Classification

	PHYSIOLOGIC VARIABLE	High Abnormal Range					Low Abnormal Range				APS Scores
		+ 4	+ 3	+ 2	+ 1	0	+1	+2	+3	+4	
A. ACUTE PHYSIOLOGY SCORE (APS)	Temperature – rectal (° C)	≥ 41	39 – 40.9		38.5 – 38.9	36 – 38.4	34 - 35.9	32 – 33.9	30 – 31.9	≤ 29.9	
	Mean arterial pressure – mmHg	≥ 160	130 - 159	110 – 129		70 - 109		50 - 69		≤ 49	
	Heart rate (ventricular response)	≥ 180	140 – 179	110 – 139		70 - 109		55 - 69	40 - 54	≤ 39	
	Respiratory rate (non-ventilated or ventilated)	≥ 50	35 – 49		25 - 34	12 - 24	10 - 11	6 - 9		≤ 5	
	Oxygenation: A - aDO_2 or PaO_2(mmHg) a. if $FIO_2 \geq 0.5$ record A - aDO_2	> 500	350 – 499	200 – 349		< 200					
	b. if $FIO_2 < 0.5$ record only PaO_2					PO_2 -> 70	PO_2 61 - 71		PO_2 55-60	PO_2 < 55	
	Arterial pH	≥ 7.7	7.6 – 7.69		7.5 – 7.59	7.33 – 7.49		7.25 – 7.32	7.15 – 7.24	< 7.15	
	Serum sodium (mMol/L)	≥ 180	160 – 179	155 – 159	150 - 154	130 - 149		120 - 129	111 - 119	≤ 110	
	Serum potassium (mMol/L)	≥ 7	6 – 6.9		5.5 – 5.9	3.5 – 5.4	3 – 3.4	2.5 – 2.9		≤ 2.5	
	Serum creatinine (mMol/L) (double point score for acute renal failure)	≥ 0.300	0.171-0.299	0.121-0.17		0.05-0.12		< 0.05			
	Haematocrit (%)	≥ 60		50 – 59.9	46 – 49.9	30 – 45.9		20 – 29.9		< 20	
	White blood count (total/mm^3) (in 1,000s)	≥ 40		20 – 39.9	15 – 19.9	3 – 14.9		1 – 2.9		< 1	
	Glasgow Coma Score (GCS) **(see next page for GCS guide)** (Score = 15 minus actual GCS)										
	Serum HCO_3 (venous – mMol/L) (**Only use this if no ABGs available**)	≥52	41 – 51.9		32 – 40.9	22 – 31.9		18 – 21.9	15 – 17.9	<15	

#Acute renal failure: *"If abnormal serum creatinine values reflect acute renal failure as opposed to chronic renal failure then the points assigned to the creatinine values should be doubled. Acute renal failure is defined as any creatinine value that is not within the normal range designated by the APACHE II system."* Thus for the purposes of this study if your patient has any points for an increased creatinine and they are not documented to have chronic renal failure then the creatinine points should be doubled.

B. AGE POINTS

Assign points to age as follows:

Age (yrs)	Points
☐ ≤ 44	0
☐ 45–54	2
☐ 55–64	3
☐ 65–74	5
☐ ≥ 75	6

C. CHRONIC HEALTH POINTS

If patient has history of severe organ system insufficiency or is immuno–compromised, assign points as follows:	Points
☐ **a**. for non-operative or emergency post-operative patients	5
☐ **b**. for elective post-operative patients	2

DEFINITIONS: Organ insufficiency or immuno-compromised state must have been evident **prior** to this hospital admission and conform to the following criteria:

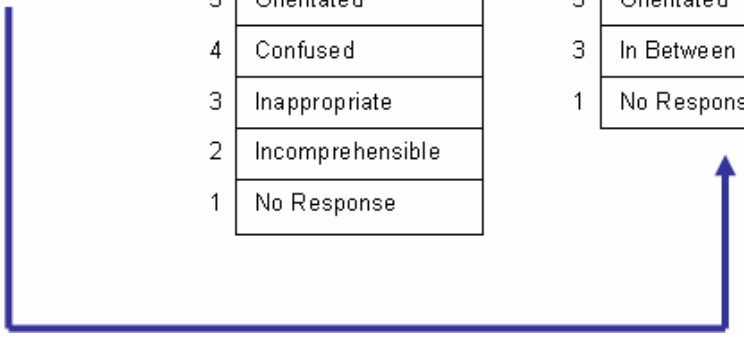
LIVER	Biopsy proven cirrhosis & documented portal hypertension (PH); episodes of upper GI bleeding due to PH; or prior episodes of hepatic failure/encephalopathy/coma
RENAL	Receiving chronic dialysis
CARDIOVASCULAR	New York Heart Association Class IV
RESPIRATORY	Chronic restrictive, obstructive or vascular disease resulting in severe exercise restriction (i.e. unable to climb stairs, perform household duties); or documented chronic hypoxia, hypercapnia, 2° polycythemia, severe pulmonary hypertension (>40mmHg) or respiratory dependency
IMMUNOCOMPROMISED	Patient has received therapy that suppresses resistance to infection, eg. immuno-suppression, chemotherapy, radiotherapy, long term or recent high dose steroids, or has a disease sufficiently advanced to suppress resistance to infection (eg leukaemia, lymphoma, AIDS)

APACHE II SCORE - a sum of:	**A.** APS points =____	**B.** Age points =____	**C.** Chronic Health points = __	**Sum of A + B + C = __**(0 to 71)

GCS Guide:

*For **intubated** patients use verbal scoring column allocated*

Best Verbal Response		"Verbal" Intubated		Best Motor Response		Best Eye Opening	
5	Orientated	5	Orientated	6	Obeys	4	Spontaneous
4	Confused	3	In Between	5	Localises	3	To Command
3	Inappropriate	1	No Response	4	Flexion – Withd.	2	To Pain
2	Incomprehensible			3	Flexion – Decort.	1	No Response
1	No Response			2	Extension		
				1	No Response		



APPENDIX 3 – SOFA SCORE WORKSHEET

ORGAN SYSTEM	0	1	2	3	4	9	Organ Scores
Respiration PaO_2/FIO_2 **(in mmHg)**	>400	301-400	<301	≤200 With Respiratory Support*	≤100 With Respiratory Support*	Variable not measured	
Coagulation **Platelets($x10^3/mm^3$)**	>150	101-150	51-100	21-50	≤20	Variable not measured	
Liver **Bilirubin (mg/dL)** **(μmol/L)**	<1.2 <20	1.2 - 1.9 20 - 32	2.0 - 5.9 33 - 101	6.0 - 11.9 102 - 204	>12.0 >204	Variable not measured	
Cardiovascular **Hypotension**	MAP > 70 mm Hg without vasopressors	MAP <70 mm Hg without vasopressors	Dopamine ≤5 or dobutamine (any dose)"	Dopamine >5 or adr ≤0.1 or noradr ≤0.1"	Dopamine >15 or adr >0.1 or noradr >0.1"	Variable not measured	
Renal **Creatine (mg/dL)** **(μmol/L)** **or urine output**	<1.2 <110	1.2 - 1.9 110 - 170	2.0 - 3.4 171 - 299	3.5 - 4.9 300 - 440 or <500 mL/day	>5.0 >440 or <200 mL/day	Variable not measured	

adr, adrenaline = epinephrine; noradr, noradrenaline = norepinephrine.
"Adrenergic agents administered for at least 1 hr (doses given are in μg/kg/min).
*Respiratory support is defined as any form of invasive or non-invasive ventilation including mask CPAP or CPAP delivered through a tracheostomy/tracheotomy or endotracheal tube
PLEASE NOTE: The highest score for someone **without** respiratory support is **2**.

APPENDIX 4: Table of Events - Standard care and supplemental PN Groups

Study Day	Baseline	1	2	3	4	5	6	7	8	9	10	11	12	13	14	21	28	ICU D/C	Ward	Hospital D/C	3 mths post D/C	6 mths post D/C
Incl & excl criteria	X																					
Consent	X																					
Randomisation	X																					
Demographics	X																					
Apache II score	X																					
Apache III diag	X																					
Daily Data* (ICU)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
LFTs, WBC	X	x	x	x	x	x	x	X	x	x	x	x	x	x	X	X	X					
Use of new antibiotics	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
SOFA Score	X	X	X	X				X							X	X	X					
TG	X			X				X							X							
CRP	X							X							X		X					
Dur MV																		X				
LOS ICU																		X				
LOS Hosp																				X		
Survival status																		X		X	X	X
Mid-upper arm muscle circumference	X									Measured once patient is ready for ICU D/C										X		
Hand grip										Measured once patient is ready for ICU D/C										X		
6 minute walk test																				X		
QOL																				X	X	X

X denotes must be collected on specified day

X denotes collect only if measured, no need to specially collect

*Daily Data: The following variables will be collected daily: Target energy and protein requirements, received energy and protein amounts, received EN and PN volumes, AM BGL levels, Units of insulin delivered, Gastric residual volumes, Documented episodes of vomiting, Documented episode of abdominal distension, Documented episode of witnessed aspiration

Appendix 5: Table of Events - Sub-study patients

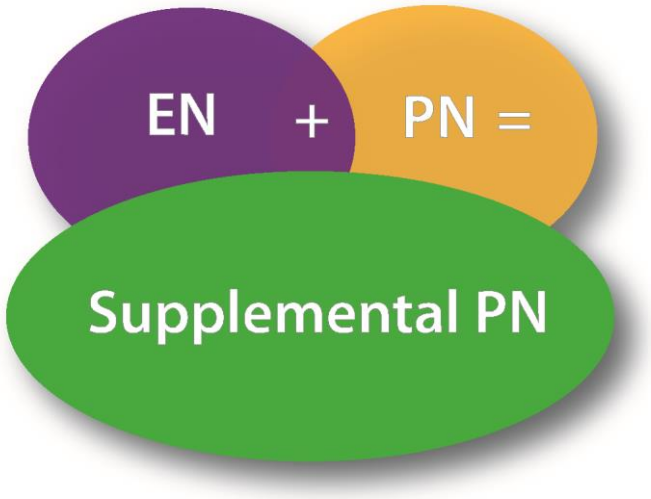
Study Day	Baseline	1	2	3	4	5	6	7	8	9	10	11	12	13	14	21	28	ICU D/C	Ward	Hospital D/C	3 mths post D/C	6 mths post D/C
Incl & excl criteria	X																					
Consent	X																					
Randomisation	X																					
Demographics	X																					
Apache II score	X																					
Apache III diag	X																					
Daily Data* (in ICU)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
LFTs, WBC	X	x	x	x	x	x	x	X	x	x	x	x	x	x	X	X	X					
Use of new antibiotics	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
SOFA Score	X	X	X	X				X							X	X	X					
TG	X			X				X							X							
CRP	X							X							X		X					
Indirect calorimetry	X	Twice weekly							Twice weekly										Twice weekly			
Nitrogen balance		X		X				X							X		X					
Estimated nutrition intake (ward)		Commences once oral intake resumes- daily in ICU																	2nd daily			
Mid-upper arm muscle circumference	X										Measured once patient is ready for ICU D/C									X		
6 minute walk test																				X		
Hand grip											Measured once patient is ready for ICU D/C									X		
Dur MV																		X				
LOS ICU																		X				
LOS Hosp																				X		
Survival status																		X		X	X	X
QOL																				X	X	X

X denotes must be collected on specified day
X denotes collect only if measured, no need to specially collect

*Daily Data: The following variables will be collected daily: Target energy and protein requirements, received energy and protein amounts, received EN and PN volumes, AM BGL levels, Units of insulin delivered, Gastric residual volumes, Documented episodes of vomiting, Documented episode of abdominal distension, Documented episode of witnessed aspiration

Supplemental Parenteral Nutrition:

A Pilot Randomised Controlled Trial



Standard Operating Procedures

Protocol AD003 Version 8 10 07 14

SOP Version 3 01 08 14

anzic research centre

Contents

Table of Contents

Coordinating Centre

ANZIC-RC	Postal Address	Delivery Address
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Website: http://www.anzicrc.monash.org

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Role: 1. Management committee member 2. Lead Research Co-ordinator	Site: Auckland City Hospital, CVICU
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Dr Colin McArthur	
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Email: [redacted]	
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Email: [redacted]	
Dr Paul Young	
Role: Site PI	Site: Wellington
Email: [redacted]	

Important points about this SOP

Light bulbs

- When you see a light bulb like this one, it means you should read the instructions carefully as there is something significant to take note of regarding study processes.
- Throughout the SOP there are references to study tools that have been provided to assist you. These are listed as appendixes and will be sent to each site.

Study Administration Structure

Coordinating Centre

Australian and New Zealand Intensive Care Research Centre (ANZIC-RC), Department of Epidemiology and Preventative Medicine (DEPM) Monash University, Victoria, Australia

Responsibilities:

- Overall management of the study including assistance with HREC applications
- Management of study budget and liaison with funding bodies
- Protocol and case report form (CRF) design and production
- Database design and management
- Protocol training of research coordinators and PHARLAP study team
- Preparation and arrangement of investigator payments
- Study set-up
- Randomisation
- Coordination of data entry and feedback of data enquiries
- Monitoring and close-out site visits
- Organisation of investigator meetings
- Serious adverse event notification
- Data analysis and collaboration on publications

Management Committee

Responsibilities:

- Overseeing all aspects of the study management including:
- Liaison with coordinating centre staff
- Liaison with Australian & New Zealand Intensive Care Society Clinical Trials Group
- Liaison with Clinical Informatics and Data Management Unit
- Overseeing funding applications
- Overseeing disbursement & administration of funds
- Ensuring fiscal responsibilities are maintained
- Development and approval of final protocol and study materials
- Development and approval of data collection tools and methods
- General study management issues

Members

Dr Shay McGuinness	Supplemental PN Chief Investigator, Intensivist, CVICU, Auckland City Hospital
Dr Andrew Davies	Senior Research Fellow, ANZIC-RC
Ms Emma Ridley	Supplemental PN Project Manager and ICU Nutrition Research Program Manager, ANZIC-RC, Monash University
Dr Rachael Parke	Research Coordinator, CVICU, Auckland City Hospital
Dr Colin McArthur	Intensivist, DCCM, Auckland City Hospital
Dr Owen Roodenburg	Intensivist, The Alfred Hospital
Dr Neil Orford	Director of ICU, Barwon Health
Lyn Gillanders	Senior Dietitian, Auckland City Hospital
Prof Jamie Cooper	Director, ANZIC-RC

Study synopsis

Background

Early initiation of enteral nutrition (EN) improves clinical outcomes in critically ill patients (1) and the provision of EN is now established as an important aspect of management in most Intensive Care Units (ICUs). Many studies have demonstrated that patients often receive insufficient amounts of their predicted nutrition requirements (ie. underdosing) from EN for multiple reasons. Because EN leads to insufficient nutritional intake, the early commencement of parenteral nutrition (PN) as a supplement to EN would seem a useful solution to increasing this amount. A landmark multicentre, randomized controlled trial in 4640 patients found early initiation of PN did not improve survival, but did delay recovery and increase complications when compared to late initiation of PN (2). There are several concerns regarding the generalisability and outcomes of this study, particularly in an Australian and New Zealand setting. Before dismissing the intervention of early supplemental PN, follow on studies are required to identify if there are patient populations that may benefit. Such studies need to enrol a more severely unwell population, use a modern lipid PN product, not start PN before the 3rd day of ICU admission, use a less stringent glucose control aim, avoid over nutrition in the supplemental PN arm, and should only deliver PN as it is used in standard care in the control arm.

Aim

To determine whether a supplemental PN strategy will reliably and safely deliver more total energy than a standard EN strategy in a group of patients with at least one organ system failure.
We also aim to understand the nutritional requirements and intake of critically ill patients who have been transferred from the ICU to hospital ward areas.

Objectives

<u>The principal objectives are:</u>

1) To determine whether the supplemental PN strategy leads to the delivery of increased amounts of total nutrition (measured as energy delivered), and is safe in regards to adverse effects.
2) To measure the clinical outcomes in patients receiving both study strategies to provide information to assist design of a larger randomized controlled trial.

<u>Secondary objectives in a sub-set of patients are:</u>

3) To determine whether the supplemental PN strategy leads to improved nitrogen balance.
4) To determine both the nutritional requirements and nutritional intake of critically ill patients during the period of hospitalization after transfer from the ICU.

Patient population

Mechanically ventilated critically ill patients over the age of 16 years who are mechanically ventilated and expected to remain so the day after tomorrow, have at least 1 organ failure and who have not been in ICU for greater than 72 hours at the time of screening.

Methods

<u>General Study Procedures:</u>
100 patients will be enrolled into the study from 6 sites in Australia and New Zealand. All patients will have:

- Nutrition requirements calculated using a standardised fixed prescription.

Study synopsis- continued

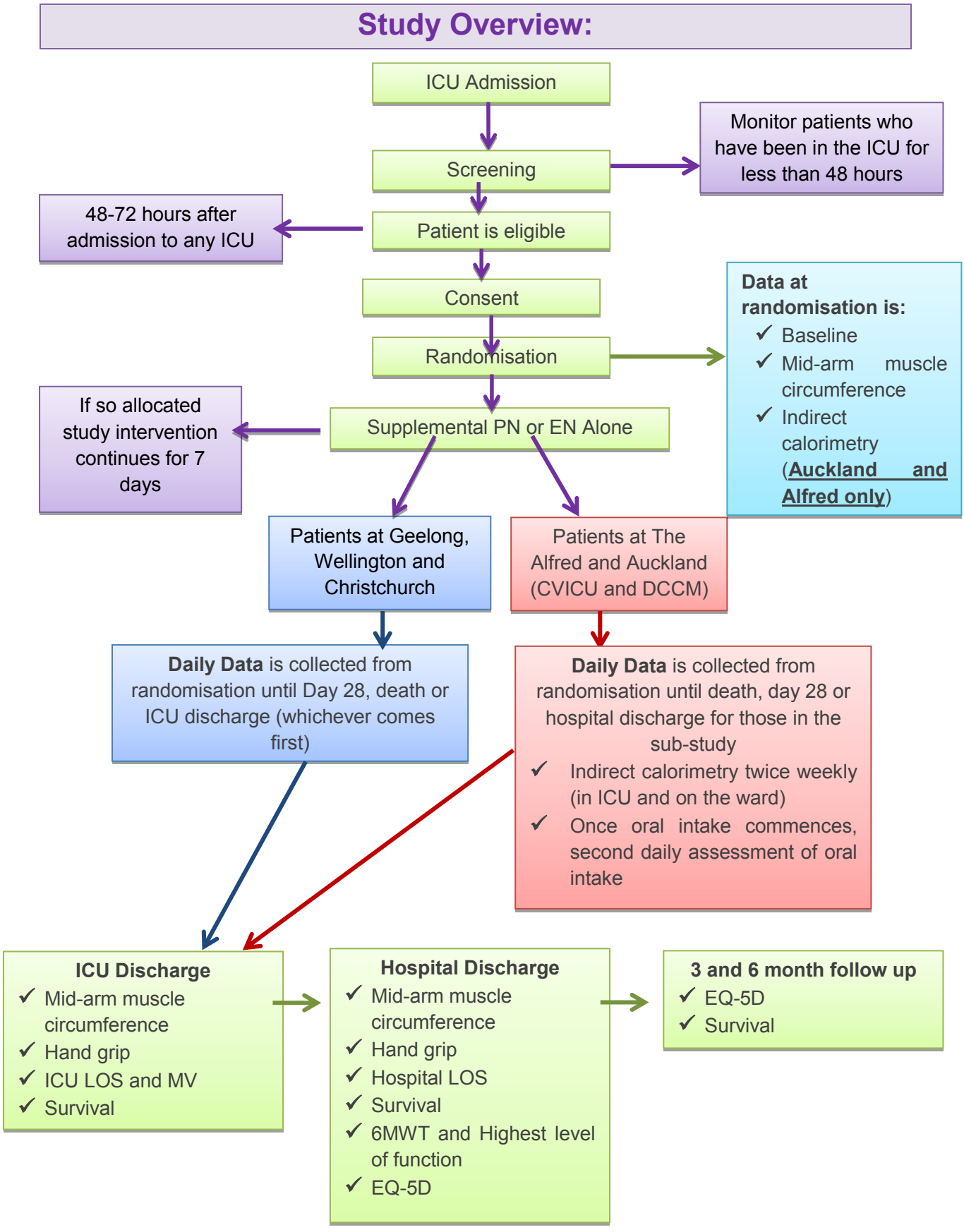
- Blood glucose control aim of < 10 mmol/l (3).
- All nutrition input and infectious complications followed until day 28 after enrolment unless death or ICU discharge occurs prior to this.
- Follow up until hospital discharge for survival status and duration of hospitalization. Patients will also complete a 3-month and a 6-month quality of life questionnaire.

Standard Care Group:
Patients will commence or continue with EN via an enteral tube according to standard practice at each site which is based on clinical practice guidelines. PN will only be used once all methods outlined in clinical practice guidelines have been attempted, or are contra-indicated.

Supplemental PN Group:
EN will be run in the same manner as the standard group, based on clinical practice guidelines, and will not be reduced based on PN. The starting dose of PN will be determined by the amount of energy received in the 24 hours prior to randomisation. The adequacy of nutrition provision from both PN and EN will be assessed at midday each day for 7 days or until ICU discharge. The dose of PN will be adjusted accordingly. If a patient has an actual or anticipated interruption to EN for greater than 2 hours the PN will be run at 20 kcal/kg ideal body weight during the period EN is withheld. Supplemental PN will be ceased completely after a maximum of 7 days of the study and only used subsequently in patients with severe nutrition intake insufficiency.

Outcomes

The primary outcome for this study is the total energy amount delivered by either form of nutrition (ie. EN and PN, if delivered) over the 7 days of the study period. Secondary outcomes are total protein delivered over the 7 days of the study period, energy and protein delivered over the whole ICU stay (up to 28 days), total infectious complication rate, organ failure scores, duration of mechanical ventilation, duration of hospital stay and in-hospital mortality.


Study Overview:
ICU Admission
Screening
Monitor patients who have been in the ICU for less than 48 hours
48-72 hours after admission to any ICU
Patient is eligible
Consent
Randomisation
Data at randomisation is:
✓ Baseline
✓ Mid-arm muscle circumference
✓ Indirect calorimetry (Auckland and Alfred only)
If so allocated study intervention continues for 7 days
Supplemental PN or EN Alone
Patients at Geelong, Wellington and Christchurch
Patients at The Alfred and Auckland (CVICU and DCCM)
Daily Data is collected from randomisation until Day 28, death or ICU discharge (whichever comes first)
Daily Data is collected from randomisation until death, day 28 or hospital discharge for those in the sub-study
✓ Indirect calorimetry twice weekly (in ICU and on the ward)
✓ Once oral intake commences, second daily assessment of oral intake
ICU Discharge
✓ Mid-arm muscle circumference
✓ Hand grip
✓ ICU LOS and MV
✓ Survival
Hospital Discharge
✓ Mid-arm muscle circumference
✓ Hand grip
✓ Hospital LOS
✓ Survival
✓ 6MWT and Highest level of function
✓ EQ-5D
3 and 6 month follow up
✓ EQ-5D
✓ Survival

Inclusion criteria

Patients in intensive care who meet all of the following:

- ✓ Admitted to intensive care between 48 hours and 72 hours previously
- ✓ Mechanically ventilated at the time of enrolment and expected to remain ventilated until the day after tomorrow
- ✓ At least 16 years of age
- ✓ Have central venous access suitable for PN solution administration

AND

- ✓ Have 1 or more of the following organ system failure (respiratory, cardiovascular or renal) related to their acute illness defined as:

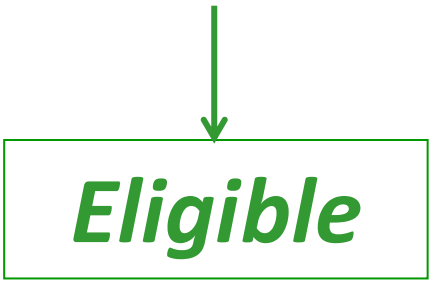
1. $PaO_2/FiO_2 \leq 300$ mmHg
2. Currently on 1 or more continuous vasopressor infusion which were started at least 4 hours ago at a minimum dose of :
    a. Dopamine greater than 5 mcg/kg/min
    b. Noradrenaline ≥ 0.1mcg/kg/min
    c. Adrenaline ≥ 0.1 mcg/kg/min
    d. Any dose of total vasopressin
    e. Milrinone >0.25mcg/kg/min)
3. Renal dysfunction defined as

    In patients without known renal disease:

    a. serum Creatinine > 171 mmol/l OR
    b. Currently receiving renal replacement therapy

    In patients with known renal disease:

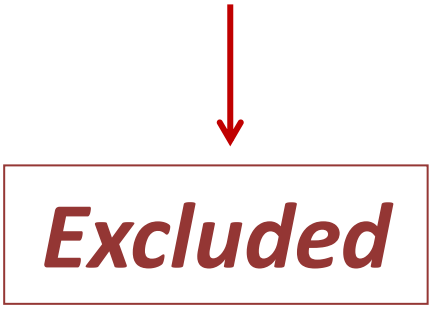
    c. an absolute increase of > 50% in Creatinine from baseline OR
    d. Currently receiving renal replacement therapy
4. Currently has an intracranial pressure monitor or ventricular drain in situ
5. Currently receiving extracorporeal membrane oxygenation
6. Currently has a ventricular assist device



Exclusion criteria

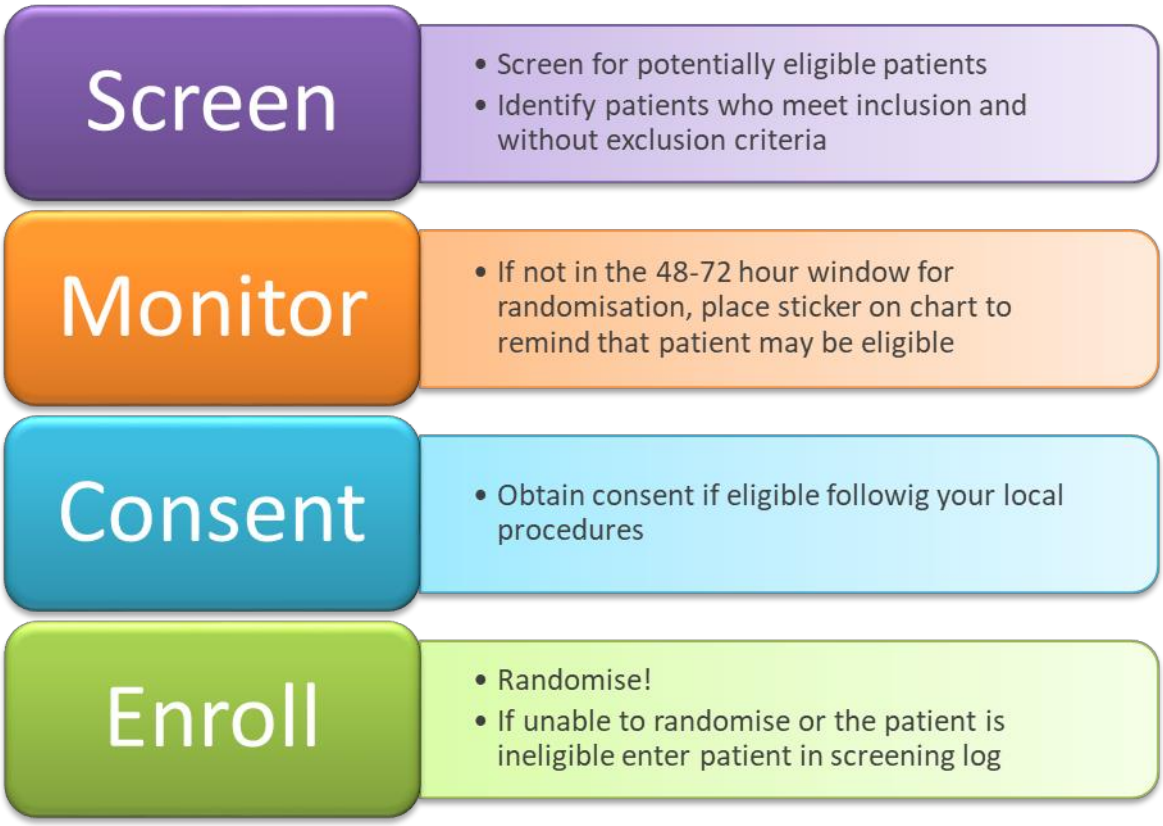
Patients will be excluded if:

- Both EN and PN cannot be delivered at enrolment (i.e. either an enteral tube or a central venous catheter cannot be placed or clinicians feel that EN or PN cannot be safely administered due to any other reason).
- Currently receiving PN
- Standard PN solutions cannot be delivered at enrolment (i.e. clinicians believe that a patient definitely needs a specific parenteral nutrition formulation (e.g. glutamine-supplementation or specific lipid formulation).
- Death is imminent or deemed highly likely in the next 96 hours.
- There is a current treatment limitation in place or the patient is unlikely to survive to 6 months due to underlying illness
- More than 80% of energy requirements have been satisfactorily delivered via the enteral route in the last 24 hours.
- Are known to be pregnant
- The treating clinician does not believe the study to be in the best interest of the patient



Screening

Remember! Patients can only be enrolled between 48 and 72 hours post admission to the ICU (including if they were transferred from another ICU).



Co-enrolment

Co-enrolment has been approved for the following studies:

- ✓ HEAT
- ✓ EPO-TBI
- ✓ SPICE
- ✓ PHARLAP
- ✓ ADRENAL
- ✓ DahLIA
- ✓ Cubist VAP
- ✓ ARISE
- ✓ TEAM
- ✓ POLAR (standard care only)
- ✓ TRANSFUSE
- ✓ ZORO

Consent Process

- The consent process outlined in the original ethics application must be adhered to.
- Patients in this study will not have capacity to consent for themselves at time of enrolment because of the nature of their illness (sedated and ventilated).
- The person who can provide consent for the patient is the "person responsible" or "Next of Kin" (NOK) or "legal surrogate" or "relative/friend/whānau member" or "parent or guardian". For the purposes of this eCRF the term "person responsible" has been used to cover all of the terms above
- The person responsible or Next-of-Kin (NOK) will be approached for consent or acknowledgement (depending on your state or national law) for the patient.
- A verbal presentation should be conducted with the person responsible or NOK.
- The person conducting the consent consultation must be authorised to do so by the site principal investigator (authorisation is provided by completing the Site Signature & Responsibilities Log).
- Document the consent process in the patient's medical record and include the following points:
  - ✓ State the study title (the short title is fine)
  - ✓ The name of the person seeking consent
  - ✓ The name of the person responsible or NOK and their relationship to the patient
  - ✓ Date and time that consent was granted
  - ✓ Briefly outline any issues that were raised by the person responsible or NOK and the explanation given
  - ✓ State if an interpreter was required
  - ✓ State if verbal consent via telephone was obtained prior to randomisation
  - ✓ State if the consent consultation relates to written consent after verbal consent via telephone or Procedural Authorisation (Victorian sites only)

Verbal Consent

- If the person responsible or NOK cannot be present at the hospital within the eligibility window, verbal consent via telephone is acceptable for this study <u>if your Human Research Ethics Committee (HREC)/ Health and Disability Ethics Committee (HDEC) has approved this consent process</u>.
- Each institution will have a local requirement for the process for verbal consent via telephone. The local requirements may be a formal document or a check list or an entry in the patient's medical record. Please follow the process approved at your site.

- We recommend the following procedure if the HREC/HDEC does not have a specific procedure to follow:
  - ✓ If a telephone is used, use speaker mode.
  - ✓ Two people should witness the consent consultation one of which must be authorised by the principal investigator following protocol training
  - ✓ Follow a prepared script to make sure all the required information is covered in the consent consultation
  - ✓ Document the consent discussion in the medical record, include the name of the person who granted consent and their relationship to the patient
  - ✓ Make arrangements for a consent consultation to be conducted with the person who provided verbal consent via telephone and ask them to sign the Person Responsible or NOK Consent/Acknowledgment (and date it on the day they sign it).

Procedural Authorisation (Victorian sites only)

In cases where there is no known person responsible or they cannot be contacted within the time constraints for study enrolment, procedural authorisation may be implemented if approved by the site ethics committee, if enrolment is not contrary to the best interests of the patient and the practitioner does not have any reason to believe that the carrying out of the procedure would be against the patient's wishes.

Please see appendix **1** for the Procedural Authorisation SOP

Consent Form Completion

- Please use the current, approved consent document
- The consent document should be signed by all parties on the same date and time and if not, briefly explain why in the medical history (the family may have taken the document away to read or to consult with others)
- All parties must date their own signature
- The witness to the person responsible or NOK signature should be an impartial witness
- An impartial witness is a person independent of the study
- If the study has been explained with the aid of an interpreter, the interpreter must sign as witness to person responsible or NOK signature
- File the original signed consent document in the patient's Medical Record and file a copy in the study Patient CRF Worksheet File or vice versa, which ever process is preferred by your institution (but please be consistent).

- Please make sure a copy of the completed form is given to the person responsible or NOK for them to keep.

- The completed consent documents must be made available for inspection at monitoring visits.

Withdrawal of Consent

- If consent is withdrawn please ask if we can use data that has been collected to date, if we can conduct the 3 and 6 month follow up and if we can use the participant's blood samples that may have been collected prior to withdrawal of consent.

Participant Consent Following Person Responsible

- The participant should be approached in the general ward if they recover sufficiently to make an informed decision and asked to consider consent to continue participation in the study. If they agree they are required to sign the participant information and consent form to continue after person responsible or NOK.

- If the participant decides they do not wish to continue in the study the person giving the consent discussion should ask the participant if we can use the data collected to date of withdrawal and process specimens collected for the study. They should also ask if the participant would object to being contacted at 6 months for follow up.

- A participant information consent form following person responsible should be signed and witnessed as per the person responsible consent form.

- A copy should be placed in the patient's medical history with a description of the discussion as per the person responsible consent process

- A copy should be given to the participant and the original (or copy depending on your institution) should be kept in the study Patient CRF Worksheet File.

Website

- Randomise participants via secure study website at
  http://nutrition.spinnakersoftware.com/Login/

- Log-in to the study website using confidential username and password provided.

- Once logged in click *"randomise"* tab.

- Enter answers into all fields – an error message will appear if any answers are incorrect or missing.

- Click on randomise at the bottom of the page.

- Once patient randomised, randomisation details will appear.

- This page can be printed by pressing “print this page” located at the top of the page
- Please refer to the Data Dictionary and Website Instructions for further information regarding the website.

The following algorithm can be used to change infusion doses into mcg/kg/min

Calculating infusion rates

Mg/hr x 1000

↓

Mcg/hr/60

↓

Mcg/min/wt

= mcg/ min/kg

Determining energy provision pre randomisation

One of the exclusion criteria states **"More than 80% of energy requirements have been delivered via the enteral route in the last 24 hours".**

Remember: Only use calories from enteral nutrition to determine this criteria

Step 1:
Estimate the patient's weight. Use the dietitian's estimate as a preference. If you can not obtain the dietitian's estimate, estimate yourself.

Step 2:
Measure the patient's demi-arm span. If this is not possible estimate the patients actual height.

→ Instructions for demi armspan can be found on page 23 and the conversion table found at Appendix 2

Step 3:
Enter the patients actual weight and height determined by demi-arm span into the excel tool provided. This will give you the patients CBW.

Step 4:
Determine the patients daily energy requirement.

→ Use 25 * CBW for patients who are not currently or not expected to receive RRT or ECMO in the next 24 hours. Use 30 * CBW for patients who are currently or are expected to receive RRT or ECMO in the next 24 hours. Refer to appendix 3

Step 5:
Determine the volume of enteral nutrition received by the patient in the previous 24 hours.

← **Remember!** Subtract any discarded residual volumes from the total enteral nutrition received.

Step 6:
Determine the energy contribution from the volume of feed. Refer to appendix 4

Step 7:
Enter the patients energy requirement and the energy contribution from enteral nutrition into the excel spread sheet provided to determine eligibility

Example: Determining energy entry criteria

Study Tools to assist you in assessing this criteria:

1. Supp PN eligibility and energy calculation tool V1_05082013
2. Height Using Demispan (appendix 2)
3. Energy requirements table V1 010713 (appendix 3)
4. Nutrition Composition V1 050813 (appendix 4)

A female patient who is 45 years old meets all other inclusion criteria for the study. To determine the energy criteria the following is conducted.

Step 1: The Dietitian has conducted an assessment and the patients estimated weight is 80kg.

Step 2: Demi arm span is measured. It is 79 cm. Her height equivalent is 1.65m

Estimating height using demispan

Table 7 Estimating height using demispan

Height (m)	Men (16-54 years)	1.97	1.95	1.94	1.93	1.92	1.90	1.89	1.88	1.86	1.85	1.84	1.82	1.81	1.80	1.78	1.77	1.76
	Men ≥55 years)	1.90	1.89	1.87	1.86	1.85	1.84	1.83	1.81	1.80	1.79	1.78	1.77	1.75	1.74	1.73	1.72	1.71
	Demispan (cm)	99	98	97	96	95	94	93	92	91	90	89	88	87	86	85	84	83
Height (m)	Women (16-54 years)	1.91	1.89	1.88	1.87	1.85	1.84	1.83	1.82	1.80	1.79	1.78	1.76	1.75	1.74	1.72	1.71	1.70
	Women (≥55 years)	1.86	1.85	1.83	1.82	1.81	1.80	1.79	1.77	1.76	1.75	1.74	1.73	1.71	1.70	1.69	1.68	1.67
Height (m)	Men (16-54 years)	1.75	1.73	1.72	1.71	1.69	1.68	1.67	1.65	1.64	1.63	1.62	1.60	1.59	1.58	1.56	1.55	1.54
	Men (≥55 years)	1.69	1.68	1.67	1.66	1.65	1.64	1.62	1.61	1.60	1.59	1.57	1.56	1.55	1.54	1.53	1.51	1.50
	Demispan (cm)	82	81	80	79	78	77	76	75	74	73	72	71	70	69	68	67	66
Height (m)	Women (16-54 years)	1.69	1.67	1.66	1.65	1.63	1.62	1.61	1.59	1.58	1.57	1.56	1.54	1.53	1.52	1.50	1.49	1.48
	Women (≥55 years)	1.65	1.64	1.63	1.62	1.61	1.59	1.58	1.57	1.56	1.55	1.54	1.52	1.51	1.50	1.49	1.47	1.46

Remember! Make sure you are looking at the correct gender, age and corresponding row to determine height.

Step 3: The patients weight and height are entered into the excel spread sheet provided (file name Supp PN eligibility and energy calculation tool V1_05082013).

Calculated Body weight (CBW) is returned as 71 kg.

Example: Determining energy entry criteria (continued)

Step 4: The patient is not receiving RRT or ECMO and either is not expected to commence. The study tool at appendix 3 is used to determine the energy requirement.
NB: The calculation is 25*71= 1775 calories per day.

Patients calculated body weight	Daily requirement at 25 kcal/kg	Daily requirement at 30 kcal/kg
68	1700	2040
69	1725	2070
70	1750	2100
71	1775	2130
72	1800	2160
73	1825	2190
74	1850	2220
75	1875	2250

25 kcal/kg is used because there is not and not expected to be any RRT or ECMO in the next 24 hours.

Step 5: The patient had received 1400 mls of enteral formula in the previous 24 hours prior to the time of screening. They had had 400 mls of discarded GRV. Therefore the total amount of enteral formula received for the assessment is 1400-400= 1000ml. The formula is Protein Plus Multi-fibre. The energy contribution table can be used to determine how much energy is provided by the volume of formula (Appendix 4).

Nutricia				
Cubison	1	4200	1000	55
Diason	1	4200	1000	43
Nutrison 1 Cal	1	4200	1000	40
Nutrison Multifibre	1	4200	1000	40
Nutrison Protein Plus MF	1.25	5250	1250	63

Protein Plus Multi-fibre provides 1.25 calories per ml. The total energy received is 1000 * 1.25= 1250 calories.

Step 6: Enter the patients energy requirement (1775 calories) and the energy received from enteral nutrition (1250 calories) into the excel spread sheet provided to determine if the patient is eligible.

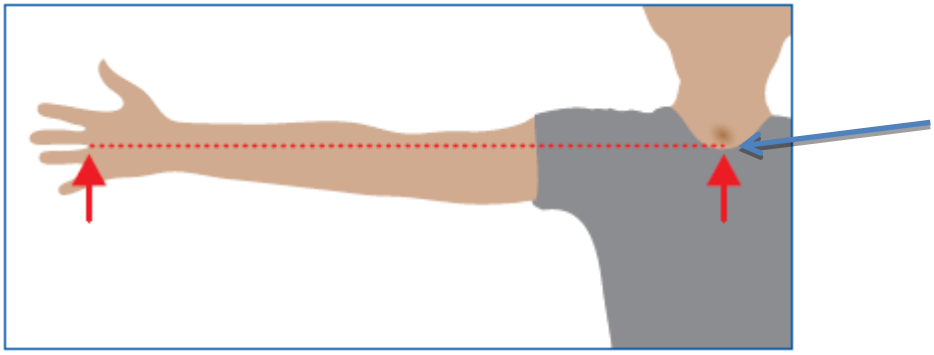
Alternatively you can calculate the percentage of requirements met by dividing the energy received from enteral nutrition by the energy requirement and multiplying by 100:

1250/1775*100= 70% (this needs to be < 80% for eligibility)

The patient is eligible and can be randomised.

Demi-arm span measurement procedure

Use the tape measure provided to measure the patients demi-arm span. Follow these instructions.



1. Lie the patient flat on their back (or as flat as you can)
2. Extend the patients' *right* arm until it is horizontal with the shoulder. Ensure the wrist is straight. The patients' arm may need to be supported.
3. Stand on the right side of the patient.
4. Locate and mark the middle of the sternal notch
5. Place the tape measure between the middle and ring finger of the patients' right hand. The tape measure should be at zero at the base of the fingers (finger "web"). The tape should follow the patients arm in a straight line, and not be twisted or at an angle when measuring the distance.
6. Extend the tape measure along the arm to the mid-point of the sternal notch.
7. Refer to the provided table for the corresponding height (hyperlink)

Adapted from from: The 'MUST' Explanatory Booklet: A Guide to the 'Malnutrition Universal Screening Tool' ('MUST') for Adults. BAPEN. 2011 and Anthropometric Procedures Manual: Early parenteral nutrition vs. standard care in patients not expected to be fed within 24 h of ICU admission. http://www.evidencebased.net/files/EarlyPN_APM.pdf

Randomisation

- Once a patient is determined as eligible and consent has been obtained, they can be randomised via the website.
- Patients will be randomised to one of two groups: Supplemental PN group or standard care.
- Patients at The Alfred and Auckland City Hosptial (CVICU and DCCM) will automatically be included in the sub-study. ***Please take care to note the additional procedures for these patients.***

Study Days:

- Study Days are defined as follows, regardless of when randomisation occurs:
  - ✓ Baseline: 24 hours prior to randomisation

- ✓ Study day 1: Day of Randomisation until 23:59 of that same calendar day (this might be a very short period)
- ✓ Study day 2: From 00:00 to 23:59 the next day
- ✓ ICU and Hospital discharge: measurements can be performed 48 hours either side of the actual discharge date.

Procedures common to both groups

1. Calculated body weight (CBW) shall be used for the calculation of nutritional targets. CBW is determined by the website or alternatively you can use the excel spreadsheet titled Supp PN eligibility and energy calculation tool V1_0508201 to assist you prior to randomisation.
2. Each patient will have their energy requirements estimated prior to randomisation using a fixed prescription of 25 kcal/kg of CBW to estimate their total daily energy requirement
   NB: If the patient is currently receiving renal replacement therapy or ECMO then 30 kcal/kg will be used to estimate the nutrition requirement.
3. **Changes to energy requirements**
   - ✓ Patients not in the sub-study: **The energy requirement should not be changed during the study (defined as up until D28 post enrolment, the patient resumes eating or is discharged from the ICU)**, except in the instance of commencement or discontinuation of renal replacement therapy or ECMO in which case the need for a change in energy requirement should be reviewed at 12 midday.
   - ✓ For those in the sub-study**: Energy requirements should not be changed unitl D28 post enrolment**, except in the instance of commencement or discontinuation of renal replacement therapy or ECMO (even if transferred to the ward).
4. The target rate (in mls/hour) for continuous EN delivery will be calculated with the assumption that all patients should receive 100% of their estimated energy requirements from administration of EN and rounded up to the nearest 5 ml/hour.
5. The choice of EN formula will be as per individual unit protocol.
6. Protein requirements will be set as per the treating dietitian's usual practice.
7. Blood glucose control will be according to local protocols with the aim being < 10 mmol/l in both groups. Care should be taken to avoid hypoglycaemia when adjustments to nutrition are made.
8. Patients will have daily data collected until Day 28, death or discharge from ICU. Those in the sub-study will have daily data collected until Day 28, death or hospital discharge including indirect calorimetry measurements and oral intake assessments.

Blood and other tests

- ◆ The following blood tests will be collected throughout the study period. Please note the specific days they are required on. On other days the data can be collected if it is available however the tests do not have to be requested.
  - ✓ Liver function tests (daily, if performed; but specifically on days 0, 7, 14, 21 & 28 if in ICU)

- ✓ White blood cell count (daily, if performed; but specifically on days 0, 7, 14, 21 & 28 if in ICU).
- ✓ Triglyceride level on days 0, 3, 7 & 14 (if in ICU)
- ✓ C-reactive protein on days 0, 7, 14 & 28 (if in ICU)
- ✓ Nitrogen Balance (The Alfred and Auckland City Only): Days 1, 3, 7, 14 and 28 (if remaining in ICU)

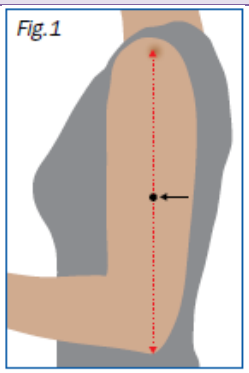
Baseline procedures for all patients:

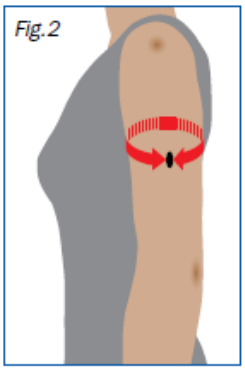
After randomisation the following procedures need to be carried out for all patients and entered into the study website:

- ✓ Demographics
- ✓ APACHE II Score
- ✓ APACHE III Diagnosis
- ✓ SOFA Score
- ✓ Triglycerides
- ✓ C-Reactive Protein (CRP)
- ✓ Mid arm muscle circumference
- ✓ Indirect calorimitry for patients at The Alfred and Auckland City Hospitals

- ◆ Baseline bloods can be within 24 hours of randomisation but must be before the intervention is started (if allocated to the Supplemental PN Group).
- ◆ Baseline bloods do not have to be returned before the intervention can commence.

Mid Arm Muscle Circumference Procedure





1. Use left arm if possible
2. Locate the top of the shoulder (acromion) and the point of the elbow (olecranon process).
3. Measure the distance between the 2 points, identify the mid point and mark on the arm. Record this point on the record sheet provided.
4. Ask subject to let arm hang loose and with tape measure, measure circumference of arm at the mid point.
5. Do not pull the tape measure tight - it should just fit comfortably round the arm.
6. If you are unable to perform the measurement please record the reason why.

Taken from: The 'MUST' Explanatory Booklet: A Guide to the 'Malnutrition Universal Screening Tool' ('MUST') for Adults. BAPEN. 2011

Standard Care Group- At Randomisation

1. After enrolment, patients allocated to the standard care (control) group will commence or continue nutrition via an enteral tube to a target rate according to unit protocol including the use of promotility agents and the placement of nasojejunal feeding tubes if required.

2. PN will only be used if the above methods have been attempted, or an absolute contraindication to EN develops.

3. Unless there is specific indication for a compounded PN solution, the PN used in the standard care group up until study day 7 will be the same as used in the intervention arm (Olimel/Triomel).

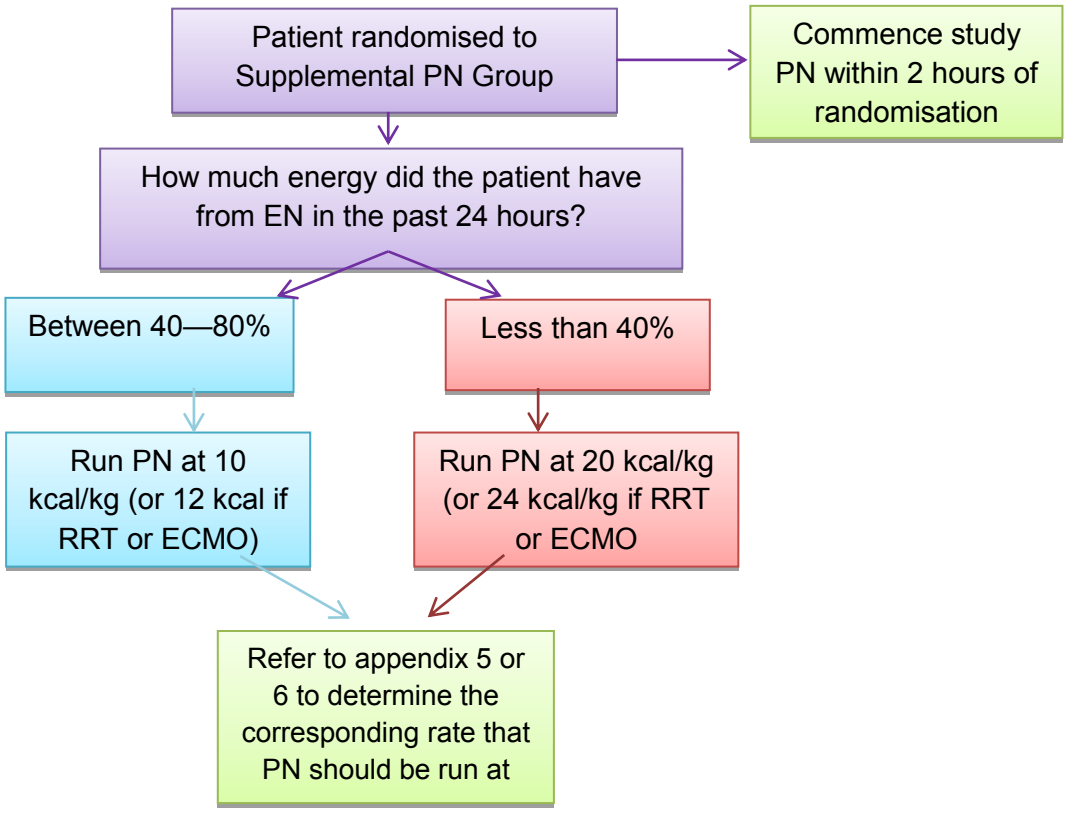
Supplemental PN Group- At randomisation

After randomisation, if the patient is randomised to the Supplemental PN group you need to do the following.

PN needs to be commenced within 2 hours of randomisation.

Study Tools provided to assist you with this

1. Study PN Rate Table not on RRT V1 300713 (appendix 5)
2. Study PN Rate Table on RRT V1 300713 (appendix 6)



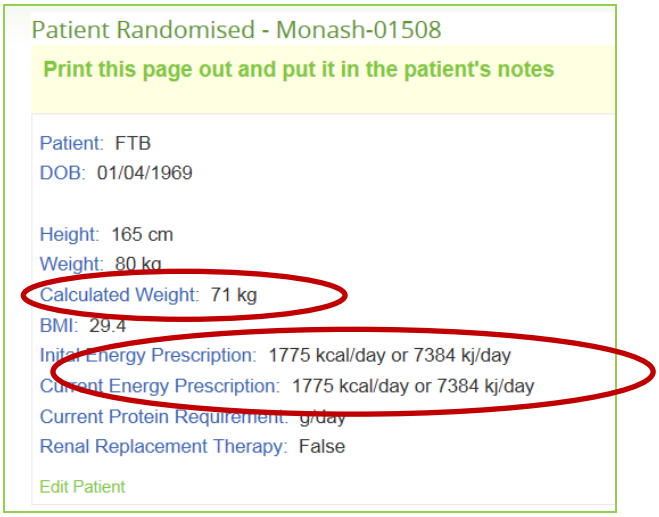
Remember!

1. **Once the PN rate is set it must not be adjusted even if EN delivery improves. Only research staff should change the rate of PN at the daily assessment.**
2. **EN must continue to be optimised regardless of PN rate.**
3. **If there is an actual interruption for ≥ 2 hours remember to turn the PN up to 20kcal/kg for the period of the interruption (refer to appendix 5 or 6 to determine the rate). Tools will be provided for the bedside nurses.**

Example: Determining the rate for PN to be run at after randomisation

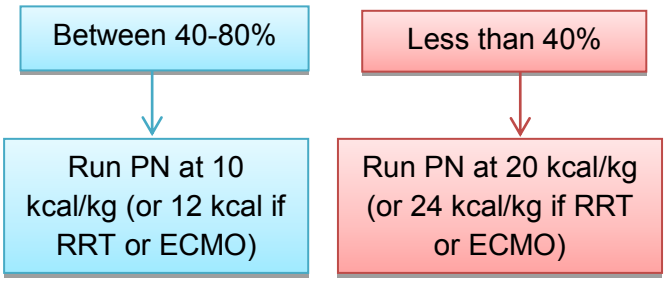
If we return to our previous example of the 45 year old female.

Step 1: Recall the energy requirement and the calculated body weight from the website on randomisation. It was 1775 kcal and her CBW is 71kg (using 25 kcal/kg of her CBW and we did not expect her to receive RRT or EMCO in the next 24 hours).



Step 2: Recall how much EN was received in the 24 hours prior to randomisation.
1250 calories so 1250/1775*100= 70%

Step 3: Determine the rate at which the PN should be run.
Remember: If the patient received:



Therefore, the PN should be run at the equivalent hourly rate for 10kcal/kg.

Refer to the "Study PN rate table for patients not on RRT/ECMO" at appendix 5 to determine the rate of PN.

Patients calculated body weight	Rate for 10kcal/kg	Rate for 20kcal/kg
68	25	55
69	25	55
70	25	55
71	30	55
72	30	55
73	30	55

The rate for CBW at 71kg, equivalent to 10kcal/kg is 30 ml/hr

Step 4: Make a note of this rate on the bedside tool provided so the bedside nurse knows the rate. Also document the rate for 20kcal/kg (55ml/hr) in case there is an interruption greater than 2 hours so the PN can be increased.

Daily procedures: All groups

- All patients should have the following assessments made daily:
  - ✓ Daily data
  - ✓ On specific study days, additional items are requested. Please ensure that they are ordered on the specified study day if they are not performed as part of routine care.

	B/Line	1	2	3	4	5	6	7	8	9	10	11	12	13	14	21	28
Daily Data* (ICU)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
LFTs, WBC	X	x	x	x	x	x	x	X	x	x	x	x	x	x	X	X	X
Use of new antibiotics	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SOFA Score	X	X	X	X				X							X	X	X
TG	X			X				X							X		
CRP	X							X							X		X

- ✓ **X** denotes must be collected on specified day
- ✓ X denotes collect only if measured, no need to specially collect

And for those having additional measurements performed, in addition to the above:

	B/Line	1	2	3	4	5	6	7	8	9	10	11	12	13	14	21	28
Indirect calorimetry	X	Twice weekly							Twice weekly								
Nitrogen balance		X		X				X							X		X
Estimated nutrition intake		Commences once oral intake resumes- daily in ICU															

- ✓ **X** denotes must be collected on specified day
- ✓ X denotes collect only if measured, no need to specially collect

Daily adjustment of PN Rate (Supplemental PN Group)

Every day at 12pm (or closest to), the patients in the Supplemental PN group should be assessed to determine what rate the PN should be run at for the subsequent 24 hours.

Remember! Use calories from all sources in the past 24 hours (approximately 1200-1200) for this daily assessment (propofol, enteral nutrition, glucose ≥ 25% AND study PN if received in place of EN because of fasting).

Study Tools provided to assist you with this

1. Energy requirements table V1 010713 (appendix 3)
2. Nutrition Composition V1 050813 (appendix 4)
3. Supp PN eligibility and energy calculation tool V2_01082014
4. Study PN Rate Table **not on** RRT or ECMO V1 300713 OR (appendix 5)
5. Study PN Rate Table **on** RRT or ECMO V1 300713 (appendix 6)

Step 1:
Determine what the patients energy requirement will be in the next 24 hours.

If RRT or ECMO will be on or is expected to be on for any period in the next 24 hours use 30 kcal/kg of CBW as the energy requirement. If not, use 25kcal/kg of CBW.

Refer to appendix 3 to determine the energy requirement.

Step 2:
Add up the energy received from all of the following for the 24 hour period you are reviewing:

1. Propofol
2. EN (minus discarded residuals)
3. Glucose ⩾ 25% and
4. Study PN (ONLY IF RECEIVED WHEN FASTING IN PLACE OF EN)

Determine how much energy has been provided from all sources.
Use the energy tool or excel spread sheet energy table to determine the total energy provision

Remember to subtract and discarded residuals from the enteral nutrition volume

Study PN has 1070 kcal per litre

Step 3:
Determine the percentage of requirements met in the past 24 hours and decide what rate the PN should be at or if it should be turned off.

If the patient has received **>80% of energy from all sources in the previous 24 hours** the PN should be stopped for the subsequent 24 hours

If the patient has received between 40-80% of energy from all sources the PN will be run at a rate of 10 kcal/kg (or 12 kcal/kg if on RRT).

Refer to Appendix 5 or 6 for the PN rate table

If the patient has received < 40% of energy from all sources the PN will be run at a rate of 20 kcal/kg (or 24 kcal/kg if on RRT).

Refer to Appendix 5 or 6 for the PN rate table

Example- reviewing the daily PN target.

If we continue on with the previous example, a review of the bedside chart from 1200-1200 reveals the patient has received:

- 500 ml of Protein Plus enteral nutrition (minus discarded gastric residual volumes)
- 1200 mg of propofol (To convert this to mls divide by 10) =120mls of propofol
- No dextrose
- 300ml of Study PN due to fasting from yesterday

Step 1: Determine the patient energy requirement. RRT or ECMO are not planned today, so the requirement does not change. Recall the requirement, 1775 kcal/day.

Step 2: Determine how much energy the patient has received (see above) from EN, propofol, IV dextrose and study PN when fasted and calculate the energy this provides. Refer to the Nutrition Composition Table at Appendix 4.

Protein Plus has 1.25 kcal/ml so 500ml*1.25= 625 kcals

Propofol 1% has 1.1 kcal/ml so 120*1.1= 132 kcals

No dextrose

Study PN has 1070 kcal/L so 0.3*1070= 321 kcals

The total energy received in the past 24 hours is 625 + 132 + 321= 1078 kcals.

Step 3: Determine the percentage of requirements met over the 24 hour period.

1078/1775*100= 61%

This means the rate should continue at the equivalent rate for 10 kcals/kg. Also provide the rate for 20 kcals/ kg in case there is an interruption to the PN for greater than 2 hours.

This should be noted on the bedside study tool.

Only include study PN in the calculation when it has been received in place of EN for fasting

Interruptions to EN

Remember! If the is an actual interruption for ≥ 2 hours, the PN should be run at a rate equivalent to 20 kcal/kg of CBW for patients not on RRT or ECMO or 24 kcal/kg of CBW for patient on RRT and/or ECMO.

Refer to appendix 5 and 6 for the rate table

Supplemental PN Group

- All patients randomised to the Supplemental PN Study Group need to have study PN available at all times regardless of if the study PN is actually running on a particular day.
- This is so if there is ever an actual or anticipated interruption to EN the PN can be restarted.
- On your daily assessment, please provide the rate that corresponds to 20 (or 25kcal/kg) to the bedside nurse in case there is an interruption. This can be documented on the bedside tool.
- Once the patient is able to recommence EN post the interruption, EN should be recommenced as per the usual local procedure and the PN should be returned to the rate that was set at the last daily assessment.
- If a patient in the Supplemental PN Study Group develops significant EN intolerance during the course of the day and EN is being run at a very low rate or is turned off please manage this as per the usual interruption plan ie. If it gets to 2 hours and the EN is not going on again it is appropriate to turn the PN on or up to the 20 or 24 kcal/kg rate.

Standard Care Group

- Patients in the standard care group who have interruptions to EN should be managed as per the usual unit practice.

Product information and dispensing for Supplemental PN

Product information

- The Study PN is a 1.5L bag of Olimel/Triomel N9-840E with vitamins and trace elements pre added and is manufactured by Baxter. Refer to appendix 7 for full composition information.

Ordering, storage and delivery

- The Study PN will be delivered by Baxter to the nominated address, already reconstituted and with additions. **As such it must be stored in the fridge between 2 and 8 degrees Celsius and be used within 90 days.**
- A pre-prepared order form will be provided to the sites. **Please allow at least 2 working days to receive any order.**

Logs and dispensing

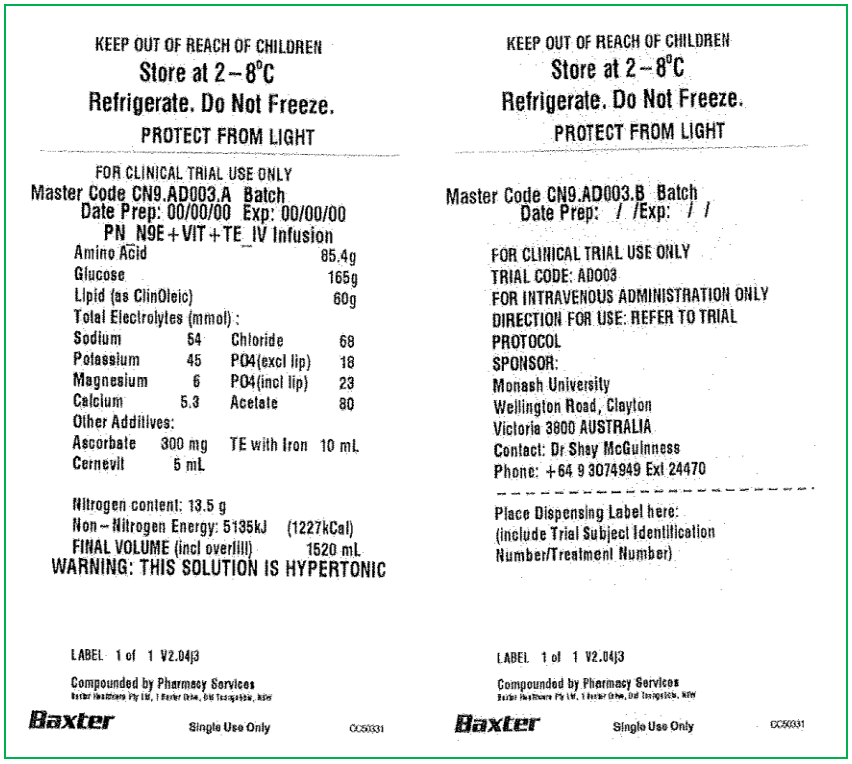
- A temperature log is provided and must be used by all sites. Daily maximum and minimum temperatures are required (appendix 8).
- An inventory log (appendix 9) should be filled out to track receipt and dispensing or expiry of study product.

Stock control and PN provision

- **Study PN needs to be provided within 2 hours of randomisation for those randomised to the intervention arm.**
- Once a patient is randomised to the intervention arm they will require at least one bag of PN to be available for study days 2-7.
- **It is recommended that at least 3 additional bags for newly randomised patients are located at each site at all times, in addition to those needed for patients already randomised.**
- This will need to be carefully monitored depending on how many patients are in the study at any one time.
- It is ideal to have a dedicated lumen for the study PN. The bag can be left hanging even if not running and changed every 24 hours.
- Please refer to the full PI for further information.

Product dispensing information

- The study PN must be dispensed following receipt of a signed PN prescription form from the study investigator or treating dietitian. The local PN prescription form is acceptable for use.
- The study PN will have the following labelling:


KEEP OUT OF REACH OF CHILDREN
Store at 2–8°C
Refrigerate. Do Not Freeze.
PROTECT FROM LIGHT

FOR CLINICAL TRIAL USE ONLY
Master Code CN9.AD003.A Batch
Date Prep: 00/00/00 Exp: 00/00/00
PN_N9E+VIT+TE_IV Infusion

Amino Acid			85.4g
Glucose			165g
Lipid (as ClinOleic)			60g
Total Electrolytes (mmol):			
Sodium	54	Chloride	68
Potassium	45	PO4(excl lip)	18
Magnesium	6	PO4(incl lip)	23
Calcium	5.3	Acetate	80
Other Additives:			
Ascorbate	300 mg	TE with Iron	10 mL
Cernevit	5 mL		

Nitrogen content: 13.5 g
Non–Nitrogen Energy: 5135kJ (1227kCal)
FINAL VOLUME (incl overfill) 1520 mL
WARNING: THIS SOLUTION IS HYPERTONIC

LABEL 1 of 1 V2.04j3
Compounded by Pharmacy Services
Baxter Single Use Only CC50331

KEEP OUT OF REACH OF CHILDREN
Store at 2–8°C
Refrigerate. Do Not Freeze.
PROTECT FROM LIGHT

Master Code CN9.AD003.B Batch
Date Prep: / /Exp: / /

FOR CLINICAL TRIAL USE ONLY
TRIAL CODE: AD003
FOR INTRAVENOUS ADMINISTRATION ONLY
DIRECTION FOR USE: REFER TO TRIAL PROTOCOL
SPONSOR:
Monash University
Wellington Road, Clayton
Victoria 3800 AUSTRALIA
Contact: Dr Shay McGuinness
Phone: +64 9 3074949 Ext 24470

Place Dispensing Label here:
(include Trial Subject Identification Number/Treatment Number)

LABEL 1 of 1 V2.04j3
Compounded by Pharmacy Services
Baxter Single Use Only CC50331

Day 1

1. Commence the Supplemental PN within 2 hours of randomisation to the supplemental PN Group.
2. Discard this first bag as per local practice (regardless of wastage).
3. Hang a new bag in accord with local practice and continue to run this bag until next required to change as per your local practice.

Subsequent Days:

1. Determine the amount of PN in kcal/kg of CBW that is to be provided as per the procedures outlined on page 29
2. Determine the hourly rate of PN using the rate table at appendix 5 or 6
3. To determine the total volume of PN required in the next 24 hour period multiply the hourly rate by 24 hours. The PN bags are 1.5L volume so determine how many bags you think the patient will require.
4. All patients randomised to the supplemental PN group will required to have at least one bag of PN available to them for the first 7 days of the study period to ensure that if there is an anticipated or actual interruption the PN can be recommenced.
5. In the event that a patient is tolerating EN well and there are no anticipated interruptions and the patient has had no use for PN for 48 hours, the PN be taken down. Please however ensure that it is available and that there is access for it to run at short notice should it be required.

Permanent withholding or withdrawing criteria:

The permanent withholding criteria should be considered to be the following:

1. The patient is found to be pregnant after enrolment.
2. Any serious adverse event or protocol deviation where, in the attending physician's opinion, the patient should not receive any further study PN.
3. Consent has been withdrawn or consent to continue has not been granted.
4. The patient has a confirmed line infection with a positive blood culture and the line for PN delivery can not be reinserted.

Ceasing study intervention

- Study-related PN will be ceased at ICU discharge or after 7 days of enrolment into the study.
- Following the end of the study period, PN may be continued if clinically indicated according to local policy.
- Clinicians will be able to continue using the usual PN used in their ICU or ward if this is clinically indicated for severe nutrition intake insufficiency.

ICU Discharge

The following outcomes should be collected at ICU Discharge:

- ✓ Hand Grip Strength
- ✓ Mid Arm Muscle Circumference
- ✓ Duration of MV
- ✓ ICU LOS
- ✓ Survival

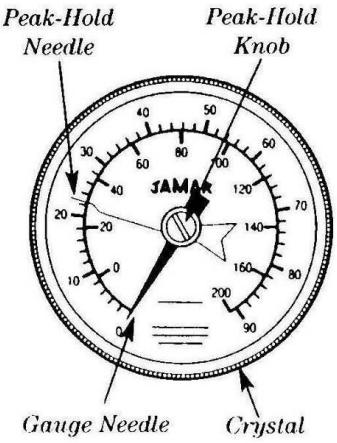
It is acceptable to try and achieve these outcomes 48 hour either side of actual discharge ie. If you know the patient is going to be discharged and you may miss them over the weekend you can attempt this early or if you miss the actual day you can attempt it for up to 48 hours post discharge. Otherwise mark the outcome as missed.

Hand Grip Strength Instructions

- The hand grip strength determines muscle strength in the dominant hand.
- Follow these instructions to conduct this test at **ICU discharge and at hospital discharge** so that there are 2 sets of readings for comparison.
- If hospital discharge occurs soon after ICU discharge, proceed with repeating the hand grip strength at hospital discharge. **Exception:** In the event hospital discharge occurs

on the day of or the day after ICU discharge, one set of hand grip strength readings is adequate.

1. Set the adjustable handle on the dynamometer to the desired spacing. (Before moving the handle from one position to another, note that the handle clip is located at the lower post (furthest from the gauge). If the handle is not replaced in the correct position, the reading will not be accurate.
2. After removing the Dynamometer, check that the black Gauge Needle is above the “0”.



3. If the gauge needle is not above the zero, remove the crystal and using a flathead screw driver move the needle until it is set above the “0” mark.
4. Have the patient sit down on a chair with an arm rest. The patients elbow should be flexed at a 90°angle.
5. Place the wrist strap on the patient’s **dominant hand** and carefully hand over the instrument. Let the patient comfortably arrange the instrument in his/her hand.
6. Have the patient squeeze with their maximum strength. Sustain for 5 seconds. The peak-hold needle will automatically record the highest force exerted.
7. Record the readings **in kilograms** and reset the peak—hold needle to zero.
8. Repeat this 2 more times and record all 3 readings on the CRF.
9. Enter the best reading into the database
10. Use an alcohol wipe to clean/sterilize the handle of the dynamometer before use on the next patient.

Hospital Discharge

The following outcomes should be collected at hospital discharge

- ✓ 6-Minute Walk Test (6MWT)
- ✓ Highest level of function scale
- ✓ Hand Grip Strength
- ✓ Mid Arm Muscle Circumference
- ✓ Hospital LOS
- ✓ ICU LOS
- ✓ Survival
- ✓ Quality of life (EQ5D)

It is acceptable to try and achieve these outcomes 48 hour either side of actual discharge ie. If you know the patient is going to be discharged and you may miss them over the weekend you can attempt this early or if you miss the actual day you can attempt it for up to 48 hours post discharge. Otherwise mark the outcome as missed.

Please refer to the data dictionary for details instructions on what is collected for the highest level of function.

6MWT

This test measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes. This test should be conducted just prior to hospital discharge.

Contraindications

Absolute contraindications for the 6MWT include the following:

1. Unstable angina during the previous month

Relative contraindications

1. Resting heart rate of more than 120 mm Hg
2. Systolic blood pressure of more than 180 mm Hg
3. Diastolic blood pressure of more than 100 mm Hg
4. Myocardial infarction during the previous month

- Patients with any of these findings should be referred to the PI for individual clinical assessment and a decision about the conduct of the test.
- The results from a resting electrocardiogram done during the previous 6 months should also be reviewed before testing.
- Stable exertional angina is not an absolute contraindication for a 6MWT, but patients with these symptoms should perform the test after using their anti-angina medication, and rescue nitrate medication should be readily available.

Safety Issues

Reasons for immediately stopping a 6MWT include the following:

1. Chest pain
2. Intolerable dyspnea
3. Leg cramps
4. Staggering
5. Diaphoresis
6. Pale or ashen appearance

- If the staff member conducting the test recognizes these problems and the appropriate responses, stop the test and allow the patient to sit or lie supine as appropriate depending on the severity or the event and the staff members assessment of the severity of the event and the risk of syncope.

- The following should be obtained based on the judgment of the staff member: blood pressure, pulse rate, oxygen saturation, and a physician evaluation. Oxygen should be administered as appropriate.

- Patient Preparation

1. Comfortable clothing should be worn.
2. Appropriate shoes for walking should be worn.
3. Patients should use their usual walking aids during the test (cane, walker, etc.).
4. The patient's usual medical regimen should be continued.
5. A light meal is acceptable before early morning or early afternoon tests.
6. Patients should not have exercised vigorously within 2 hours of beginning the test.

Measurement

- A long corridor (30 metres) should be marked at the start and the end (1 lap = 60 metres). The length of the corridor should be marked every 3 m. A treadmill may NOT be used as a replacement. Ensure that the patient has a source of O2 (if needed) and a chair nearby.

- Obtain the patient's current weight and record on the worksheet on Appendix H.

- A "warm-up" period before the test should NOT be performed.

- The patient should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. As a general guideline, you may want to measure pulse and blood pressure, if needed and make sure that clothing and shoes are appropriate.

- Refer to the 6MWT script that is provided to see instructions for conducting the test (Appendix 10).

Follow up procedures at 3 and 6 months

A suggested EQ5D and follow up script is provided to assist you with these procedures

- It is imperative that patient loss to follow up is minimised.

- All survivors after hospital discharge will be followed up at 3 and 6 months.

- The follow up due date will be listed on the patient summary page of the study website.

- The purpose of the call is to:
  - ✓ Find out if the patient has survived to 3 and 6 months.

- ✓ Remind the patient/NOK about the study in general and about what is required for the 3 and 6 month follow up.
- ✓ In some cases this may be the first discussion with the patient themselves. If so briefly explain the study to the patient and ask if they will participate in the follow up.
- ✓ Explain that the outcome assessment will take approximately 5-10 mins.

- For full instructions on how to complete the EQ 5-D please refer to the full manual provided on the study USB
- We will be using the EQ-5D 3L tool including the health state item (See appendix 11 for tool sample and the full instructions provided.

Finance

- Patient payment AUD $600 at The Alfred
- Patient payment AUD $650 at Geelong Hospital, Wellington, Christchurch and Auckland City Hospitals (CVICU and DCCM)
- Patient payment AUD $550 for additional items for patients in the sub-study (Auckland only)
  - ✓ AUD $400 will be paid upon electronic Case Report Form from enrolment to hospital discharge processing of study laboratory tests.
  - ✓ AUD $250 will be paid after the 6 month follow up and completion of the eCRF
  - ✓ If the patient dies in hospital the full $600 will be paid in one payment
  - ✓ If consent is withdrawn or consent to continue is refused the full $600 will be paid in one payment
  - ✓ Please invoice quarterly where possible
  - ✓

See appendix 12 for instructions on how to raise an invoice for Monash.

CVs

- All site personnel listed on the Site Signature and Responsibilities Log, in the Site Investigator File are required to provide a CV.
- The principal investigator and lead research coordinator are required to provide a full CV signed and dated. A copy current within 6 months is acceptable.
- Other members of the study team (associate investigators, RC providing leave cover, Dietitians etc) may provide an abridged version of their CV signed and dated. A template is provided for your convenience and to assist with the task of collecting the CVs, it is not mandatory to use it.

Logs

There are 4 Logs

- Screening Log
- Master List of Enrolled Patients Log
- Monitoring Log
- Site Signature and Responsibilities Log

All logs will be provided electronically and/or in the site file prior to commencement of the study.

Screening Log

All screening data must be entered into the electronic database via the study website.

Please enter the screening data by the first Monday of each month.

A Screening Log worksheet has been provided in the Site Investigator File for sites who wish to collect the screening data on the paper form before entering it online later.

Please do not fax the Screening Log worksheet to the coordinating centre.

Instructions are provided in the Data Dictionary.

Master List of Enrolled Patients

The Master List of Enrolled Patients may be kept on the paper form provided in the Site Investigator File or electronically on the USB provided.

At the end of the study the log should be kept with other documents in the site research office according to local practice.

Monitoring Log

The Monitoring Log is provided in Site Investigator File and will be completed for all visits by an ANZIC-RC representative.

Site Signature and Responsibilities Log

The Site Signature and Responsibilities Log is provided in the Site Investigator File. The principal investigator must sign for each contributing staff member to certify that they are qualified and have received training to perform tasks. All site personnel who complete the log are required to provide a signed and dated CV.

Local Laboratory accreditation and Normal Ranges

- Please print off the pathology normal ranges, on letterhead from your hospital intranet and file in your site folder or electronically. It is not necessary to have the lab ranges signed if it is on letterhead.

Registration

- The trial is registered on ClinicalTrials.gov and the registration number is NCT01847534

Monitoring

- The study will be monitored by a representative of ANZIC-RC. A site initiation teleconference or visit will be conducted before site activation; at least 1 routine monitoring visit will be conducted during the recruitment period; and a close out visit.
- Remote monitoring of data and screening logs will occur via the study website. Email and telephone communication will supplement site visits.
- The aims of monitoring visits are to:
  - ✓ Check the accuracy of the data base by performing source data verification of the electronic CRF against the original source documents
  - ✓ Check for protocol deviations and report these to the chief investigator as necessary
  - ✓ Review primary and secondary outcome data available for each patient
  - ✓ Confirm the consent procedures approved by the site's HREC have been followed and view each original signed consent form
  - ✓ Check data security and access
  - ✓ Review all serious adverse events (SAEs) and follow up all reported SAEs
  - ✓ Review investigator site files for completeness and accuracy
  - ✓ Assist the study staff with any queries or problems they may have in relation to the study
  - ✓ Check any specific study activities for accuracy

Monitoring Plan:

1. There are two possible monitoring visits: early monitoring visit (EMV) (all sites) and a routine monitoring visit (if required)
2. All sites will be monitored;
   a. Patients 2 and 4 at each site will be 100% Source Data Verified (SDV) EMV. In the event that patients 2 and 4 are both in the one allocation group then a substitute patient should be selected so that there at least one patient in each of the two possible allocations.
3. The number of visits will be determined by the recruitment rate.
4. 100% Consent check will be conducted on all enrolled patients including non-English language countries (arrangements will be made for these documents to be monitored if logistically the coordinating centre cannot conduct a visit).

2. If a further Routine Monitoring Visit (RMV) is required a further 2 patients will be 100% Source Data Verified (SDV). These two patients will be selected when the visit is being arranged.
5. Prior to the monitoring visit, the site data will be reviewed for completeness, unresolved data management queries, obvious data errors (in this case a data management query will be raised before the visit), the number of daily forms will be noted for time management purposes
6. The number of visits will be determined by the recruitment rate.
7. 100% Consent check will be conducted on all enrolled patients (arrangements will be made for these documents to be monitored if logistically the coordinating centre cannot conduct a visit).

Early Monitoring Visit

1. An EMV will be conducted after the first 2 to 4 patients have been enrolled and data entered in to the study website.
2. 100% SDV will be conducted on patients 2 and 4 to identify consistent errors, provide further training for site staff if necessary and to provide site support.
3. In additional to patients 2 and 4, at the time of monitoring, all patients randomised at the site will have the following procedures monitored:
    a. Consent
    b. Eligibility criteria
    c. At least 2 days of the daily review procedures for patients in the intervention arm of the study

In addition to the above, the following items will be discussed at the EMV:

- ✓ Review of website and any issues found by the site for discussion
- ✓ Review of the screening log
- ✓ Review of the study site file
- ✓ Review of the storage for study PN, inventory log
- ✓ Review of the metabolic cart testing process and FitMate procedures (sub study sites only).

Routine Monitoring Visit

An additional monitoring visit will be made to sites if:

1. More than 10 patients are randomised.
2. There are several protocol deviations at one site.
3. There are several noted data entry errors or inconsistencies in the database
4. The chief investigator and/or management committee feel that a site should have an additional monitoring visit.
5. A monitoring visit upon request from the site will be considered.

In addition to the list of data fields above, if any consistent errors are identified at EMV these errors should be monitored for the next 2 or more patients until the errors are no longer consistent.

Additional procedures (for sub study)

- A subset of patients at Auckland City Hospital (CVICU and DCCM) and The Alfred Hospital will have additional assessments (but no additional interventions will be performed).
- All other processes previously outlined will be the same.
- Additional data collection for patients in this subset will be:
  - ✓ Nitrogen balance studies.
  - ✓ Assessment of energy requirements using indirect calorimetry twice weekly during period of ICU stay and the period during hospitalization between transfer from ICU and hospital discharge. On the ward this will be performed using a desktop indirect calorimetry machine.
  - ✓ Estimated nutritional intake (by a dietitian or qualified nutrition assistant) once oral intake commences until hospital discharge.

Nitrogen Balance Procedures:

- Nitrogen Balance should be performed on day 1, 3, 7, 14 & 28 (only if in ICU).
- We are estimating Nitrogen Balance using a 6 hour extrapolation method.
- On the day of the assessment, at 0900, advise the nursing staff to empty the catheter bag and collect the urine specifically for the next 6 hours.
- Provide a container for urine collection. Return to the bedspace at 1500 to collect the container.
- Send the container to pathology for assessment of urinary urea nitrogen content.
- Once the lab has returned your result to you, enter it into the study website on the appropriate day. **Remember- if the lab hasn't extrapolated the result to a 24 hour estimation you need to do this by multiplying by 4**.
- Enter the patients total Nitrogen intake into the website for the day on which the nitrogen balance is performed.
- To calculate nitrogen intake, add up protein intake from all sources and divide by 6.25.
- For example, if the total protein intake for a day is 90, the nitrogen intake is 90/6.25 = 14.4

The assessment does not have to be performed at 0900, this is just a suggestion. Please ensure however, that for each patient, the nitrogen balance collection is conducted at the same time for each patient.

Indirect Calorimetry (sub study)

- All staff who are conducting indirect calorimetry measurements should have undergone specified training to do so.
- Please refer to the full product manuals for detailed operation instructions for both the Quark RMR and the FitMate.
- Measurements should be performed at:
  - ✓ Baseline (within 24 hours of randomisation)
  - ✓ Twice Weekly there after until hospital discharge as per the specified schedule on page 46
- Reasons why the measurements could not be collected need to be recorded on the CRF.

General IC procedure considerations:

- In ICU whilst patients are receiving mechanical ventilation, measurements are performed using the Cosmed Quark RMR Indirect Calorimeter.
- Once patients are extubated, measurements are performed using the Cosmed FitMate.
- Measurements should preferably be conducted at a similar time and by the same clinician
- The patient should be in a rested state for 30 minutes prior and during the measurement
- If the patient is particularly agitated then the measurement should not be performed, but postponed for a few hours.
- Ventilator setting and oxygen level changes should be avoided for 30 mins prior and during measurements.
- The following considerations are **contraindications to IC measurements** in ICU using the Quark RMR **(if any are present, IC measurement should not be conducted and the reason why recorded on the CRF)**
  - ✓ Air leaks in ventilation circuit, or from chest tubes (ICC)
  - ✓ $FIO_2 > 0.60$
  - ✓ ECMO
  - ✓ PEEP greater than 12 mm/H_2O
  - ✓ Significant patient agitation
  - ✓ Surgery in the previous 4 hours

- If the patient is stable and an accurate measurement can be achieved in 10 minutes then this is acceptable. For more unstable patients (for example, difficulty with ventilation, agitation) then the measurements should be continued for a maximum duration of 30 minutes capped at 28 days post enrolment to hospital.
- Please discard the first 5 minutes of the test to allow for fluctuations in measurement

Considerations for the FitMate:

- To perform a test using the FitMate patients must be able to sit and breathe through the mouthpiece for at least 10 minutes.
- If possible use a nose clip on the patients nose to prevent loss of oxygen.
- If the patient can not tolerate the nose clip but can breathe comfortably through the mouth piece please conduct the test anyway.
- Explain the test to the patient.
- Allow the patient to breathe through the mouthpiece for a few minutes to allow them to get used to it.
- Monitor the quality of the test using the fitmate parameters on the screen.
- Coach the patient to breathe differently if needed based on the parameters on the fitmate screen (aiming to keep it in the green area).

Measurement Schedule:

IC measurements should be conducted according to the following schedule after the baseline measurement day 28 or hospital discharge.

- ✓ Day 4-7
- ✓ Day 8-11
- ✓ Day 12-15
- ✓ Day 16-19
- ✓ Day 20-23
- ✓ Day 24-28

Ongoing Nutrition Assessment:

- Patients will have ongoing nutrition assessment following ICU discharge. If oral intake commences prior to ICU discharge then assessment should be commenced whilst the patient is in ICU.

Assessing oral intake:

In ICU:

- If Oral intake commences with the intent to provide nourishment in ICU, it should be assessed **daily (Monday to Friday)** until transfer to the ward.
- PART 4 of the daily paper CRF allows you to keep this information together.

On the ward:

- On the ward, oral intake should be assessed second daily, Monday to Friday.
- Oral intake is defined as food or fluid that is intended to provide nourishment.
- A pre prepared food record chart is provided to assist with this assessment.
- There is a separate paper CRF to keep this ward assessment information together.
- An estimate of the daily intake should be attempted by:
  - ✓ Visualisation of the patients tray
  - ✓ Recall with the patient and/or family
  - ✓ Use of food record charts (filled out by the patient themselves, family and/or nursing staff)
- Estimation of nutrition intake should then be performed by the dietitian using a hospital ready reckoner or food works if the ready reckoner is not sufficient.
- If you are unable to assess the patients intake please record the reason why and enter this into the data base.

Adverse Events

- Adverse events (AEs) are defined as any untoward medical occurrence in a patient or clinical investigation subject administered an investigational intervention and which does not necessarily have to have a causal relationship with this treatment (adapted from the *Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95* July 2000).

- It is recognised that the patient population will experience a number of common aberrations in laboratory values, signs and symptoms due to the severity of the underlying disease and the impact of standard therapies. These will not necessarily constitute an adverse event unless they require significant intervention or are considered to be of concern in the investigator's clinical judgement.

- Reportable Adverse Events are*:*
  - ✓ Allergic Reaction
  - ✓ Other- provide details

Serious Adverse Events

Urgent Reporting of Serious Adverse Events Related to Study Treatment: +64 9 3074949 ext 24470

Safety Reporting Instructions:

- Report SAE to ANZIC-RC within 1 working day (24 hrs) of the event becoming known to study staff by completing an online SAE Form. A confirmation email will be sent to the project manager, the site principal investigator and research coordinator/s that the submission of the SAE Form has been successful.
- SAEs will be reported from randomisation up to study day 180.
- Only serious adverse events **unexpected in the study population** or **possibly/probably/definitely related to study treatment** will be reported.
- **All deaths regardless of causality** will be reported as SAEs (from randomisation to 180 days after randomisation).

Please contact the following management committee members if you wish to discuss the event and/or reporting requirements

Name	Role	Site	Phone	Fax	Mobile	Email
Dr Shay McGuinness	Chief Investigator Site PI	Auckland City Hospital, CVICU	+64 9 3074949 ext 24470	+6493074906		ShayMc@adhb.govt.nz
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- SAEs are defined in accordance with the Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95 July 2000) as any untoward medical occurrence which may or may not have a causal relationship with the study treatment that:
  - ✓ Results in death
  - ✓ Is life-threatening
  - ✓ Requires inpatient hospitalisation or prolongation of existing hospitalisation
  - ✓ Results in persistent or significant disability/incapacity
  - ✓ Is a congenital anomaly/birth defect
  - ✓ Is an important medical event which may require intervention to prevent one of the previously listed outcomes

Protocol deviations

- A protocol deviation is ***an unanticipated or unintentional departure from the expected conduct of an approved study that is not consistent with the current research protocol or consent document***.
- A protocol deviation ***may be an omission, addition or change in any procedure described in the protocol***.
- ***The implemented deviation or change must be reported in a protocol deviation on the website by the principal investigator and reported to ANZIC-RC and HREC (if applicable).***
  - ✓ Patient randomised but not eligible
  - ✓ Study PN not given when indicated
  - ✓ Study PN run at the incorrect rate (ie. Turned off when it should have continued, run at 10kcal/kg instead of 20kcal/kg)
  - ✓ Other types:
    - Did not receive study PN on the day of randomisation
    - Dispensing dosing error
    - Unapproved procedure
    - Other: free text

FAQs from our sites

- The following is a list of FAQs from the sites in relation to the study. These have been included in the newsletters as well.

Website FAQs

Q: Can I add/invite a site user to my own site?
A: Yes- go to 'manage users', 'add a user' on the website

Q: Can other users see my password?
A: No

Q: How do I reset my password?
A: Select 'edit' and change your password in the password box

Q: What happens if I have partially entered data into the website?
A: You can not partially enter and save data. 'N/A' fields have been supplied so you can select this box for blank fields and then you can save what you have done. Please remember to go back and update the data when it becomes available if it is not truly unknown.

Study management FAQs

Q: If CRP and TG are not routinely done, when should they be completed to be called 'baseline bloods'?
A: Before the study PN is hung (if so allocated).

Q: What if a patient is on their second ICU admission- can we enrol them if eligible?
A: No, unfortunately not. We only want patients who have been in ICU for less than 72 hours on their first admission.

Q: What if a patient comes into ICU and is not intubated but gets intubated within the 48-72 hour window. Can we recruit them?
A: Yes, as long as they meet all the other criteria at the time of randomisation.

Q: What if my patient has a central line but no access for the PN?
A: At the time of randomisation the patient needs to be able to have PN if so allocated. Consider changing the line to allow more lumens or change to a longer term line if that is appropriate (ie a PICC). Also talk to pharmacy regarding consolidation of infusions.

Q: What if the patient's weight has been wrongly estimated at the beginning of the admission? A: Unfortunately it can not be changed, please estimate carefully.

Q: What if the feeds are turned off completely due to intolerance and the PN was already scheduled to be off?

A: If your patient suddenly stops tolerating EN and they are in the intervention arm please manage them as you would if there was a actual or anticipated interruption. If it gets to 2

hours and the feeds are not going back on, please commence the PN at the 20 or 24 kcal rate as per the interruption procedure. As soon as the EN is put back on with the intent to aim for target please turn the PN back off and aim to optimise the EN. At the next daily review the team will decide what needs to happen for the subsequent 24 hours.

Q: What happens with the study PN if a patient is extubated before day 7 (in the intervention group)?

A: The daily review and need for study PN should continue until Day 7 (or until the patient starts eating with the intent of providing nutrition via oral intake within the 7 day period).

Q: Does it matter how the study PN is started?

A: As this study is aiming to reduce energy deficit we would like the study PN started at target unless the treating team/dietitian feels strongly otherwise.

Appendices

1. Procedural Authorisation SOP (Victorian sites only)

SUPPLEMENTAL PN CONSENT PROCESS AND USING SECTION 42T CERTIFICATE

Patient's who meet eligibility criteria for this trial will not have the capacity to consent for themselves as they will be intubated, ventilated and sedated.

The Guardianship and Administration Act provides that where reasonable steps have been taken to contact a person responsible for a patient, but it has not been possible to identify or contact such a person, a registered medical practitioner can still carry out, or supervise the carrying out, of a medical research procedure on that patient if certain criteria are met.

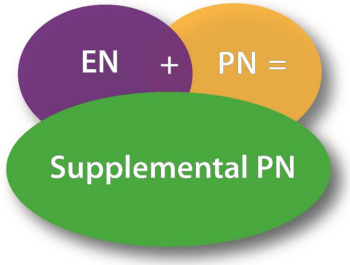
For patient's to be enrolled into Supplemental PN using Section 42T the treating practitioner must believe that enrolling the patient into the study is not contrary to the best interests, or wishes, of the patient.

STEPS FOR ENROLLING A PATIENT INTO SUPPLEMENTAL PN USING SECTION 42T:

1. **Patient meets all inclusion criteria and no exclusion criteria.**
2. **The treating physician believes it is not contrary to the best interests of the patient to be randomised to the trial.**
3. **Research co-ordinator/study investigators will discuss with the bedside nurse/treating practitioner to ascertain the appropriate patient's person responsible for consent discussions.**
4. **If a person responsible is nominated and contactable a consent discussion will take place with the person responsible in person.**
5. **If they are not likely to be visiting the patient within the near future a telephone consent will be attempted.**
6. **If there is no person responsible for the patient or the person responsible is not contactable the patient may be enrolled as per the Guardianship and Administration Act 1986 under Section 42T procedural authorisation.**
7. **A registered practitioner who is supervising the procedure will complete the Section 42T certificate. This includes completing the cover page with details of the Hospital HREC to where the certificate will be faxed. They also must complete questions 1 to 5 and complete their details and sign section 6.**
8. **The research coordinator will then complete section 6 as the person submitting the certificate and fax the certificate to the Office of the Public Advocate and to the site HREC within 48 hours.**

9. **Details of enrolment using Section 42T will be documented in the patient's medical history by the research coordinator or study investigator. The documentation should include:**
   - **The project HREC number.**
   - **That the procedure is not contrary to the best interests of the patient.**
   - **That the patient is unlikely to regain capacity within a reasonable time.**
   - **The patient's person responsible has not been able to be located and or contacted.**
   - **That the patient has been enrolled into the study under Section 42T as per the Guardianship and Administration Act.**
10. **A copy of the certificate will be placed in the patient's medical history.**
11. **The research coordinator will keep the original in the patients file in a secure cabinet in their office.**
12. **The research coordinator, study investigator and practitioner are required to continue to take reasonable steps to try to ascertain whether there is a person responsible while the study is taking place. This will be done by asking the treating team on a daily basis if a person responsible has been identified or contacted.**
13. **The research coordinator or study investigator will document in the patient's history their ongoing attempt to locate the person responsible.**
14. **If after 1 month the patient has not regained capacity to consent to continue and a person responsible has not been located the study investigator must re send another Section 42T certificate to the Public Advocate and the Ethics Committee.**
15. **If contact is made with a person responsible before the patient regains capacity to consent the person responsible will be asked to provide consent for the patient to continue in the study.**
16. **When and if the patient regains capacity to provide consent for themselves they will be asked to provide consent to continue following procedural authorisation and/or person responsible consent (whichever has been the last form of consent).**
17. **Participants in this study are from a critically ill cohort and there may be occasions when the participant dies before consent for continuing participation can be obtained from the person responsible. In this instance a letter will be sent to the person responsible giving them the option to receive further details about the study or to refuse for the patient's data and samples to be kept for the study. It will be documented in the patient's history when the letter was sent, or a Note To File if the history is not available.**
18. **If the patient is deceased before consent can be obtained and no person responsible is located this will be documented in the patient's medical history by the research coordinator.**

2. Demiarm span conversion table



Estimating height using demispan

Table 7 Estimating height using demispan

Height (m)	Men (16-54 years)	1.97	1.95	1.94	1.93	1.92	1.90	1.89	1.88	1.86	1.85	1.84	1.82	1.81	1.80	1.78	1.77	1.76
	Men ≥55 years)	1.90	1.89	1.87	1.86	1.85	1.84	1.83	1.81	1.80	1.79	1.78	1.77	1.75	1.74	1.73	1.72	1.71
	Demispan (cm)	99	98	97	96	95	94	93	92	91	90	89	88	87	86	85	84	83
Height (m)	Women (16-54 years)	1.91	1.89	1.88	1.87	1.85	1.84	1.83	1.82	1.80	1.79	1.78	1.76	1.75	1.74	1.72	1.71	1.70
	Women (≥55 years)	1.86	1.85	1.83	1.82	1.81	1.80	1.79	1.77	1.76	1.75	1.74	1.73	1.71	1.70	1.69	1.68	1.67
Height (m)	Men (16-54 years)	1.75	1.73	1.72	1.71	1.69	1.68	1.67	1.65	1.64	1.63	1.62	1.60	1.59	1.58	1.56	1.55	1.54
	Men (≥55 years)	1.69	1.68	1.67	1.66	1.65	1.64	1.62	1.61	1.60	1.59	1.57	1.56	1.55	1.54	1.53	1.51	1.50
	Demispan (cm)	82	81	80	79	78	77	76	75	74	73	72	71	70	69	68	67	66
Height (m)	Women (16-54 years)	1.69	1.67	1.66	1.65	1.63	1.62	1.61	1.59	1.58	1.57	1.56	1.54	1.53	1.52	1.50	1.49	1.48
	Women (≥55 years)	1.65	1.64	1.63	1.62	1.61	1.59	1.58	1.57	1.56	1.55	1.54	1.52	1.51	1.50	1.49	1.47	1.46

Taken from: The 'MUST' Explanatory Booklet: A Guide to the 'Malnutrition Universal Screening Tool' ('MUST') for Adults. BAPEN. 2011

3. Energy requirements table

Supplemental PN: Energy requirement table

Always use the patients CBW from the study website when calculating the requirement

Patients calculated body weight	Daily requirement at 25 kcal/kg	Daily requirement at 30 kcal/kg	Patients calculated body weight	Daily requirement at 25 kcal/kg	Daily requirement at 30 kcal/kg	Patients calculated body weight	Daily requirement at 25 kcal/kg	Daily requirement at 30 kcal/kg
40	1000	1200	68	1700	2040	96	2400	2880
41	1025	1230	69	1725	2070	97	2425	2910
42	1050	1260	70	1750	2100	98	2450	2940
43	1075	1290	71	1775	2130	99	2475	2970
44	1100	1320	72	1800	2160	100	2500	3000
45	1125	1350	73	1825	2190	101	2525	3030
46	1150	1380	74	1850	2220	102	2550	3060
47	1175	1410	75	1875	2250	103	2575	3090
48	1200	1440	76	1900	2280	104	2600	3120
49	1225	1470	77	1925	2310	105	2625	3150
50	1250	1500	78	1950	2340	106	2650	3180
51	1275	1530	79	1975	2370	107	2675	3210
52	1300	1560	80	2000	2400	108	2700	3240
53	1325	1590	81	2025	2430	109	2725	3270
54	1350	1620	82	2050	2460	110	2750	3300
55	1375	1650	83	2075	2490	111	2775	3330
56	1400	1680	84	2100	2520	112	2800	3360
57	1425	1710	85	2125	2550	113	2825	3390
58	1450	1740	86	2150	2580	114	2850	3420
59	1475	1770	87	2175	2610	115	2875	3450
60	1500	1800	88	2200	2640	116	2900	3480
61	1525	1830	89	2225	2670	117	2925	3500
62	1550	1860	90	2250	2700	118	2950	3500
63	1575	1890	91	2275	2730	119	2975	3500
64	1600	1920	92	2300	2760	120	3000	3500
65	1625	1950	93	2325	2790	121	3025	3500
66	1650	1980	94	2350	2820	122	3050	3500
67	1675	2010	95	2375	2850	123	3075	3500

4. Nutrition composition table

Nutrition Composition Table for Enteral Formula

Non Nutrition energy sources				
Name	**Calories/ml**	**Energy (kilojoules)**	**Energy (calories)**	**Protein (g/L)**
Propofol (per ml)	1.1	4.6	1.1	0
25% Dextrose (per L)	1	4175	1003	0
50% Dextrose (per L)	1	8350	2007	0
Abbott International				
Name	**Calories/ml**	**Energy/L (kilojoules)**	**Energy/L (calories)**	**Protein (g/L)**
Ensure	1.1	4480	1060	37
Ensure Plus HN	1.5	6310	1500	62
Glucerna SR	1	4200	1000	42
Glucerna Select	1	4200	1000	50
Jevity	1	4420	1051	40
Jevity HiCal	1.5	6404	1522	64
Jevity Plus	1.2	5057	1202	55
Nepro	1.8	7536	1800	81
Osmolite	1.1	4223	1060	40
Perative	1.3	5439	1300	67
Promote	1	4184	1000	63
Promote with Fibre	1	4184	1000	63
Pulmocare	1.5	6276	1500	63
Suplena	2	8390	2000	30
Two Cal HN	2	8368	2000	84
Vital HN	1	4180	1000	42
Supplement: Prosure powder (per 100g powder)	4 kcal/1g	1699	402	21
Nestle				
Fibresource HN	1.2	4990	1200	53
Impact 1.5	1.5	6000	1435	76
Isosource HN	1.2	4990	1200	53
Isosource 1.5Cal	1.5	6270	1500	68
Resource 2.0	2	8360	2000	83
Novosource 2.0 with Fibre	2	8400	2000	90
Nutren Pulmonary	1.5	6270	1500	68
Peptamen	1.2	5020	1200	40
Beneprotien (per 7g scoop)	3.5 kcal/1g	105	25	6
Nutricia				
Cubison	1	4200	1000	55
Diason	1	4200	1000	43
Nutrison 1 Cal	1	4200	1000	40
Nutrison Multifibre	1	4200	1000	40
Nutrison Protein Plus MF	1.25	5250	1250	63
Nutrison Protein Plus	1.25	5250	1250	63
Nutrison Energy Multi Fibre	1.5	6300	1500	60
Nutrison Energy	1.5	6300	1500	60
Nutrison Low Sodium	1	4200	1000	40
Nutrison Concentrated	2	8400	2000	75

5. Study PN Rate Table- NOT on Renal Replacement Therapy OR ECMO

Supplemental PN: Study PN Rate Table (for patients <u>not on renal replacement therapy</u>)

Always use the patients CBW from the study website when choosing the rate

Patients calculated body weight	Rate for 10kcal/kg	Rate for 20kcal/kg	Patients calculated body weight	Rate for 10kcal/kg	Rate for 20kcal/kg	Patients calculated body weight	Rate for 10kcal/kg	Rate for 20kcal/kg
40	15	30	68	25	55	96	35	75
41	15	30	69	25	55	97	40	75
42	15	35	70	25	55	98	40	75
43	15	35	71	30	55	99	40	75
44	15	35	72	30	55	100	40	80
45	20	35	73	30	55	101	40	80
46	20	35	74	30	60	102	40	80
47	20	35	75	30	60	103	40	80
48	20	35	76	30	60	104	40	80
49	20	40	77	30	60	105	40	80
50	20	40	78	30	60	106	40	85
51	20	40	79	30	60	107	40	85
52	20	40	80	30	60	108	40	85
53	20	40	81	30	65	109	40	85
54	20	40	82	30	65	110	45	85
55	20	45	83	30	65	111	45	85
56	20	45	84	35	65	112	45	85
57	20	45	85	35	65	113	45	90
58	25	45	86	35	65	114	45	90
59	25	45	87	35	70	115	45	90
60	25	45	88	35	70	116	45	90
61	25	50	89	35	70	117	45	90
62	25	50	90	35	70	118	45	90
63	25	50	91	35	70	119	45	95
64	25	50	92	35	70	120	45	95
65	25	50	93	35	70	121	45	95
66	25	50	94	35	75	122	50	95
67	25	50	95	35	75	123	50	95

6. Study PN Rate Table- on Renal Replacement Therapy AND/OR ECMO

Supplemental PN: Study PN Rate Table (for patients <u>on renal replacement therapy</u>)

For patients receiving renal replacement therapy rates are adjusted by 20%

Always use the patients CBW from the study website when choosing the rate

Patients calculated body weight	Rate for 12 kcal/kg	Rate for 24 kcal/kg	Patients calculated body weight	Rate for 12 kcal/kg	Rate for 24 kcal/kg	Patients calculated body weight	Rate for 12 kcal/kg	Rate for 24 kcal/kg
40	20	35	68	30	65	96	45	90
41	20	40	69	30	65	97	45	90
42	20	40	70	35	65	98	45	90
43	20	40	71	35	65	99	45	95
44	20	40	72	35	65	100	45	95
45	20	45	73	35	70	101	45	95
46	20	45	74	35	70	102	50	95
47	20	45	75	35	70	103	50	95
48	20	50	76	35	70	104	50	95
49	25	50	77	35	70	105	50	100
50	25	50	78	35	75	106	50	100
51	25	50	79	35	75	107	50	100
52	25	50	80	35	75	108	50	100
53	25	50	81	40	75	109	50	100
54	25	50	82	40	75	110	50	105
55	25	50	83	40	80	111	50	105
56	25	50	84	40	80	112	50	105
57	25	55	85	40	80	113	55	105
58	25	55	86	40	80	114	55	105
59	30	55	87	40	80	115	55	105
60	30	55	88	40	80	116	55	110
61	30	55	89	40	85	117	55	110
62	30	60	90	40	85	118	55	110
63	30	60	91	45	85	119	55	110
64	30	60	92	45	85	120	55	110
65	30	60	93	45	85	121	55	115
66	30	60	94	45	90	122	55	115
67	30	65	95	45	90	123	55	115

7. Composition of study PN- Olimel

Supplemental PN: Composition of study PN and additives

Study PN alone (no additives):

For OLIMEL N9-840E

	1000 mL	1500 mL	2000 mL
Nitrogen	9.0 g	13.5 g	18.0 g
Amino acids	56.9 g	85.4 g	113.9 g
Glucose	121.0 g	181.5 g	242.0 g
Lipids	40 g	60 g	80 g
Energy:			
Total calories	1070 kcal	1600 kcal	2140 kcal
Non-protein calories	840 kcal	1260 kcal	1680 kcal
Glucose calories	440 kcal	660 kcal	880 kcal
Lipid calories (1)	400 kcal	600 kcal	800 kcal
Non-protein calories / nitrogen ratio	93 kcal/g	93 kcal/g	93 kcal/g
Glucose / lipid calories ratio	52 / 48	52 / 48	52 / 48
Lipid / total calories	37 %	37 %	37 %
Electrolytes:			
Sodium	35.0 mmol	52.5 mmol	70.0 mmol
Potassium	30.0 mmol	45.0 mmol	60.0 mmol
Magnesium	4.0 mmol	6.0 mmol	8.0 mmol
Calcium	3.5 mmol	5.3 mmol	7.0 mmol
Phosphate (2)	15.0 mmol	22.5 mmol	30.0 mmol
Acetate	54 mmol	80 mmol	107 mmol
Chloride	45 mmol	68 mmol	90 mmol
pH	6.4	6.4	6.4
Osmolarity	1310 mOsm/L	1310 mOsm/L	1310 mOsm/L

(1) Include calories from egg lecithin (purified egg phosphatide)

(2) Includes phosphate from lipid emulsion (egg phospholipids)

Baxter Trace Element Solution (MTEFE):

Please note, information is per ml, 10ml is provided per bag of PN

Baxter Trace Element Solutions

PER mL	Zn	Cu	Mn	Cr	Se	I	Mo	Iron
Starting Material as (salt of)	Chloride	Sulfate	Sulfate	Chloride	Dioxide	Sodium	Sodium	Gluconate
Baxter MTEFE (*mcg*)	650	130	27	1	3.2	13	1.9	120
(micromol)	10	2	0.5	0.02	0.04	0.1	0.02	2

Cernavit:

Cernevit

Name of the medicine:

CERNEVIT

CERNEVIT is a multivitamin preparation, lyophilised, sterile powder, for reconstitution in 5 mL of Water for Injection or other compatible parenteral fluids.

Composition:

Content of lyophilisate in each vial:

Active Ingredients:		**Corresponding to:**	
Retinol (present as retinyl palmitate)	3500 IU	Vitamin A	3500 IU
Cholecalciferol	5.5 µg	Vitamin D_3	5.5 µg
dl-α-tocopherol	10.20 mg	Alpha tocopherol (Vitamin E)	11.20 IU
Ascorbic acid	125 mg	Vitamin C	125 mg
Cocarboxylase tetrahydrate	5.80 mg	Thiamine (Vitamin B_1)	3.51 mg
Riboflavine sodium phosphate	5.67 mg	Riboflavine (Vitamin B_2)	4.14 mg
Pyridoxine hydrochloride	5.50 mg	Pyridoxine (Vitamin B_6)	4.53 mg
Cyanocobalamin	6 µg	Vitamin B_{12}	6 µg
Folic acid	414 µg	Folic acid	414 µg
Dexpanthenol	16.15 mg	Dexpanthenoic acid	17.25 mg
d-Biotin	69 µg	Biotin	69 µg
Nicotinamide	46.0 mg	Niacin (Vitamin PP)	46 mg

8. Temperature Log

Temperature Log

Site: Site Number:

Olimel/Triomel N9 840E
Store at 2 – 8º Celsius

Instructions:

- For the purposes of the study please use the site's current temperature monitoring chart if it complies with the requirements of the study.
- If not, complete this form daily including maximum and minimum temperature.
- Notify the Project Manager on +61 3 9903 0350 of any temperature excursions.

Date	Minimum Temperature	Maximum Temperature	Signature

9. Product Inventory Log

Supplemental Parenteral Nutrition: A Pilot Randomised Controlled Trial

Inventory Log

Site: Site Number:

Olimel/Triomel N9 840E

Date	Patient Study Number	Patient Initial	Quantity (syringe)		Balance (syringe)	Signature	Comments
			Received	Dispensed			
13 Oct 2009	_	_	2	_	3	Mak	
14 Oct 2009	001	AYM	_	1	2	Mak	

10. 6MWT Script

Supplemental PN: 6MWT Script

- Set the timer to 6 minutes. Assemble all necessary equipment (timer, clipboard, worksheet) and move to the starting point.
- Give the following instructions to the patient (as a general guideline and can be modified to meet your patient's needs):
- "The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able. You will be walking back and forth around the cones (or marked area). You should pivot briskly around the cones (or marked area) and continue back the other way without hesitation.
- Now I'm going to show you. Please watch the way I turn without hesitation." Demonstrate by walking one lap yourself. Walk and pivot around a cone (or marked area) briskly.
- "Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog. Start now, or whenever you are ready."
- Position the patient at the starting line. You should also stand near the starting line during the test. Do not walk with the patient. As soon as the patient starts to walk, start the timer.
- Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the patient. Do not get distracted and lose count of the laps. Each time the participant returns to the starting line, mark the lap on the worksheet. Let the participant see you do it. Exaggerate the click using body language, like using a stopwatch at a race.
- After the first minute, tell the patient the following (in even tones): "You are doing well. You have 5 minutes to go." When the timer shows 4 minutes remaining, tell the patient the following: "Keep up the good work. You have 4 minutes to go." When the timer shows 3 minutes remaining, tell the patient the following: "You are doing well. You are halfway done." When the timer shows 2 minutes remaining, tell the patient the following: "Keep up the good work. You have only 2 minutes left."
- When the timer shows only 1 minute remaining, tell the patient:
"You are doing well. You have only 1 minute to go."

- Do not use other words of encouragement (or body language to speed up). If the patient stops walking during the test and needs a rest, say this:
  “You can lean against the wall if you would like; then continue walking whenever you feel able.”

- Do not stop the timer. If the patient stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), wheel the chair over for the patient to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping prematurely.

- When the timer is 15 seconds from completion, say this:
  “In a moment I’m going to tell you to stop. When I do, just stop right where you are and I will come to you.” When the timer rings (or buzzes), say this: “Stop!”

- Walk over to the patient. Consider taking the chair if they look exhausted. Mark the spot where they stopped by placing a bean bag or a piece of tape on the floor.

- Record the total distance walked, rounding to the nearest meter, and record it on the study tool provided.

- Congratulate the patient on good effort and offer a drink of water.

11. EQ-5D example

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility
- I have no problems in walking about ❑
- I have some problems in walking about ❑
- I am confined to bed ❑

Self-Care
- I have no problems with self-care ❑
- I have some problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*
- I have no problems with performing my usual activities ❑
- I have some problems with performing my usual activities ❑
- I am unable to perform my usual activities ❑

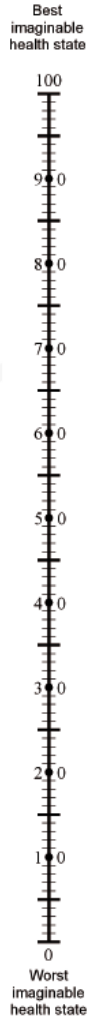
Pain/Discomfort
- I have no pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have extreme pain or discomfort ❑

Anxiety/Depression
- I am not anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked **100** and the worst state you can imagine is marked **0**.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



12. Instructions for raising an invoice for Monash

Monash University, ANZIC-RC Invoice details

For Monash University to make site payment, an original invoice must be received in order to authorise payment.

This invoice must include the following:

- Letterhead incorporating an ABN number
- Invoice number
- Invoice date
- Study name
- Text description of payment details .i.e. patient payments for 3 patients (001,002,003)
- Amount of payment plus GST
- Name of account for payment
- EFT/bank details for payment
- Mark the invoice attention to the specific project manager
- Address:

ANZIC-RC, DEPM, Monash University
Alfred Hospital,
99 Commercial Road
Melbourne, Vic 3004

N.B payment can be made by cheque but this is not M.U preferred method of payment so would not prefer this is entered as option in invoice directions to site unless site specifically requested this method.

References

1. Doig GS, Heighes PT, Simpson F, Sweetman EA, Davies AR. Early enteral nutrition, provided within 24 h of injury or intensive care unit admission, significantly reduces mortality in critically ill patients: a meta-analysis of randomised controlled trials. Intensive Care Med. 2009;35(12):2018-27.
2. Casaer MP, Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt G, et al. Early versus Late Parenteral Nutrition in Critically Ill Adults. N Engl J Med. 2011.
3. Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360(13):1283-97.