

NIHR HTA Programme

04 January 2013

The NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), based at the University of Southampton, manages evaluation research programmes and activities for the NIHR



calories

CALORIES: A phase III, open, multicentre, randomised controlled trial comparing the clinical and cost-effectiveness of early nutritional support in critically ill patients via the parenteral versus the enteral route

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04 October 2012

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04 October 2012

Please note: This protocol should not be applied to patients treated off trial. The trial will be monitored for adverse events and the ICNARC CTU can only ensure that active trial investigators are updated of any amendments to the protocol.

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2.2	31/08/2012	3.0		<ul style="list-style-type: none"> Administrative changes Updates for clarification

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Abbreviations

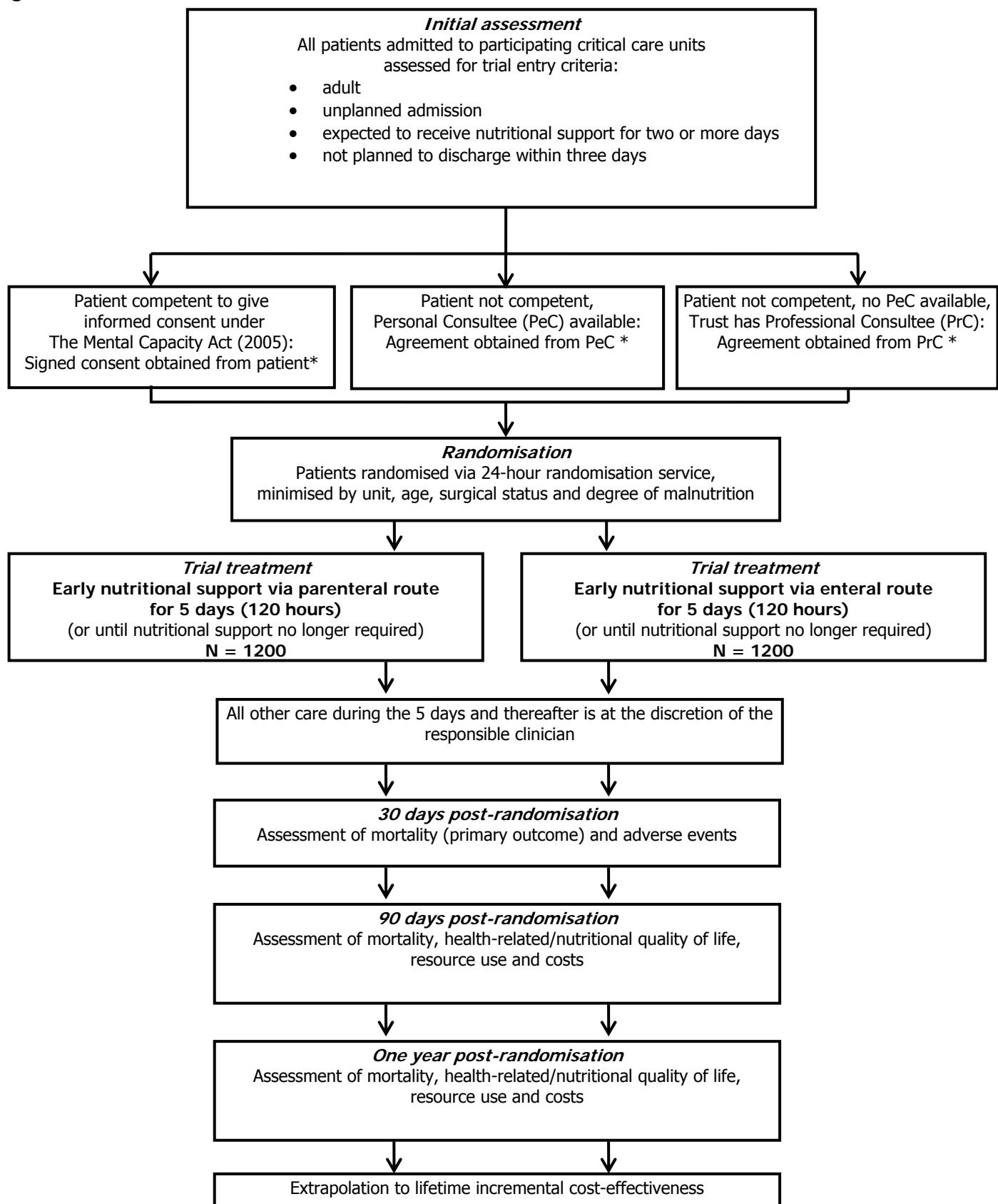
AE	Adverse Event
APACHE	Acute Physiology And Chronic Health Evaluation
BMI	Body Mass Index
CEA	Cost Effectiveness Analysis
CCMDS	Critical Care Minimum Dataset
CONSORT	Consolidated Standards of Reporting Trials
CMP	Case Mix Programme
CMPD	Case Mix Programme Database
CRF	Case Report Form
CTU	Clinical Trials Unit
DMEC	Data Monitoring and Ethics Committee
EN	Nutritional support via the enteral route
GP	General Practitioner
GCP	Good Clinical Practice
HTA	Health Technology Assessment
HRG	Healthcare Resource Group
ICNARC	Intensive Care National Audit & Research Centre
ICH	International Conference on Harmonisation
ISRCTN	International Standard Randomised Clinical Trial Number
ICU	Intensive Care Unit
ISF	Investigator Site File
MRC	Medical Research Council
NICE	National Institute of Clinical Excellence
NHS	National Health Service
NIHR	National Institute for Health Research
NPSA	National Patient Safety Agency
PI	Principal Investigator
PINNT	Patients on Intravenous and Nasogastric Nutrition Therapy
PN	Nutritional support via the parenteral route
PeC	Personal Consultee
PrC	Professional Consultee
QALY	Quality Adjusted Life Years
RCT	Randomised Controlled Trial
R&D	Research & Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SD	Standard Deviation
SOFA	Sequential Organ Failure Assessment
SOP	Standard Operating Procedure
SWFL	Satisfaction with Food-related Life measure
TMG	Trial Management Group
TSC	Trial Steering Committee

1.0 Protocol summary

Summary of Trial Design

Title:	A phase III, open, multicentre, randomised controlled trial comparing the clinical and cost-effectiveness of early nutritional support in critically ill patients via the parenteral versus the enteral route
Short Title/acronym:	CALORIES
Sponsor name & reference:	ICNARC & ICNARC01/02/2010
Funder name & reference:	NIHR HTA Programme & 07/52/03
ISRCTN no:	ISRCTN17386141
NIHR CRN Portfolio no:	10098
CSP reference no:	22078
Design:	Phase III, open, multicentre, randomised controlled trial
Overall aim:	To compare early nutritional support in critically ill patients via the parenteral versus the enteral route
Primary objectives:	<ul style="list-style-type: none"> • To estimate the effect of early (defined as within 36 hours of the date/time of original critical care unit admission) nutritional support via the parenteral route (PN) compared with the enteral route (EN) on mortality at 30 days; • To estimate the incremental cost-effectiveness of early PN compared with early EN at one year.
Secondary objectives:	<p>To compare PN with EN for:</p> <ul style="list-style-type: none"> • duration of specific and overall organ support in the critical care unit; • infectious and non-infectious complications in the critical care unit; • duration of critical care unit and acute hospital length of stay; • mortality at discharge from the critical care unit and from hospital; • mortality at 90 days and at one year; • nutritional and health-related quality of life at 90 days and at one year; • resource use and costs at 90 days and at one year; • estimated lifetime incremental cost-effectiveness.
Target accrual:	2400 patients
Inclusion criteria:	<p>Patients who either on, or soon after admission (but within a timeframe to consent/obtain agreement, randomise and start nutritional support within 36 hours of the date/time of original admission to a critical care unit) are:</p> <ul style="list-style-type: none"> • adult (defined as age 18 years or over); • an unplanned admission (including planned admissions becoming unplanned e.g. unexpected post-operative complications); • expected to receive nutritional support for two or more days in your unit; • not planned to be discharged within three days (defined by clinical judgment) from your unit.
Exclusion criteria	<ul style="list-style-type: none"> • patients who have been in a critical care unit for more than 36 hours (i.e. from the date/time of original admission to a critical care unit); • patients previously randomised into CALORIES; • patients with pre-existing contraindications to PN or EN; • patients who have received PN or EN within the last seven days; • patients admitted with a percutaneous endoscopic gastrostomy, percutaneous endoscopic jejunostomy, needle/surgical jejunostomy or nasojejunal tube in situ; • patients admitted to the critical care unit for treatment of thermal injury (burns); • patients admitted to the critical care unit for palliative care; • patients whose expected stay in the UK is less than six months; • women who are pregnant.
Planned number of sites:	Minimum 20
Anticipated duration of recruitment:	24 months
Duration of patient follow up:	90 days and one year post-randomisation
Definition of end of trial:	End of trial is defined as, last patient, last follow-up

Figure 1 Trial Schema



*Eligible patients for whom informed consent/agreement is not obtained will be recorded in the Screening Log (see: Section 6.0)

2.0 Background

Malnutrition remains a common problem in critically ill patients in NHS critical care units. The consequences of malnutrition include vulnerability to complications, such as infection. Early nutritional support is therefore recommended for critically ill patients¹ to address both deficiencies in nutritional state and related disorders in metabolism.

However, evidence is conflicting regarding the optimum route (parenteral or enteral) of delivery. Three meta-analyses of trials comparing parenteral with enteral nutritional support in critically ill patients have been published²⁻⁴ and are summarised below. Interpretation of their results is complicated by: the small sample sizes of the trials included; significant problems with the quality of the trials (only one fitting the criteria for a level I study, i.e. concealed randomisation, blinded outcome adjudication and analysis on intention-to-treat); and the patient populations in whom the trials were conducted.

In 2003, Heyland et al³ reported no difference in mortality between patients given parenteral and enteral nutritional support, but enteral was associated with a significant reduction in infections. Safety, cost and feasibility led them to recommend enteral over parenteral in the critically ill adult patient. In 2004, Gramlich et al² also found no difference in mortality but a significant reduction in infections with enteral nutrition. In addition, they reported no difference in length of unit stay or days on ventilation but indicated that there were insufficient data to analyse these statistically. Using a different methodological approach to assessing quality of included studies (one less biased toward including the poorer quality studies), Simpson and Doig, in 2005⁴, found a significant reduction in mortality but a significant increase in infections with parenteral nutritional support compared with the enteral nutritional support. However, the significant mortality benefit with parenteral nutrition appeared to exist when compared to the provision of delayed, rather than early enteral nutritional support and thus this was not a like-for-like comparison. Similar time-based analyses for infections were not possible due to insufficient data.

We have updated the most recent systematic review by Simpson and Doig⁴. Highly sensitive search criteria identified a further 570 potentially relevant studies since May 2003. Following detailed review of these studies, two additional randomised controlled trials (RCT) comparing the parenteral and enteral nutrition were identified^{5, 6}. The results of the updated meta-analysis indicate a non-significant survival benefit for parenteral nutritional support (relative risk 0.82, 95% confidence interval 0.60 to 1.11) but an increased risk of infection (relative risk 1.77, 95% confidence interval 1.19 to 2.63) compared with enteral nutrition. Consequently, parenteral nutritional support in the critical care unit remains controversial and no clear evidence exists as to the optimum method of delivery of nutritional support to critically ill patients.

All the meta-analyses highlighted the problems of combining data from poor quality studies conducted on heterogeneous patient populations (all were on select sub-groups, such as head trauma, acute pancreatitis etc.) plus variation in the timing of measurement of mortality and, perhaps more importantly, the nature and definitions for infections included and pooled (pneumonia, urinary tract, bacteraemia, wound, line sepsis etc.). Due to incomplete reporting, it was not possible to classify and combine infections based on risk of outcome (e.g. severe infection, moderate infection, sub-clinical infection).

A cluster-RCT of the introduction of algorithms for parenteral nutritional support in seven of fourteen intensive care units (ICUs) in Canada found that early enteral and/or parenteral nutritional support, was associated with significantly shorter mean hospital stay (no difference in ICU stay) and indicated a trend towards reduced mortality⁷. A subsequent cluster-RCT found no difference between active (multi-faceted educational interventions including web-based tools) or passive (posting) dissemination of algorithms/protocols/guidelines⁸. These results indicate that

implementation of evidence-based recommendations might improve the provision of nutritional support.

Currently, the enteral route is the mainstay of nutritional support in critical care but it is frequently associated with gastrointestinal intolerance and underfeeding. In contrast, the parenteral route though more invasive and expensive is more likely to secure delivery of the intended nutrition. Historically, nutritional support via the parenteral route has been associated with more risks and complications (e.g. infectious complications) compared with the enteral route but recent improvements in the delivery, formulation and monitoring of parenteral nutrition justify further comparison and evaluation of these routes of nutritional support, particularly in the early phase of the illness. In view of this, in late 2007, the National Institute of Health Research (NIHR) Health Technology Assessment (HTA) Programme put out a call for a large pragmatic RCT to be conducted in critically ill patients to determine the optimal route of delivery of nutrition (see: Appendix 1). CALORIES is a NIHR HTA Programme commissioned trial which is comparing the effect of early nutritional support in critically ill patients via the parenteral versus the enteral route.

3.0 Trial objectives

3.1 Primary objectives:

- To estimate the effect of early (defined as within 36 hours of the date/time of original critical care unit admission) nutritional support via the parenteral route (PN) compared with the enteral route (EN) on mortality at 30 days;
- To estimate the incremental cost-effectiveness of early PN compared with EN at one year.

3.2 Secondary objectives:

To compare PN with EN for:

- duration of specific and overall organ support in the critical care unit;
- infectious and non-infectious complications in the critical care unit;
- duration of critical care unit and acute hospital length of stay;
- mortality at discharge from the critical care unit and from hospital;
- mortality at 90 days and at one year;
- nutritional and health-related quality of life at 90 days and at one year;
- resource use and costs at 90 days and at one year;
- estimated lifetime incremental cost-effectiveness.

4.0 Trial design

CALORIES is a pragmatic, open, multicentre, randomised controlled trial in critically ill adult patients.

Eligible patients who have provided informed consent, or where agreement has been obtained from a Consultee (see: Section 6.0), will be randomly allocated to receive either PN or EN. There will be equal numbers of patients in each arm and patients will receive nutritional support for five days (i.e. 120 hours) unless the patient transitions to exclusive oral feeding, or is discharged from the critical care unit. Patients may start oral feeding if clinically indicated during the five days. All other care is the responsibility of the treating clinician.

Patients will be followed up at 30 days post-randomisation for assessment of mortality (primary outcome) and adverse events, and at 90 days and one year post-randomisation for assessment of

mortality, health-related and nutritional quality of life, resource use and costs. Follow-up ends one year post-randomisation. Patient flow through the trial is summarised in Figure 1.

5.0 Selection of participants

5.1 Unit inclusion criteria

Patients will be recruited from NHS university and non-university, adult, general critical care units in England and Wales.

Units must fulfil the following inclusion criteria:

- Timely submission and validation of data to the Case Mix Programme (CMP), the national, comparative clinical audit of patient outcomes from critical care, now ongoing in over 190 (90%) adult, general critical care units in England, Wales and Northern Ireland ⁹;
- Pre-existing, established protocols for EN and PN reflecting mainstream practice (reviewed and approved by CALORIES Trial Management Group);
- Pre-existing implementation of bundles as promoted by the NHS (NHS Saving Lives: reducing infection, delivering clean and safe care - High Impact Intervention Number 1: Central venous catheter and Number 5: Ventilator) to prevent the development of bloodstream infection and ventilator-associated pneumonia;
- Agreement to incorporate CALORIES into routine unit practice, including prior agreement from all consultants in the unit to adhere to the patient's random allocation for nutritional support (PN or EN);
- Agreement to recruit all eligible patients to CALORIES and to maintain a Screening Log of eligible patients who are not randomised, and patients who fulfil the inclusion criteria but meet one or more of the exclusion criteria (see: 5.3), irrespective of whether informed patient consent/consultee agreement is obtained, to establish an unbiased case selection and for full reporting according to the Consolidated Standards of Reporting Trials (CONSORT) statement ¹⁰;
- Sign up from the unit Clinical Director, Senior Nurse Manager, Dietician/Clinical Nutritionist and Pharmacist;
- Identification of a dedicated CALORIES Research Nurse.

A Principal Investigator (PI), who will be responsible for the conduct of the trial locally, will be identified at each participating unit.

5.2 Patient inclusion criteria

Patients who either on, or soon after admission (but within a timeframe to obtain patient consent/consultee agreement, randomise and start nutritional support within 36 hours of the date/time of original critical care unit admission) are:

- adult (defined as age 18 years or over);
- an unplanned admission (including planned admissions becoming unplanned e.g. unexpected post-operative complications);
- expected to receive nutritional support for two or more days in your unit;
- not planned to be discharged within three days (defined by clinical judgment) from your unit.

5.3 Patient exclusion criteria

- patients who have been in a critical care unit for more than 36 hours (i.e. from the date/time of original critical care unit admission);
- patients previously randomised into CALORIES;
- patients with pre-existing contraindications to PN or EN;
- patients who have received parenteral or enteral nutrition within the last seven days;
- patients admitted with a percutaneous endoscopic gastrostomy, percutaneous endoscopic jejunostomy, needle/surgical jejunostomy or nasojejunal tube in situ;
- patients admitted to the critical care unit for treatment of thermal injury (burns);
- patients admitted to the critical care unit for palliative care;
- patients whose expected stay in the UK is less than six months;
- women who are pregnant.

N.B. If during screening, a patient is found to be participating in another interventional study/trial, then please contact the ICNARC CTU on 020 7269 9290 to discuss their participation in CALORIES.

5.4 Pre-randomisation care of potentially eligible patients

Prior to randomisation, if potentially eligible patients are to receive a glucose infusion, this should be administered to a maximum of 800 calories over 24 hours, unless the patient has a life threatening hypoglycaemia.

Glycaemic control should be maintained in accordance with international guidelines. Blood glucose levels should remain below 10mmol l^{-1} and should be monitored and controlled as per local hospital policies/guidelines.

6.0 Informed consent

All patients admitted to a participating critical care unit will be screened against the inclusion/exclusion criteria prior to the patient or their consultee being approached to discuss participation in CALORIES. Patients who are eligible but not randomised and those who fulfil the inclusion criteria but meet one or more of the exclusion criteria will be recorded in the CALORIES Screening Log, irrespective of whether patient consent/consultee agreement is obtained.

6.1 Competent patients

Once eligibility has been confirmed, and if the patient is competent to give informed consent, authorised unit staff (doctors or nurses) will describe the CALORIES trial to the patient. A standard Patient Information Sheet will be provided which will identify the title of the trial, the PI and include information about: the purpose of the trial, the consequences of participating, or not (i.e. none), patient confidentiality, use of personal data, data security, the future availability of the results of the trial and funding. A Consent Form will be provided indicating that: the information given, orally and in writing, has been read and understood; participation is voluntary and can be withdrawn at any time without consequence; and that consent is given for: accessing medical records, collection and storage of personal information, information to be gathered from the NHS Central Database flagging system Data Linkage Service, the General Practitioner (GP) to be contacted, and follow-up at 90 days and at one year. Patients will be allowed time to read the Patient Information Sheet and have an opportunity to ask any questions they may have about participation in CALORIES.

After the doctor or nurse has checked that the Patient Information Sheet and Consent Form are understood, the doctor or nurse will invite the patient to sign the Consent Form and will then add their own name and countersign it. A copy will be given to the patient, a copy placed in the patient's medical notes, and a copy kept in the Investigator Site File (ISF).

6.2 Incompetent patients

Previous work on informed consent in critical care studies, conducted by the Intensive Care National Audit & Research Centre (ICNARC) alongside the PAC-Man Study (a RCT of 1014 patients in 65 ICUs), indicate that only a minority (2.5%) of patients may be able to provide informed consent¹¹.

If, as is most likely, the patient will not be competent to give informed consent, authorised unit staff will identify a Personal Consultee (PeC), who may be a relative or close friend with whom to discuss the patient's participation in the trial. Authorised staff will describe the trial to the patient's PeC and explain that they are seeking the PeC's opinion as to whether patient would wish to take part in the trial, backing up their oral information with the Patient Information Sheet. After the doctor or nurse has checked that the Patient Information Sheet and Personal/Professional Consultee Agreement Form are understood, the doctor or nurse will invite the PeC to sign the Personal/Professional Consultee Agreement Form and will then add their own name and countersign it. A copy will be given to the PeC, a copy placed in the patient's medical notes, and a copy kept in the ISF.

If there is no PeC present, agreement can be obtained via the telephone. If agreement is obtained via the telephone, the doctor or nurse will complete the Personal/Professional Consultee Telephone Agreement Form. A copy of this should be placed in the patient's medical notes and a copy kept in the ISF.

If the patient's PeC is not available, or if there is no PeC, then the patient will be provided with a Professional Consultee (PrC) – this may be an Independent Mental Capacity Advocate appointed by the NHS Hospital Trust. Agreement will be sought in the same manner as for the PeC (described above). Copies of the signed Personal/Professional Consultee Agreement Form or Consultee Telephone Agreement Form will be placed in the patient's medical notes and a copy kept in the ISF.

If a patient, or their representative (PeC or PrC), refuses to give consent/agreement for participation in CALORIES, the patient will receive usual care and treatment as determined by the responsible clinician.

If the patient subsequently becomes able to give informed consent, after agreement has been obtained from the PeC or PrC, a Retrospective Consent Form will be completed following the procedures described above. All patient consent and consultee agreement procedures adhere to the Mental Capacity Act (2005).

7.0 Randomisation procedures

A dedicated 24-hour/seven days per week telephone randomisation service will be provided by Sealed Envelope (<http://www.sealedenvelope.com/>)

Randomisation telephone number: 020 3384 7644
Emergency 24/7 telephone number: 020 7269 9290

Given that telephone randomisation services can "go down" for short periods, emergency randomisation procedures will be in place for these infrequent but important occasions. During recruitment, a rotation of clinical co-investigators will be available 24 hours/seven days per week to address any emergency recruitment and/or randomisation issues.

For PN and EN to be considered early, randomisation will occur as soon as eligibility has been confirmed and informed consent/agreement procedures have been completed, with the aim to commence PN or EN within 24 hours but no later than 36 hours after the date/time of original critical care unit admission.

Allocation to one of the two arms, PN or EN, will be by minimisation with a random component (each patient being allocated with 80% probability to the arm that would minimise imbalance). Minimisation will be based on the following factors: unit; age (<65 years or ≥65 years); surgical status (surgery within 24 hours prior to unit admission); and subjective assessment of severe malnutrition. As this is a large, multicentre trial, the risk of chance imbalance is low and so minimisation criteria have been limited to a small number of important prognostic factors.

Every patient randomised will be assigned a unique Trial Number, provided at the end of the randomisation phone call to Sealed Envelope.

8.0 Trial Treatment

It is important that the nutritional support (PN or EN) is started as soon as possible following randomisation and no later than 36 hours after the date/time of original critical care unit admission.

8.1 Nutritional support via the parenteral route (intervention)

Parenteral nutrition will be sourced from the unit's usual suppliers as per local hospital policies/procedures. For CALORIES, units should use a standard bag of parenteral nutrition which contains the major constituents within the ranges shown in Table 1 below.

Table 1 Ranges for energy and nitrogen in a standard bag of parenteral nutrition

Constituent	Per standard bag	Per ml
Energy (total kcal)	1365 – 2540	0.9 – 1.1
Nitrogen (g)	7.2 – 16.0	0.005 – 0.007

The main suppliers of parenteral nutrition all produce bags which fall within these ranges. Units are able to add additional micronutrients to the bag, if clinically indicated and as prescribed by a clinician and/or dietitian in accordance with local policies and practices. Each unit's pharmacy department and all research staff should use this product in line with the manufacturer's guidelines.

8.2 Nutritional support via the enteral route (control)

Enteral nutrition will be sourced from the unit's usual suppliers as per local hospital policies/procedures. Each unit's pharmacy or dietetic department and all research staff should use this product in line with the manufacturer's guidelines.

8.3 Delivery of nutritional support via the parenteral and enteral routes

Pragmatically, as a trial comparing PN with EN, CALORIES will not dictate the use of one PN protocol and one EN protocol, but will review all PN and EN protocols in use by participating units to ensure that they fall within common boundaries as stated below.

The protocol for PN (intervention):

- initial central venous catheter (including peripherally inserted central venous catheter) insertion and positioning should be in accordance with NHS guidelines ¹² with a dedicated lumen;
- standard feed should be obtained from the unit's usual stock/supplier, used within the licence indication and fall within the following ranges: energy 1365-2540 total kcal bag⁻¹ and nitrogen 7.2-16.0 total kcal bag⁻¹;
- units should aim to feed patients to a target of 25 kcal kg day⁻¹ within 48-72 hours, using actual body weight;
- enteral "trickle feeding" is not permitted for the five days (120 hours).

Local practice and policies should be followed for PN and should include provision for:

- ensuring that the patient receives a nutritionally complete feed;
- inclusion of additional micronutrients if clinically indicated, and as prescribed by the clinician/and or dietitian in accordance with National Institute of Clinical Excellence (NICE) guidelines. Additions must be made under appropriate pharmaceutically controlled environmental conditions before administration¹³;
- adjustment of total volume according to fluid balance requirements;
- monitoring for specific nutritional-related complications;

- regular review of patients for their ongoing nutritional support needs;
- **energy requirements for those in extreme BMI categories (e.g. <18.5 and >30kg/m²)**

The protocol for EN (control):

- initial nasogastric/nasojejunal tube insertion and positioning in accordance with National Patient Safety Agency (NPSA) guidelines;^{14,15}
- standard feed should be obtained from the unit's usual stock/supplier, used within the licence indication and fall within the following ranges: energy 1365-2540 total kcal day⁻¹ and nitrogen 7.2-16.0 total kcal day⁻¹.
- units should aim to feed patients to a target of 25 kcal kg day⁻¹ within 48-72 hours, using actual body weight.

Local practice and policies should be followed for EN and should include provision for:

- ensuring that the patient receives a nutritionally complete feed;
- adjustment of total volume according to fluid balance requirements;
- monitoring for specific nutritional-related complications;
- regular review of patients for their ongoing nutritional support needs;
- **energy requirements for those in extreme BMI categories (e.g. <18.5 and >30kg/m²)**

Both protocols will be followed for five days (120 hours), unless the patient transitions to exclusive oral feeding or is discharged from the critical care unit before this time. Patients may start oral feeding if clinically indicated during the five days.

Glycaemic control should be maintained in accordance with international guidelines. Blood glucose levels should remain below 10mmol l⁻¹ for the purposes of this trial and should be monitored and controlled as per local hospital policies/guidelines.

Patients allocated to PN who are switched to EN or patients allocated to EN who are switched to PN within five days (120 hours) of feeding will be regarded as protocol violations.

8.4 Other treatments

All other treatment and care will be at the discretion of the responsible clinician(s).

9.0 Assessments

9.1 Data collection

Data collection for CALORIES will be piggybacked onto the ICNARC CMP. Routine data from the CMP database (CMPD) v3.1 will be used to avoid duplicate data collection for CALORIES, as indicated below. Detailed guidance for the collection of the data will be provided in the trial-specific Standard Operating Procedure (SOP) provided by the ICNARC CTU. All data items will be objectively defined according to relevant national and international guidelines.

Time points for data collection

- Randomisation;
- During the first 24 hours in the critical care unit (baseline);
- Daily while in the critical care unit;
- At discharge from the critical care unit and hospital;
- 30 days post-randomisation;
- 90 days post-randomisation;
- One year post-randomisation.

9.1.1 Data collected at randomisation

Patient identification

The following identifiers are required for flagging patients with the Data Linkage Service and for follow-up at 90 days and at one year post-randomisation:

- NHS number (CMPD);
- date of birth (CMPD);
- sex (CMPD);
- full name, full address and telephone number;
- full name, full address and telephone number of family member/close friend;
- full name, full address and telephone number of GP.

Minimisation and case mix

The following data are required for minimisation, risk adjustment and stratification:

- surgical status (surgery within 24 hours prior to critical care unit admission);
- source of admission to the critical care unit (CMPD);
- severe comorbidities (CMPD);
- ventilation status;
- primary/secondary reason for admission to the critical care unit (CMPD);
- Sequential Organ Failure Assessment (SOFA) score¹⁶;
- degree of malnutrition;
- subjective recording of extent of oedema;
- weight and height.

9.1.2 Data collected during the first 24 hours in the critical care unit (baseline)

Case mix

The following data are required for risk adjustment and stratification:

- raw clinical data for the Acute Physiology And Chronic Health Evaluation (APACHE) II¹⁷ and the ICNARC risk prediction model¹⁸ (CMPD);
- Organ dysfunction.

9.1.3 Data collected daily in the critical care unit

- site of central venous catheter for PN (e.g. jugular, subclavian, femoral etc) or site of feeding tube for EN (stomach, duodenum or jejunum via nose or mouth);
- feed (type, volume and total calories delivered);
- intravenous glucose (total calories);
- additional calorific intake from drugs/other sources (including specifically daily volume of propofol);
- total insulin;
- lowest and highest blood glucose;
- liver function tests;
- infectious and non-infectious complications.

9.1.4 Data collected at discharge from the critical care unit/hospital

- date exclusive oral feeding commenced;
- date of discharge;

- infectious episodes (during critical care stay);
- survival status;
- organ monitoring and support and level of care (Critical Care Minimum Dataset - CCMDS¹⁹ (during critical care stay).

9.1.5 Data collected at 30 days post-randomisation

- survival status;
- adverse events (see: Section 11.0).

9.1.6 Data collected at 90 days post-randomisation

- survival status;
- use of health services and nutritional and health related quality of life.

9.1.7 Data collected at one year post-randomisation

- survival status;
- use of health services and nutritional and health related quality of life.

Data for CALORIES will be collected by unit research staff while the patient is in hospital using paper Case Report Forms (CRFs) and entered onto the secure, web data entry portal (see: Section 10.0).

Information on use of health services and nutritional and health-related quality of life at 90 days and at one year will be obtained using the Health Services (Appendix 2), Satisfaction With Food-related Life measure (SWFL)²⁰ and EuroQol EQ 5D²¹ questionnaires, which will be posted to patients from the ICNARC CTU.

All other assessments and interventions, including concomitant medication, will be at the discretion of the responsible clinician(s).

9.2 Follow up after hospital discharge

Following randomisation, the ICNARC CTU will write to each patient's GP to inform them of the patient's participation in CALORIES, including a brief description of the trial and a request that the GP notifies the ICNARC CTU if the patient dies.

All patients discharged from an acute hospital will be flagged with the Data Linkage Service for subsequent reporting of mortality data at 30 days, 90 days and at one year post-randomisation. Complete collection of patient identifiers (described above) by units will allow the majority (>90%) of patients to be flagged using a low cost, Band A Auto-match based on NHS number, full surname, full forename, date of birth and full post code.

Patients reported by the Data Linkage Service to be alive at 90 days and at one year post-randomisation will be contacted by letter and asked to complete the Health Services (Appendix 2), SWFL²⁰ and EuroQol EQ-5D²¹ questionnaires.

10.0 Data management guidelines

10.1 Case Report Forms (CRFs) and data entry

All patient data collected at participating sites will be entered onto paper CRFs, prior to entry onto the CALORIES secure web data entry system. The only exceptions being the patient Withdrawal of Consent Form and Death Notification Form, which should be completed on paper and sent directly to the ICNARC CTU. Data from the Health Services (Appendix 2), SWFL²⁰ and EuroQol EQ-5D²¹ questionnaires will be entered into an electronic database at the ICNARC CTU. The paper CRFs, hospital medical notes, and the health services and nutritional and health-related quality of life questionnaires will therefore be the source data in the trial. The PI will be responsible for data collection, quality and recording, however the collection of data may be delegated to a qualified member of the research team in the unit (which should be recorded in the Delegation of Trial Duties Log and authorised by the PI).

Patient data collected during the course of CALORIES will not be anonymised in order to allow patients to be traced for outcome data. This is detailed in the Patient Information Sheet and emphasised on the Consent Form and Personal/Professional Consultee Agreement Form.

During the conduct of the trial, all electronic patient data will be encrypted and all trial documents stored securely at either the participating unit or the ICNARC CTU, as appropriate. On completion of the trial, all patient data (electronic and paper) and other trial documents will be archived securely and retained for ten years at either the participating unit or the ICNARC CTU, as appropriate (see: Section 14.2).

ICNARC is registered under the Data Protection Act 1998 and all ICNARC CTU staff have undergone data protection and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) training.

10.2 Data validation

Data entered onto the CALORIES secure web data entry system will undergo validation checks at the ICNARC CTU for completeness, accuracy and consistency of data. Queries on incomplete, inaccurate or inconsistent data will be sent to the sites for resolution.

10.3 Timelines for data submission

Data entry from the paper CRFs onto the secure web data entry system must be completed by the site as soon as possible. The CRFs should be stored in a secure, accessible location at the site for quality assurance and monitoring purposes.

Sites that persistently do not enter data within timelines to facilitate follow-up of 30 days, 90 days and one year may be suspended by the ICNARC CTU from recruiting further patients into the trial.

11.0 Adverse Events

11.1 Definitions of adverse events

The following definitions have been adapted from Directive 2001/20/EC, of 4 April 2001, of the European Parliament (Clinical Trials Directive) and ICH GCP E6 guidelines:

Adverse event

Any untoward medical occurrence or effect in a patient treated on a trial protocol, which does not necessarily have a causal relationship with trial treatment. An adverse event (AE) can therefore be any unfavourable symptom or disease temporally associated with the use of the trial treatment, whether or not it is related to the trial treatment.

Serious adverse event

An AE that:

- results in death;
- is life threatening (the term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe);
- requires in-patient hospitalisation or prolongs existing hospitalisation;
- results in persistent or significant disability/incapacity;
- consists of a congenital anomaly or birth defect.

11.2 Recording and reporting procedures

All patients eligible for CALORIES are critically ill and due to the complexity of their condition are at increased risk of experiencing AEs. Many of these events are expected as a result of the patient's medical condition and standard treatment received in the critical care unit, but may not be related to participation in the trial. Consequently, any AEs, not listed in appendix 3, occurring as a result of the patient's medical condition or standard critical care treatment will not be reported. Pre-existing conditions do not qualify as AEs unless they worsen, but should be documented in the patient's medical notes.

All other AEs that occur between randomisation and 30 days post-randomisation must be recorded in the patient medical notes, on the CALORIES paper CRFs and on the CALORIES secure web data entry system. Information regarding date and time of event onset, severity and relatedness of the adverse event to trial treatment must be recorded (definitions below). Those meeting the definition of a serious adverse event (SAE) must, in addition, be reported to the ICNARC CTU, using the trial specific CALORIES SAE Reporting Form, by fax within **24 hours** of observing or learning of the SAE and recorded in the SAE Log. All sections of the CALORIES SAE Reporting Form must be completed.

The process for recording and reporting AEs and SAEs is summarised in Figure 2.

Severity

The PI, or other delegated local investigator(s) (recorded in the Delegation of Trial Duties Log), must perform an assessment of severity, for each AE, using the following criteria:

- 0 = None
- 1 = Mild
- 2 = Moderate
- 3 = Severe
- 4 = Life-threatening
- 5 = Fatal

Relatedness

The PI or other delegated local investigator(s) must perform an assessment of relatedness for each AE. This must be determined as follows:

- **None**

There is no evidence of any relationship.

- **Unlikely**

There is little evidence to suggest a relationship (e.g. because the event did not occur within a reasonable time after administration of the trial treatment). There is another reasonable explanation of the event (e.g. the patient's clinical condition, other concomitant medications).

- **Possible**

There is some evidence to suggest a relationship (e.g. because the event occurs within a reasonable time after administration of the trial procedure). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant medications).

- **Probable**

There is evidence to suggest a relationship and the influence of other factors is unlikely.

- **Definitely**

There is clear evidence to suggest a relationship and other possible contributing factors can be ruled out.

Expectedness

The PI or other delegated local investigator(s) must perform an assessment of expectedness for each SAE regardless of its relationship to the trial procedures. This assessment must be performed using the list of expected AEs in Appendix 3. This must be determined as follows:

- **Expected**

The event is listed as an expected AE in Appendix 3.

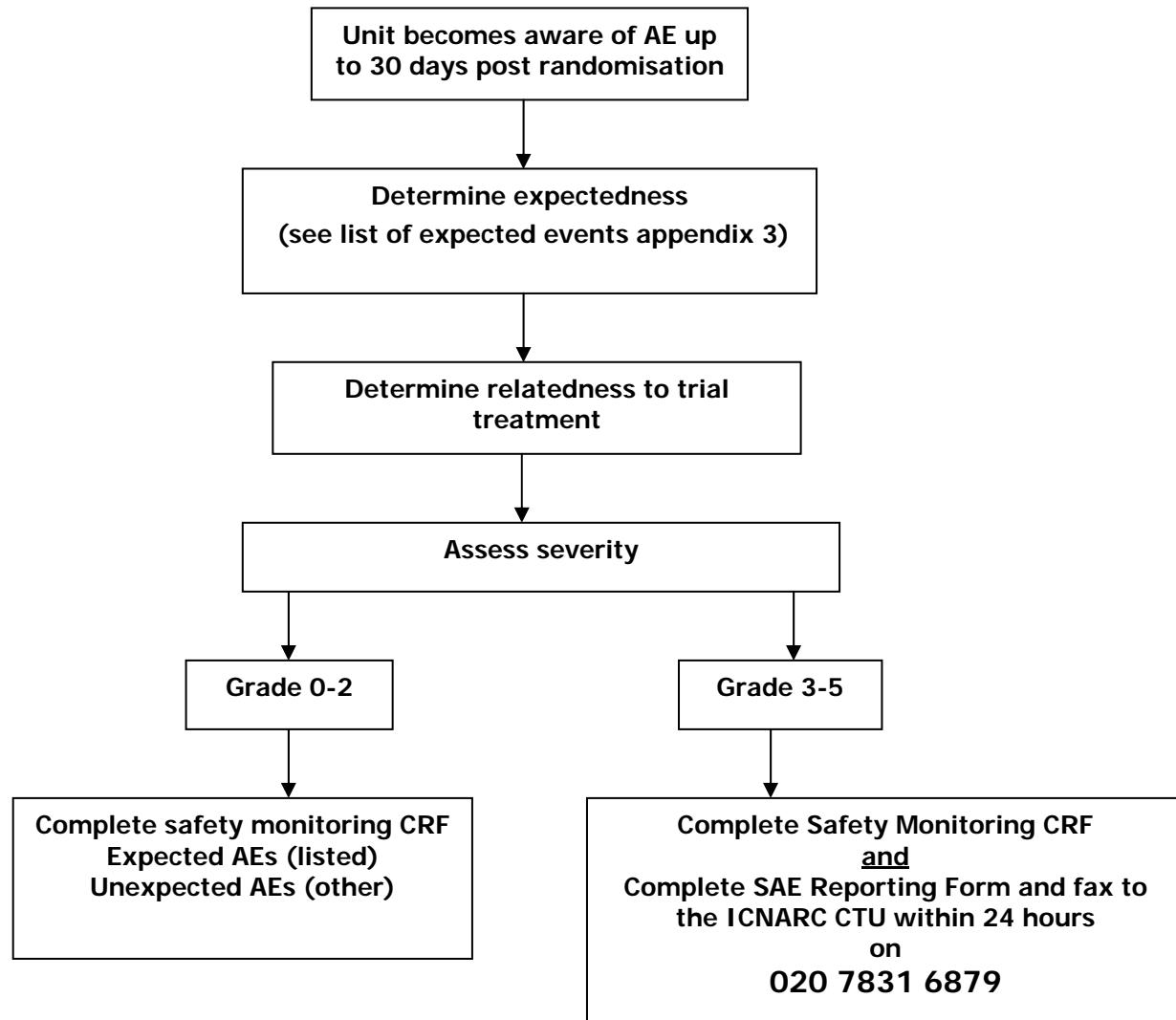
- **Unexpected**

The event is not listed as an expected AE in Appendix 3

All SAEs must be reported by faxing a completed SAE Reporting Form to the ICNARC CTU within 24 hours of becoming aware of the event

Fax: 020 7831 6879

Figure 2 Adverse Event recording and reporting flowchart



11.3 Follow-up of serious adverse events

All SAEs must be followed-up until resolution. The PI or other delegated local investigator(s) must provide follow-up SAE Report(s) if the SAE had not resolved at the time the initial report was submitted.

11.4 Central processing of serious adverse events

On receipt of the SAE report, a clinical member of the CALORIES Trial Management Group (TMG), on behalf of the Chief Investigator, will evaluate the event for severity, relatedness and expectedness to determine whether or not the case qualifies for expedited reporting to the Research Ethics Committee (REC).

If the event is evaluated by either the PI or a clinical member of the CALORIES TMG as a related and unexpected SAE, the ICNARC CTU will submit a report to the REC within 15 calendar days.

The ICNARC CTU will provide safety information to the Chief Investigator, TMG, Trial Steering Committee (TSC) and Data Monitoring and Ethics Committee (DMEC) for review on a regular basis (as deemed necessary).

11.5 Additional safety monitoring

The ICNARC CTU will also monitor data for documented AEs that are not considered to be related to the trial treatment. In the event that any trial procedure does appear to be resulting in AEs, the Chief Investigator and/or TMG will be contacted for their opinion. If it is declared necessary to review the conduct of the trial, the ICNARC CTU will inform the REC as appropriate.

11.6 Notifying the REC

AEs that do not require expedited reporting will be reported in the annual progress report which will be submitted by the ICNARC CTU to the REC annually. This will commence one year from the date of approval for the trial.

12.0 Trial monitoring and oversight

12.1 Unit monitoring

All PIs must agree to allow trial-related monitoring by the ICNARC CTU, REC review and audit by providing direct access to source data/documents as required. Trial patients and PeC/PrC will be informed of this during the informed consent process (see: Section 6.0).

A member of the CALORIES trial team will conduct at least one on-site monitoring visit during the course of CALORIES. Sites will be contacted with details prior to the visit.

Following the monitoring visit, a report will be sent, which will summarise the visit and the documents reviewed, along with any findings. The PI at each site will be responsible for ensuring that all findings are addressed appropriately.

Additional on-site monitoring visits may be scheduled where there is evidence or suspicion of non-compliance with the CALORIES Trial Protocol.

12.2 Central monitoring

PIs will be requested to submit the CALORIES Screening and Delegation of Trial Duties Logs to the ICNARC CTU on a regular basis. These will be checked for consistency and completeness.

Compliance with the CALORIES Trial Protocol will be monitored closely during the course of the trial.

Data entered onto the CALORIES secure web data entry system will be checked and undergo validation checks for completeness, accuracy and consistency of data. Data queries that arise from these checks will be sent to the site. The PI is required to ensure that queries are resolved as soon as possible, including updating the relevant paper CRFs and the CALORIES secure web data entry system as required. The ICNARC CTU will send reminders for any overdue data or outstanding queries.

13.0 Withdrawal

13.1 Withdrawal of patients

In consenting/agreeing to the trial, patients or their PeC/PrC are consenting/agreeing to trial treatment, assessments, follow-up and data collection.

13.2 Withdrawal of trial treatment

The treating clinician(s) may withdraw a patient from trial treatment whenever continued treatment is no longer in the patient's best interests. The reasons for doing so must be documented in the CRF and on the web portal. In these cases, data should continue to be collected and the patients followed-up as per the Trial Protocol.

If a patient wishes to withdraw from trial treatment, sites should explain the importance of remaining on trial for data collection and follow-up.

13.3 Withdrawal of consent

Patients or their PeC/PrC can withdraw from CALORIES at anytime during the trial. If a patient, or their PeC/PrC, explicitly state that they no longer wish to take part or to contribute further data to the trial, their decision must be respected. The Withdrawal of Consent form should be completed and sent to the ICNARC CTU. The patient's withdrawal from the trial should be recorded in the patient's medical notes and no further data collected for CALORIES. All data collected up to the point of withdrawal will be included in the trial analyses. However, if a patient withdraws consent for any of their data to be used, these will be confidentially destroyed.

Patients withdrawn from CALORIES will not be replaced and this has been taken into account in the sample size calculation (see: Section 16.1).

13.4 Withdrawal of a unit

Should a unit choose to close to patient recruitment before the end of the trial, the PI must inform the ICNARC CTU in writing. Follow up, as per the CALORIES Trial Protocol, must continue for all patients already recruited into the trial at that unit.

Units that contravene the CALORIES Trial Protocol and the Clinical Trial Site Agreement will be subject to review by the TMG and Sponsor and may be suspended or closed down by the ICNARC CTU.

14.0 Trial closure

14.1 End of trial

The end of the trial will be when the final patient has completed their one year follow-up, at which point the 'declaration of end of trial' form will be submitted to the REC by the ICNARC CTU.

14.2 Archiving trial documents

At the end of the trial, the ICNARC CTU will securely archive all centrally-held trial-related documents for a minimum of ten years in accordance with ICH GCP guidelines. Arrangements for confidential destruction of all documents will then be made. It is the responsibility of PIs to archive all locally-held trial-related documents (including CRFs and other essential documents) at the unit for a minimum of ten years after the end of the trial. Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and to show whether the unit complied with the principles of ICH GCP and other applicable regulatory requirements.

The ICNARC CTU will notify PIs when trial documents should be archived and provide guidance on archiving procedures in the trial-specific SOP.

All archived documents, held centrally and locally, should be available for inspection by appropriate authorities upon request.

14.3 Early discontinuation of the trial

The trial may be stopped early upon recommendation of the TSC (see Section: 16.4). In which case, units will be informed in writing by the ICNARC CTU of the reasons for early closure and the actions to be taken as regards the treatment of patients. All randomised patients will continue to be followed up as per the CALORIES Trial Protocol.

15.0 Trial management and Trial committees

15.1 Good research practice

CALORIES will be managed according to the Medical Research Council's (MRC) Guidelines for Good Research Practice, Guidelines for Good Clinical Practice in Clinical Trials and Procedure for Inquiring

into Allegations of Scientific Misconduct. The ICNARC CTU has developed its own policies and procedures, based on these MRC guidelines, for the conduct of all its research activities. In addition, ICNARC has contractual confidentiality agreements with all members of staff. Policies regarding alleged scientific misconduct and breach of confidentiality are reinforced by disciplinary procedures.

15.2 Trial Management Group

All day-to-day management of CALORIES will be the responsibility of the TMG. Members of the TMG will include the CALORIES Trial Manager, the Chief Investigator (Professor Kathryn Rowan) and the clinical co-investigators. The TMG will meet regularly to discuss management and progress of the trial and findings from other related research.

15.3 Trial Steering Committee

The trial will be supervised by the TSC, which will be chaired by an independent member, Dr Michael Stroud, Southampton University Hospitals NHS Trust. The TSC will include at least two additional independent members and a service user representative.

15.4 Data Monitoring and Ethics Committee

The DMEC will be chaired by Dr Elizabeth Allen, an experienced statistician who has worked on clinical trials in critically ill patients. The DMEC will also include experienced clinicians. All members of the DMEC will be independent of both the CALORIES TMG and the TSC. The DMEC will operate under the DAMOCLES Charter²², and will report to the TSC, making recommendations on the continuation, or not, of the trial. Safety will be monitored by the DMEC through mandatory reporting of SAEs throughout the trial period.

15.5 Role of the ICNARC Clinical Trials Unit

The ICNARC CTU will be responsible for the day-to-day management of the trial and will act as custodian of the data. The ICNARC CTU will ensure that all SAEs are appropriately reported to the REC.

16.0 Statistics

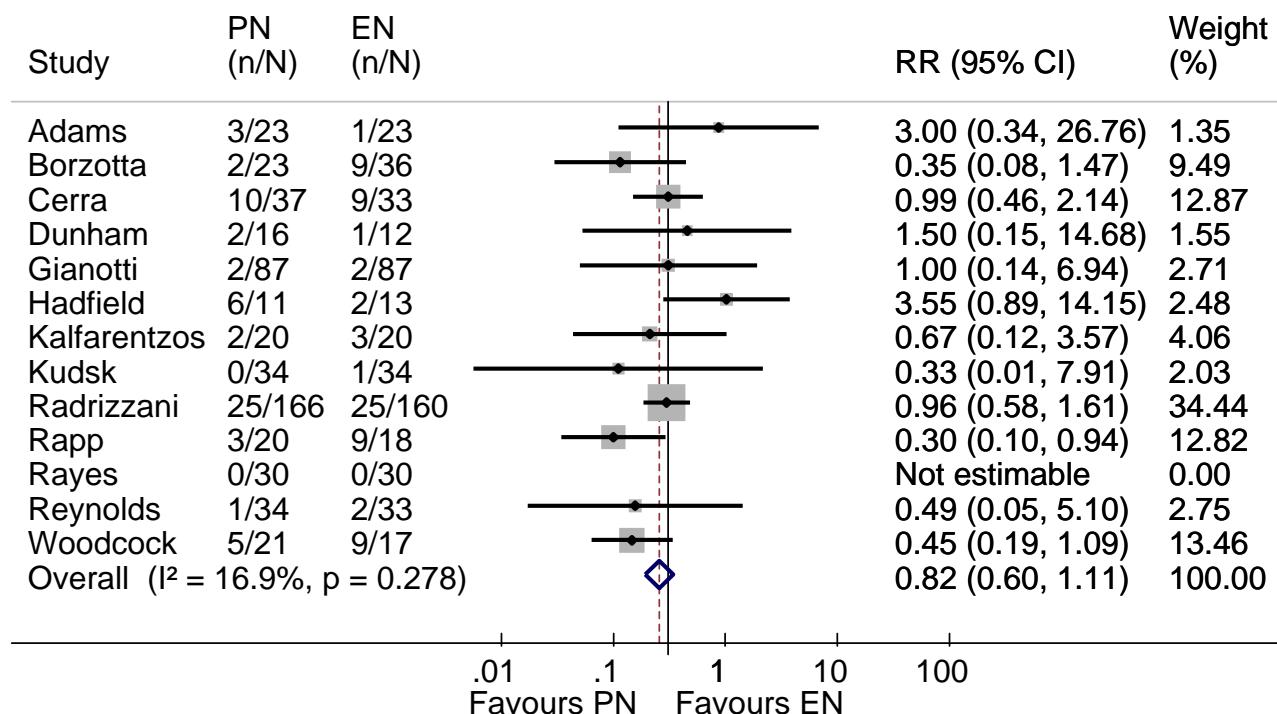
The Senior Statistician, Dr David Harrison, is responsible for all statistical aspects of the trial design and analysis.

16.1 Sample size calculation

Applying the trial entry criteria to over 500,000 admissions to adult, general critical care units in the CMPD, unplanned, ventilated, adult admissions staying three or more days have a 30-day mortality of 32%. As the predominant choice of nutritional support is currently via the enteral route (EN), we have used this as the basis to estimate the control group (EN) mortality.

A meta-analysis of existing RCTs of parenteral nutrition compared with enteral nutrition (Figure 3) indicates a potential relative risk reduction associated with parenteral nutrition of around 20%.

Figure 3 Meta-analysis of RCTs comparing parenteral with enteral nutrition



To have 90% power, with a type I error rate of 5% (two sided), to detect a 20% relative risk reduction (6.4% absolute risk reduction) from 32% in the EN arm to 25.6% in the PN arm will require a sample size of 1082 per arm (Stata/SE Version 10.1). To allow for 2% crossovers/protocol violations (in each direction) and 2% loss to follow-up/withdrawal prior to 30 days (based on observed rates from the PAC-Man Study)²³, a sample size of 1200 per arm (2400 total) will be required. No adjustment to the sample size calculation has been made to account for subgroup analyses.

Based on 20 critical care units recruiting an average of 60 patients per year, patient recruitment is anticipated to be completed within two years. Data from the CMPD indicate that an average critical care unit admits 500 patients per year, of which approximately 35% form the target population. This gives a potentially eligible population of around 175 patients per unit per year. A recruitment rate of 60 patients per unit per year would require 34% of these potentially eligible patients to be recruited, allowing for: patients meeting exclusion criteria (e.g. pregnancy, absolute contraindications to parenteral and/or enteral nutrition); difficulty in estimating likely length of stay in the critical care unit; failure to identify eligible patients within a suitable timeframe (i.e. within 36 hours of the date/time of admission to the critical care unit); failure to identify a PeC or PrC to provide agreement for the patient to participate in the trial and refusals of consent/agreement from patients PeCs or PrCs.

16.2 Statistical analysis

Baseline covariates in the PN and EN groups will be compared to ensure that balance has been achieved. These will include: age (mean, standard deviation - SD); sex (n, %); SOFA score¹⁶ (mean, SD); APACHE II Acute Physiology Score (mean, SD) and predicted risk of death¹⁷ (median, quartiles); ICNARC model physiology score (mean, SD) and predicted risk of death¹⁸ (median, quartiles); surgical status (n, %); ventilation status (n, %); actual/estimated body mass index (BMI) (median, quartiles); degree of malnutrition (n, %). Tests of statistical significance will not be conducted, in line with recommended practice¹⁰.

Analysis of the primary outcome (30-day mortality) will be performed using Fisher's exact test. The unadjusted primary outcome will be reported as the number and percentage of patients dying in each arm, the absolute risk reduction (with 95% confidence interval), the relative risk (with 95% confidence interval) and the odds ratio (with 95% confidence interval).

Adjustment for baseline covariates can increase the precision of the estimate of treatment effect, and therefore the power of the study, as well as adjusting for any chance imbalance between the trial arms. An adjusted analysis using multi-level logistic regression with unit-level random effects will be conducted. The covariates for inclusion in the adjusted analysis will be selected *a priori* based on an established relationship with outcome for critically ill patients, and not because of observed imbalance, statistical significance in univariate analyses or by a stepwise selection method. The adjusted primary outcome will be reported as the odds ratio (with 95% confidence interval).

Subgroup analyses will be performed to test for interaction between the effect of trial arm and the following baseline covariates:

- age;
- degree of existing malnutrition (high – BMI < 18.5 or weight loss > 10%; moderate BMI < 20 or weight loss > 5%; or no malnutrition);
- severity of illness (APACHE II¹⁷ and ICNARC model¹⁸ predicted risk of hospital mortality);
- mechanical ventilation at admission to the critical care unit;
- presence of cancer;
- time from critical care unit admission to commencement of nutritional support (<24 hours versus ≥24 hours).

Secondary analyses of binary outcomes (e.g. mortality, hypoglycaemia, diarrhoea) will be performed using Fisher's exact test. The number and percentage of patients experiencing the outcome in each arm and the relative risk and 95% confidence interval will be reported. Where appropriate, an adjusted logistic regression analysis will be conducted and the odds ratio and 95% confidence interval reported. Secondary analyses of continuous outcomes (e.g. days free of mechanical ventilation, unit and hospital length of stay, nutritional and health-related quality of life) will be performed using t-tests (reporting the mean and SD in each arm and the mean difference and 95% confidence interval) or by nonparametric or bootstrapped alternatives (depending on the distribution of the outcome variable). Where appropriate, adjusted linear regression analyses will also be conducted. Secondary analyses of time-to-event data (e.g. survival time, days to recommence oral feeding) will be performed by Kaplan-Meier methods and Cox proportional hazards modelling (reporting the hazard ratio and 95% confidence interval). The results from analyses of the secondary outcomes will be treated with extreme caution. No allowance has been made for multiple testing and any statistically significant results will be used as the basis for sample size calculations for future research studies and confirmed in independent datasets.

16.3 Interim analysis and data monitoring

A single interim analysis will be carried out after the first 1200 patients have been recruited and completed 30 day follow-up for evaluation of the primary outcome (mortality). The Peto-Haybittle²² stopping rule ($P<0.001$) will be used, as appropriate, to recommend termination indicating either effectiveness or harm. The Peto-Haybittle²² method allows a fixed sample analysis at the final stage with no allowance for the interim analysis if the number of interim analyses is small and early stopping is unlikely.

The interim analysis will be conducted by the Trial Statisticians. The TMG and TSC, other than the Trial Statisticians, will remain blind to the results of the interim analysis. The DMEC will use the result of the interim analysis and other relevant sources to make a recommendation to the TSC as to whether the trial should continue. The Trial Statisticians will take no part in TSC discussions that may be influenced by knowledge of interim results, and independent expert statistical advice will be sought if required. The final decision on stopping the trial will be taken by the TSC. Further interim analyses will be performed if required by the DMEC.

If the trial is discontinued prior to the planned completion of recruitment, participating units will be notified by the ICNARC CTU.

16.4 Other statistical considerations

Procedures for reporting any deviation from the original statistical analysis plan will be described and justified in the final report.

16.5 Economic evaluation

A full cost-effectiveness analysis (CEA) will be undertaken to assess whether the additional intervention costs PN or EN are justified by any subsequent reductions in morbidity costs and/or improvements in patient outcomes. Resource use and outcome data collected as part of the trial will be used to report cost-effectiveness at one year. The CEA will fully recognise the potential long-term impact of the route of nutritional support by using the trial data to project the relative cost-effectiveness over the lifetime.

The cost analysis will use detailed, micro-costing methods to record the costs of providing PN and EN. The level and type of nutritional support provided for each patient on each day during their stay in the critical care unit will be recorded. The duration (number of days) and route (PN versus EN) of nutritional support provided subsequently will be recorded, together with other resource use that may differ by intervention group (e.g. antimicrobial use). These resource use data will be combined with detailed unit costs that relate directly to the nutritional regimen for each individual (source: manufacturers' list prices, NHS Hospital Trust finance departments, British National Formulary 2007). This microcosting approach will enable the cost analysis to recognise any cost variation across different patient subgroups. Each patient's hospital admission will be assigned to the appropriate Healthcare Resource Group (HRG) using mandated data for the CCMDS¹⁹. The cost per hospital bed-day for each HRG category for critical care, and for general medical bed-days will be available from the NHS Payment by Results database.

The cost analysis will take a health and personal health services perspective as per guidance from NICE Guide to the Methods of Technology Appraisal, 2004²⁴ and 2007²⁵. Information on subsequent

hospital admissions and the use of personal health services will be extracted from the use of Health Services questionnaire (Appendix 2) at 90 days and at one year post-randomisation. Community services use will then be valued using unit costs taken from published sources²⁶. Data from the EuroQol EQ-5D¹⁸ questionnaires at 90 days and at one year post randomisation will be combined with survival data to report quality adjusted life years (QALYs).

The CEA will report the mean (with 95% confidence interval) incremental costs and QALYs of PN versus EN at 90 days and at one year, and the probability that PN is cost-effective compared with EN, at different levels of willingness to pay for a QALY gained. The CEA will use regression methods to report relative cost-effectiveness according to pre-defined subgroups (see: Section 16.2),²⁷⁻²⁹ and to address issues posed by missing EuroQol EQ-5D or cost data³⁰. Survival analysis will be used to extrapolate any within-trial differences in costs and QALYs to project lifetime cost-effectiveness. The sensitivity analysis will test whether the results are robust to methodological assumptions, for example regarding the specification of the statistical model and the data source (trial versus external data) used to extrapolate the trial results, and the source of the unit cost data for the interventions (manufacturers' list prices versus prices agreed locally).

The CEA will therefore provide a thorough assessment of whether PN rather than EN is a cost-effective use of scarce health service resources.

17.0 Ethical compliance

17.1 Central ethical compliance

CALORIES will be conducted in accordance with the approved Trial Protocol, ICH GCP guidelines, the Data Protection Act 1998, the Mental Capacity Act (2005), as well as the ICNARC CTU's research policies and procedures (see: Section 15.1).

The trial has received a favourable opinion from the North West London REC 1. The ICNARC CTU will submit annual progress reports and all amendments to the Trial Protocol to the REC for review. The ICNARC CTU will provide relevant trial documents and other related material to participating units.

17.2 Local ethical compliance

It is the responsibility of the PI to obtain the necessary local approvals for CALORIES, including approval from the NHS Hospital Trust Research & Development (R&D) department. The PI should submit the current approved versions of the Trial Protocol, Patient Information Sheets, Consent/Consultee Agreement Forms, and any other written information to be given to patients, to their local R&D department. It is also the responsibility of the PI to inform the R&D department of any subsequent revisions to the Trial Protocol or other trial documents. Evidence of local NHS Hospital Trust R&D approval must be provided to the ICNARC CTU prior to unit activation.

CALORIES will only be conducted at sites where all necessary local approvals for the trial have been obtained and a Clinical Trial Site Agreement between the NHS Hospital Trust (site) and the ICNARC CTU has been signed.

17.3 Patient confidentiality and Data protection

Identifiable patient data, including full name, full postal address, date of birth and NHS number will be required by the ICNARC CTU to successfully follow-up patients at 30 days, 90 days and at one year post-randomisation. The ICNARC CTU will act to preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified. Data will be entered and stored securely on the CALORIES secure web data entry system.

ICNARC is registered under the Data Protection Act 1998 and all ICNARC CTU staff have undergone data protection and ICH GCP training.

18.0 Sponsorship and Indemnity

18.1 Sponsor details

Sponsor Name:	ICNARC
Address:	ICNARC Napier House 24 High Holborn London WC1V 6AZ
Contact:	Keryn Vella
Telephone:	020 7831 6878
Fax:	020 7831 6879

18.2 Indemnity

ICNARC holds professional liability insurance (Markel International Insurance Co Ltd) to meet the potential legal liability of the sponsor and employees for harm to participants arising from the design and management of the research.

Indemnity to meet the potential legal liability of investigators/collaborators for harm to participants arising from the conduct of the research is provided by the NHS indemnity scheme or through professional indemnity.

19.0 Funding

The NIHR HTA Programme (Project No. 07/52/03) is supporting the central coordination of CALORIES through the ICNARC CTU, some local resources costs, and the economic evaluation.

20.0 Publication policy

Ongoing progress of the trial will be disseminated to local PIs via newsletters, emails and telephone, to the wider clinical community through relevant professional newsletters and national and international conferences/meetings, and to consumers via patient support groups and the ICNARC website.

The final report to the NIHR HTA Programme will present a detailed description of the trial and the results along with recommendations for future policy and practice and future research. Articles will be prepared for publication in peer-reviewed scientific journals, as well as relevant professional journals. All patient data will be anonymised before publication.

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Appendix 1: NIHR HTA Programme call

Nutrition in critically ill patients

Introduction

The aim of the HTA programme is to ensure that high quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage, provide care in or develop policy for the NHS. Topics for research are identified and prioritised to meet the needs of the NHS. Health technology assessment forms a substantial portfolio of work within the National Institute for Health Research and each year about fifty new studies are commissioned to help answer questions of direct importance to the NHS. The studies include both primary research and evidence synthesis.

Question

What is the clinical- and cost-effectiveness of early enteral nutrition compared to early parenteral nutrition support in critically ill patients?

- 1 **Technology:** Early parenteral nutritional support.
- 2 **Patient group:** Critically ill adult patients with unplanned admissions to intensive care units who are expected to stay for a minimum of 3 days.
- 3 **Setting:** Secondary care.
- 4 **Control or comparator treatment:** Early enteral nutritional support.
- 5 **Design:** a pragmatic, multi-centre randomised controlled trial. The analyses should be stratified in terms of both severity (e.g. APACHE scores) and degree of existing malnutrition. Researchers should define and justify the term 'early' within the context of their proposed study.
- 6 **Primary outcome:** 30 day mortality. Secondary outcomes: Researchers to define and justify. Might include any of: ICU length of stay, hospital length of stay, infective complications (including line-related sepsis, ventilator-associated pneumonia and bacteraemia), non-infective complications (including resolution time for organ failure in terms of ventilation days, biochemical abnormalities, anastomotic breakdown, glycaemic control, cholestasis), diarrhoea, delay to establishing normal diet, quality of life, costs, cost-effectiveness.
- 7 **Minimum duration of follow-up:** 6 months.

Background to commissioning brief:

Malnutrition is both a cause and a consequence of ill health. It increases a patient's vulnerability to disease, and is common in hospitalised patients in the UK, particularly those in intensive care. Nutritional support as enteral or parenteral nutrition is important in intensive care unit (ICU) patients to address malnourishment and reduce further catabolism of the body's nutrient stores. An adequate supply of nutrients also plays an important role in ensuring optimum recovery.

Three systematic reviews have compared enteral and parenteral nutrition support in critically ill patients with mixed results, and there appears to be no clear superiority of one method. A good quality, adequately powered randomised controlled trial is needed to determine the optimal route of nutritional support to this specific group of patients in intensive care units.

Appendix 2: Health Services Questionnaire



HEALTH SERVICES QUESTIONNAIRE

We would be grateful if you would complete this questionnaire. It will help us understand the care you needed after leaving the hospital.

The CALORIES trial aims to improve the care of critically ill patients.

A pen is provided and a FREEPOST envelope for return of the questionnaire. Please answer multiple choice questions by putting a in ONE BOX for each question.

Please complete today's date below:

Day / Month / Year

Please also let us know whether you completed this questionnaire:

- Alone
- With help
- Or it was completed by someone who cares for you

NOW PLEASE TURN THE PAGE TO START THE QUESTIONNAIRE ►

If you do not wish to complete this questionnaire, please return the unanswered questionnaire in the FREEPOST envelope provided.

Your current and future care will not be affected whether you decide to, or not to, fill out this questionnaire.

Health Services Questionnaire, Version 1.1, 01/04/11

The questions refer to ALL health services that you have used since leaving the hospital on [insert date], and before [insert date]

Part 1. Hospital Stay

A Since you left hospital on [insert date] have you stayed overnight in hospital for any reason?

No - Go to Part 2

Yes - Please give details about the number of stays below

B For EACH TIME you stayed in hospital please answer the following

	Number of nights	1-3 nights	4-10 nights	11 or more nights	Did you spend any part of your stay in critical care?
1 st Stay	<input type="text"/> or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2 nd Stay	<input type="text"/> or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3 rd Stay	<input type="text"/> or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4 th Stay	<input type="text"/> or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**If you have stayed in hospital overnight more than 4 times, please could you provide information on these further hospital stays in Part 6 of the questionnaire.*

Part 2. Hospital outpatient visits

Outpatient visits are when a patient comes to the hospital to see a specialist (e.g. consultant) but does not stay overnight.

A Since you left the hospital on [insert date] have you visited hospital outpatients about ANY ASPECT of your health?

No - Go to Part 3

Yes - Please give details about the number of outpatients visit(s) below

	Number of visits	1-3 visits	4-10 visits	11 or more visits
	<input type="text"/> or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Part 3. Visits to health care providers

A Since you left the hospital on [insert date] have you visited any of the health care providers listed below?

No - Go to Part 4

Yes - Please give details about your visits below

B For EACH PROVIDER please answer the following

Did you visit this provider?	Number of visits	1-3 visits	4-10 visits	11 or more visits
GP	<input type="checkbox"/> [] or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Nurse at your GP clinic	<input type="checkbox"/> [] or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Nurse at hospital or elsewhere	<input type="checkbox"/> [] or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Health visitor	<input type="checkbox"/> [] or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Part 4. Visits to your home by health care providers

A Since you left the hospital on [insert date] have you had home visits from any the following health care providers about ANY ASPECT of your health?

No - Go to Part 5

Yes - Please give details about your visits below

B For EACH HOME VIST please answer the following

Were you visited at home by this provider?	Number of visits	1-3 visits	4-10 visits	11 or more visits
GP	<input type="checkbox"/> [] or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Nurse from your GP clinic	<input type="checkbox"/> [] or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Occupational Therapist	<input type="checkbox"/> [] or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Health visitor or District nurse	<input type="checkbox"/> [] or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Part 5. Visits to other service providers

A Since you left the hospital on [insert date] please indicate whether you have had contact (either visits to the provider or home visits) with any of the following service providers about any aspect of your health?

No - Go to Part 6

Yes - Please give details below

B For EACH PROVIDER please answer the following

Have you had contact with any of these providers?	Number of visits	1-3 visits	4-10 visits	11 or more visits
Occupational therapist	<input type="checkbox"/> [] or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Psychologist	<input type="checkbox"/> [] or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Speech and Language therapist	<input type="checkbox"/> [] or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Physiotherapist	<input type="checkbox"/> [] or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Dietician	<input type="checkbox"/> [] or...	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Part 6. Other services not listed so far

A Since you left the hospital on [insert date] have you had further hospital stays or used ANY OTHER health care services for any aspect of your health that you haven't included above?

No - Go to Part 7

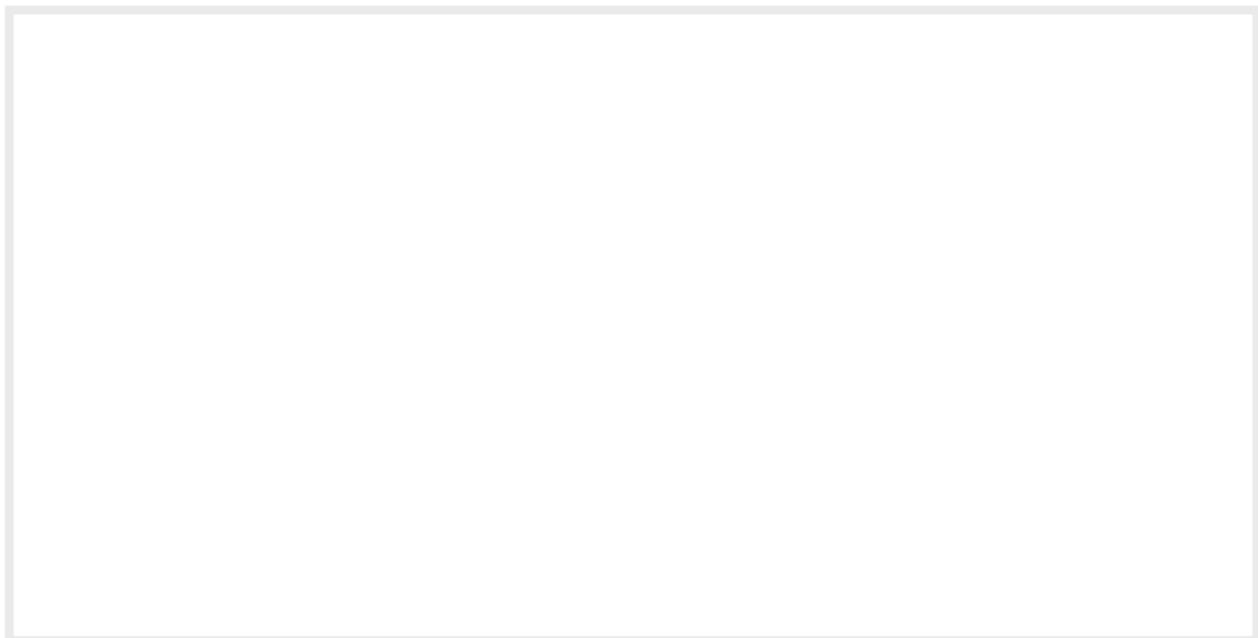
Yes - Please give details below

B For EACH PROVIDER please answer the following

Type of service provider	Number of visits	Reason

Part 7. Comments

Your views are important to us. Please feel free to provide any other comments you have in the box below.

A large, empty rectangular box with a thin gray border, designed for users to input their comments.

Thank you for help

If you would like to ask us any questions about completing the questionnaire please email or call:

Rachael Scott
calories@icnarc.org
020 7269 9277

Richard Grieve
Richard.Grieve@lshtm.ac.uk
020 7927 2255

Appendix 3: Expected Adverse events

Adverse events (*expected) that could be observed in patients up to 30 days following randomisation:

- Abdominal distension;
- Abdominal pain;
- Electrolyte disturbance;
- Haemo-pneumothorax;
- Hepatomegaly;
- Hyperosmolar syndrome;
- Hypersensitivity reaction;
- (anaphylactic reaction);
- Hypoglycaemia;
- Ischaemic bowel;
- Jaundice;
- Nausea requiring treatment;
- Pneumothorax;
- Raised liver enzyme(s);
- Regurgitation/aspiration;
- Vascular catheter related infection;
- Vomiting.

*This list is not exhaustive – if an adverse event occurs which is thought to be as a result of the trial treatment (PN or EN), this should be recorded/reported as described in section 11.0.