The CALORIES trial: statistical analysis plan

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ABSTRACT

Background: The CALORIES trial is a pragmatic, open, multicentre, randomised controlled trial (RCT) of the clinical effectiveness and cost-effectiveness of early nutritional support via the parenteral route compared with early nutritional support via the enteral route in unplanned admissions to adult general critical care units (CCUs) in the United Kingdom. The trial derives from the need for a large, pragmatic RCT to determine the optimal route of delivery for early nutritional support in the critically ill.

Objective: To describe the proposed statistical analyses for the evaluation of the clinical effectiveness in the CALORIES trial.

Methods: With the primary and secondary outcomes defined precisely and the approach to safety monitoring and data collection summarised, the planned statistical analyses, including prespecified subgroups and secondary analyses, were developed and are described.

Results: The primary outcome is all-cause mortality at 30 days. The primary analysis will be reported as a relative risk and absolute risk reduction and tested with the Fisher exact test. Prespecified subgroup analyses will be based on age, degree of malnutrition, acute severity of illness, mechanical ventilation at admission to the CCU, presence of cancer and time from CCU admission to commencement of early nutritional support. Secondary analyses include adjustment for baseline covariates.

Conclusion: In keeping with best trial practice, we have developed, described and published a statistical analysis plan for the CALORIES trial and are placing it in the public domain before inspecting data from the trial.

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Currently, the enteral route is the mainstay of nutritional support in the critically ill,[1] but it can be associated with gastrointestinal intolerance and underfeeding.[2,3] In contrast, the parenteral route, though more invasive and expensive, is more likely to secure delivery of the intended nutrition.[2] Historically, nutritional support via the parenteral route has been associated with greater risks and complications (eg, infections) compared with the enteral route.[4-6] Recent improvements in the delivery, formulation and monitoring of parenteral nutrition[7-9] justify further comparison and evaluation of these routes for nutritional support, particularly in the early phase of critical illness. In light of this, in late 2007, the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) program in the United Kingdom put out a call for a large, pragmatic, randomised controlled trial (RCT) to determine the optimal route of delivery for early nutritional support in the critically ill. As a result, the CALORIES trial was established; a pragmatic, open, multicentre, RCT of early nutritional support delivered via the parenteral route, compared with early nutritional support delivered via the enteral route, in critically ill patients. The CALORIES trial is nested in the Case Mix Programme (CMP), the national clinical audit of adult critical care in England, Wales and Northern Ireland, coordinated by the Intensive Care National Audit and Research Centre (ICNARC).[10]

We describe our proposed statistical analysis plan for evaluation of the clinical effectiveness of early nutritional support delivered by the parenteral route compared with the enteral route in the CALORIES trial. It is important to develop and describe our plan before inspecting the data so that post hoc, data-derived decisions are explicit. The full protocol for the CALORIES trial is published at http://www.nets.nihr.ac.uk/projects/hta/075203.

Trial design

Aim

Our aim is to evaluate the clinical effectiveness and cost-effectiveness of early (defined as within 36 hours of admission to a critical care unit [CCU]) nutritional support via the parenteral route compared with early nutritional support via the enteral route in unplanned adult admissions to a CCU.

Trial sites and patients

Adult, general CCUs in UK National Health Service (NHS) hospitals participating in the CMP are eligible to participate and the target is to recruit a minimum of 20 CCUs. Patients who are unplanned admissions to a CCU and who meet all inclusion and no exclusion criteria are recruited into the CALORIES trial.

Inclusion and exclusion criteria

Adult patients (≥ 18 years of age) are eligible to take part if, on or soon after admission (within 36 hours), they are:

- an unplanned admission (including planned admissions becoming unplanned, eg, unexpected postoperative complications)
- expected to receive nutritional support for 2 or more days in the CCU
- not planned to be discharged from the CCU within 3 days (determined by clinical judgement).

Patients are excluded if they:

- are identified in the CCU after 36 hours
- have previously been randomly assigned to participate in the CALORIES trial
- have pre-existing contraindications to nutritional support via either route (parenteral or enteral)
- have received nutritional support via either route within the past 7 days
- have been admitted with a percutaneous endoscopic gastrostomy, percutaneous endoscopic jejunostomy, needle or surgical jejunostomy or nasojejunal tube in situ
- have been admitted to the CCU for treatment of thermal injury (burns) or for palliative care
- are expected to stay in the UK for less than 6 months
- are women known to be pregnant.

Treatment allocation

Eligible patients are allocated 1:1 to one of two treatment groups via a dedicated, 24-hour, 7 days per week, telephone random allocation service. Allocation is by minimisation with a random component (each patient being allocated with 80% probability to the treatment group that would minimise imbalance). Minimisation is based on the following factors: CCU (site); age (< 65 years or ≥ 65 years); surgical status (surgery within 24 hours before CCU admission or not); and subjective assessment of severity of malnutrition.

Treatment groups

Patients are randomly allocated to receive early nutritional support via the parenteral route or the enteral route for 5 days (ie, for 120 hours) or until their transition to exclusive oral feeding or discharge from the CCU. Patients can start oral feeding, if clinically indicated, during the 5 days. Patients randomly allocated to the parenteral route receive standard bags of parenteral nutrition within prespecified parameters, sourced from the CCU's usual suppliers and delivered via a central venous catheter with a dedicated lumen positioned according to NHS guidelines.[11] Additional micronutrients, if clinically indicated, can be added according to the National Institute for Health and Care Excellence guidelines.[12] Enteral "trickle-feeding" is not permitted during the 5-day intervention period. Patients randomly allocated to the enteral route receive standard enteral nutrition within prespecified parameters, sourced from the CCU's usual suppliers and delivered via a nasogastric or nasojejunal tube inserted and positioned in accordance with National Patient Safety Agency guidelines.[13,14] Patients in both groups are fed to a target of 25 kcal/kg/day, using actual body weight to be achieved within 48–72 hours.

Outcomes

Evaluation of clinical effectiveness

Primary outcome

The primary outcome for evaluation of clinical effectiveness is all-cause mortality at 30 days.

Secondary outcomes

Secondary outcomes for evaluation of clinical effectiveness are:

- duration of specific and overall organ support in the CCU
- non-infectious complications in the CCU
  - episodes of hypoglycaemic events
  - elevated liver function test levels
  - nausea
  - abdominal distension
  - vomiting
  - pressure ulcers
- infectious complications in the CCU
  - confirmed or strongly suspected infections by site
  - number of confirmed or strongly suspected infections
- length of stay (LOS)
  - in the CCU, defined as the duration of days from random allocation to discharge from or death in the CCU
  - in an acute care hospital, defined as the duration in days from random allocation to discharge from or death in hospital
- duration of survival
- mortality at discharge from the CCU, at discharge from an acute care hospital, at 90 days and at 1 year from random allocation.

Evaluation of cost-effectiveness

Primary outcome

The primary outcome for economic evaluation is the incremental cost-effectiveness at 1 year.

Secondary outcomes

Secondary outcomes for economic evaluation are:

- nutritional and health-related quality of life at 90 days and at 1 year from random allocation
- resource use and costs at 90 days and at 1 year from random allocation
- estimated lifetime incremental cost-effectiveness.

The analysis plan for the economic evaluation is outside the scope of this statistical analysis plan for the evaluation of clinical effectiveness and will be described separately.

Safety monitoring

Patients are monitored for adverse events for 30 days from random allocation by the site principal investigator and by authorised, delegated site staff. Adverse events are graded for severity, relatedness to trial treatment and expectedness of the adverse event, using standard definitions.[15] Any serious adverse events are reported to the ICNARC Clinical Trials Unit (CTU), regardless of whether they are related to participation in the trial, and reviewed by the lead clinical investigator.

Data collection and follow-up

Sites are responsible for collecting data, from admission to the CCU until acute care hospital discharge. All patients surviving to discharge from an acute care hospital are checked against death registrations on the NHS Health and Social Care Information Centre Data Linkage and Extract Service (DLES) for subsequent reporting of mortality at 30 days, 90 days and 1 year.

In addition, as part of the integrated economic evaluation, patients recorded by the DLES as being alive at 90 days and at 1 year are posted questionnaires by the ICNARC CTU to collect data on their nutritional and health-related quality of life, subsequent hospital admissions and use of personal health services. Patients who do not respond are followed up with a further questionnaire and then by telephone.

Sample size

Applying the trial entry criteria to over 500 000 admissions to adult, general CCUs in the CMP database, the 30-day mortality for unplanned, ventilated, adult admissions staying 3 or more days was 32%. As the enteral route is the predominant choice for nutritional support, this mortality was used as the basis to estimate control group mortality.

In 2008, we updated the most recent systematic review and meta-analysis, by Simpson and Doig.[6] The updated meta-analysis of existing RCTs of parenteral compared with enteral nutrition indicated a potential relative risk reduction associated with parenteral nutrition of around 20%. To have 90% power, with a type I error rate of 5% (two-sided), to detect a 20% reduction in relative risk (6.4% reduction in absolute risk) from 32% in the enteral route group to 25.6% in the parenteral route group, requires a sample size of 1082 patients per treatment group (Stata/SE version 10.1 [StataCorp]). To allow 2% for crossover or protocol violation (in each direction) and 2% for loss to follow-up or withdrawal before 30 days (based on observed rates from the PAC-Man study),[16] a sample size of 1200 patients per treatment group (2400 total) is required. No adjustment to the sample size calculation was made to account for subgroup analyses.

Interim analysis

Unblinded, comparative data on recruitment, withdrawal, adherence (to the allocated treatment) and serious adverse events are regularly reviewed by an independent data monitoring and ethics committee (DMEC), chaired by an experienced trialist.

Without specific analysis of the primary outcome, the DMEC reviewed data from the first 37 trial participants and continue to review data at least six monthly to assess potential safety issues and to review adherence. A single, planned, formal, interim analysis was performed at the point that 30-day outcome data for the first 1200 patients enrolled were available. A Peto stopping rule ($P < 0.001$) was used to guide recommendations for early termination due to harm. Following the planned interim analysis, the DMEC recommended that the trial continue with no changes.

Statistical analysis

Analysis principles

We will base all analyses on the intention-to-treat principle. The patients will be analysed according to the group they were randomly assigned to, irrespective of whether the treatment allocated was received. All patients will be included in the analysis, regardless of whether they have, or have not, adhered to the protocol. Significance is set at $P < 0.05$.

As the amount of missing data are anticipated to be minimal, a sensitivity approach will be taken when the primary outcome variable is missing. We will repeat the primary analysis assuming that all patients in the enteral route group with missing outcomes survived, and all patients in the parenteral route group with missing outcomes did not survive. We will repeat it again with the opposite assumptions. This will then give the absolute range of how much the results could change if all data were complete. In adjusted analyses, missing baseline data will be handled by multiple imputation.

Trial profile

We will display the flow of patients through the trial in a modified Consolidated Standards of Reporting Trials (CONSORT) diagram.[17] The number of screened patients who met the trial inclusion criteria will be reported, and the number of screened patients who were included in the trial, as well as the reasons for exclusion for those who were not included.

Baseline characteristics

We will present baseline demographic and clinical data by treatment group but not subject the data to statistical testing. Discrete variables will be summarised as numbers and percentages, which we will calculate according to the number for whom data are available; where values are missing, the denominator will be stated in the table. Continuous variables will be summarised by standard measures of central tendency and dispersion, either mean and standard deviation (SD) and/or median and interquartile range (IQR) as specified below:

- age: mean (SD), and median (IQR)
- sex: *n* (%)
- severe comorbidity (as defined by Acute Physiology and Chronic Health Evaluation [APACHE] II past medical history definitions[18]):
  - severe liver condition: *n* (%)
  - severe renal condition: *n* (%)
  - severe respiratory condition: *n* (%)
  - severe cardiovascular condition: *n* (%)
  - condition of immunocompromise: *n* (%)
- acute severity of illness:
  - Sequential Organ Failure Assessment (SOFA) score:[19] mean (SD)
  - APACHE II Score:[18] mean (SD)
  - APACHE II Acute Physiology Score:[18] mean (SD)
  - APACHE II predicted risk of death:[18] median (IQR)
  - ICNARC model physiology score:[20] mean (SD)
  - ICNARC model predicted risk of death:[20] median (IQR)
- surgery within 24 hours before CCU admission: *n* (%)
- mechanical ventilation at admission to the CCU: *n* (%)
- malnourished (yes or no, based on clinical judgement): *n* (%)
- malnutrition degree (high, BMI < 18.5 or weight loss > 10%; moderate, BMI < 20 or weight loss > 5%; no malnutrition): *n* (%)
- actual and estimated body mass index (BMI): mean (SD) and median (IQR)
- ulna length (cm): mean (SD) and median (IQR)
- mid-upper arm circumference (MUAC) (cm): mean (SD) and median (IQR).

Clinical management

We will present clinical management of patients by treatment group but not subject the data to statistical testing. As with baseline characteristics, discrete variables will be summarised as numbers and percentages. Percentages will be calculated according to the number for whom data are available; where values are missing, the denominator will be stated in the table. Continuous variables will be summarised by mean (SD) and/or median (IQR).

Clinical management data will be summarised as the total over the 5-day (120-hour) intervention period. The treatment groups will be compared for the following:

- time from CCU admission to commencement of nutritional support (hours)
- total calories and average calories per 24 hours received during the intervention period (total calories and a breakdown of the total calories received via the enteral route, via the parenteral route, via intravenous glucose and propofol, and via oral feed)
- total protein and average protein per 24 hours received during the intervention period (total protein and a breakdown of the total protein received via the enteral and via the parenteral route)
- total aspirates and average aspirates per 24 hours during the intervention period, if receiving nutritional support via the enteral route
- total aspirates replaced and average aspirates replaced per 24 hours during the intervention period, if receiving nutritional support via the enteral route
- additives received during the intervention period (glutamine, selenium and fish oils), if receiving nutritional support via the parenteral route
- prokinetics received during the intervention period, if receiving nutritional support via the enteral route
- total insulin received during the intervention period
- vasoactive agents received during the intervention period
- incidence of diarrhoea and constipation
- time from random allocation to commencement of exclusive oral feeding (days)
- change in daily SOFA score during the intervention period.

Adherence to allocated treatment

We will report the numbers and percentages of non-adherence to randomly allocated treatment, including those in which the patient:

- actually started allocated treatment later than 36 hours after the date or time of original CCU admission
- did not receive nutritional support via either the parenteral or the enteral route in the first 120 hours of nutritional support

- was randomly assigned to the enteral route but received nutritional support via the parenteral route on the first day of nutritional support (as initial nutritional support)
- was randomly assigned to the parenteral route but received nutritional support via the enteral route on the first day of nutritional support (as initial nutritional support)
- was randomly assigned to the enteral route but subsequently changed to receiving nutritional support via the parenteral route in the first 120 hours of nutritional support
- was randomly assigned to the parenteral route but subsequently changed to receiving nutritional support via the enteral route in the first 120 hours of nutritional support
- received nutritional support via either the parenteral or enteral route, as randomly allocated, in the first 120 hours of nutritional support, but did not receive nutrition for at least a period of 1 whole day.

In addition to each individual protocol deviation, overall adherence will be reported as the number and percentage of patients not meeting any of the above criteria.

Description of analysis

Primary outcome

We will report the number and percentage of deaths by 30 days after random allocation. The primary-effect estimates will be the absolute risk reduction, the relative risk and the unadjusted odds ratio of 30-day mortality, all reported with a 95% CI. We will compare deaths by 30 days after random allocation between the groups, unadjusted, using the Fisher exact test.

We will also conduct an analysis adjusted for baseline data using multilevel logistic regression; the data adjusted for will be age, ICNARC model physiology score,[20] surgical status, degree of malnutrition, and a site-level random effect (used as stratification for random allocation). These baseline variables are selected for inclusion in the adjusted analysis according to their anticipated relationship with outcome. We will report the results of the multilevel logistic regression model as an adjusted odds ratio with 95% CI. The unadjusted odds ratio will be presented for comparison.

Secondary outcomes

We will report the mean number of days alive and free from advanced respiratory, advanced cardiovascular, renal, neurological and gastrointestinal support, as defined by the Critical Care Minimum Data Set,[21] up to 30 days after random allocation for each treatment group. Days of organ support will be recorded while the patient is in the CCU. Any days outside the CCU are assumed to be free from organ support. Any patients who die within the first 30 days will be allocated 0 days alive and free from organ support. Differences between the groups will be tested using the *t* test, using bootstrapping to account for anticipated non-normality in the distribution.[22]

We will report the number and percentage of patients with each complication of non-infectious or infectious origin, as well as the overall mean number of strongly suspected or confirmed infections in the CCU (from random allocation) for each treatment group. Differences between the groups will be tested using the *t* test.

We will report the median LOS in the CCU for each treatment group, calculated as the sum of the duration(s) (in days) from the date and time of random allocation to the date and time of discharge from the CCU during the acute care hospital stay. Differences in LOS in the CCU between the groups will be tested using the Wilcoxon rank-sum test, stratified by survival at CCU discharge.

We will report the median LOS in an acute care hospital for each treatment group, calculated as the duration in days from the date and time of random allocation to the date and time of acute care hospital discharge or death. Differences in LOS between the groups will be tested using the Wilcoxon rank-sum test, stratified by survival at acute care hospital discharge.

We will report the number and percentage of deaths at CCU and acute care hospital discharge, and deaths within 90 days and 1 year after random allocation, for each treatment group. Differences in mortality will be compared, unadjusted, using the Fisher exact test and, adjusted, using multilevel logistic regression (adjusted for the same baseline variables as used in the primary analysis). Kaplan–Meier curves, by group, will be plotted up to 90 days and to 1 year after random allocation and compared using the log-rank test. We will perform an adjusted comparison using a Cox proportional hazards model adjusted for the same baseline variables as used in the primary analysis.

Serious adverse events

We will report the number and percentage of serious adverse events between random allocation and 30 days for each treatment group. Differences between groups will be compared using the Fisher exact test.

Subgroup analysis

These analyses will test for an interaction between the subgroup categories and the treatment group in a multilevel logistic regression model, adjusted for the same baseline variables as used in the primary analysis.

We will analyse the primary outcome (30-day mortality) by age (in quartiles), degree of existing malnutrition (high,

moderate or none), acute severity of illness (APACHE II[18] and ICNARC model[20] predicted risk of mortality, in quartiles), mechanical ventilation at admission to the CCU, presence of cancer and time from CCU admission to commencement of nutritional support (< 24 hours v ⩾ 24 hours).

Adherence-adjusted analysis

The intention-to-treat analysis provides the best estimate of the clinical effectiveness of early nutritional support via the parenteral route compared with the enteral route. It is also of interest to estimate what the efficacy of early nutritional support delivered via the parenteral route compared with the enteral route would be, if delivered as intended. In an RCT, the allocated treatment can be used as an "instrumental variable", ie, a variable associated with receipt of the intervention and only associated with the outcome through its association with the intervention.[23] This relationship enables us to estimate what the treatment effect would be for patients who are adherent to the protocol. The primary analysis will be repeated adjusting for adherence using a structural mean model[24] with an instrumental variable of allocated treatment, assuming a linear relationship between the degree of adherence (duration of allocated treatment received) and treatment effect.

Figures and tables

Planned figures include:

- a CONSORT[25]-style diagram illustrating the flow of patients through the trial
- curve showing change in daily SOFA score during the intervention period, by treatment group
- Kaplan–Meier curves showing survival to 30 days, 90 days and to 1 year after random allocation, by treatment group.

Planned tables include:

- baseline characteristics, by treatment group
- clinical management, by treatment group
- non-adherence to allocated treatment, by treatment group
- primary and secondary outcomes, by treatment group
- serious adverse events within 30 days after random allocation, by treatment group
- results for subgroup and secondary analyses.

Funding, registration and ethics approval

Our trial is funded by the NIHR Health Technology Assessment Programme (07/52/03) and is registered on the NIHR Clinical Research Network (CRN) portfolio (10098) and the International Standard Randomised Controlled Trials Number registration (ISRCTN17386141). The trial is endorsed by the NIHR CRN Critical Care Specialty Group, sponsored by ICNARC and coordinated by the ICNARC CTU (UK Clinical Research Collaboration registration: 42). Approval for the trial was received from the North West London Research Ethics Committee (approval 10/H0722/78). The trial results will be published in full in *Health Technology Assessment*.

Competing interests

None declared. The views and opinions expressed are ours and do not necessarily reflect those of the Health Technology Assessment Programme, NIHR, NHS or the Department of Health.

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Appendix 1. Comorbidity definitions

As in the APACHE II definitions,[18] all comorbidities must be present in the patient's medical history within the 6 months before the critical care unit (CCU) admission. Definitions are as follows:

- Severe liver condition: portal hypertension, biopsy-proven cirrhosis or hepatic encephalopathy.
- Severe renal condition: conditions requiring chronic renal replacement therapy for irreversible end-stage renal disease.
- Severe respiratory condition: permanent shortness of breath with light activity due to pulmonary disease, or patients on home ventilation.
- Severe cardiovascular condition: fatigue, claudication, dyspnoea or angina at rest, due to myocardial or peripheral vascular disease (New York Heart Association Functional Class IV).
- Immunosuppression: patients who have received radiotherapy, chemotherapy or daily high-dose steroid treatment (prednisolone [or equivalent] $\geqslant$ 0.3 mg/kg) during the 6 months before CCU admission, or those with HIV/AIDS, metastatic disease, lymphoma, acute or chronic myelogenous or lymphocytic leukaemia, multiple myeloma or a congenital immunohumoral or cellular immune deficiency state.

Appendix 2. The CALORIES trial personnel

Management group

Kathy Rowan (Chief Investigator), Monty Mythen (Lead Clinical Investigator), Kimberley Anderson, Richard Beale, Danni Bear, Geoff Bellingan, David Harrison, Sheila Harvey, Richard Leonard, Blair McLennan, Hannah Muskett, Francesca Parrott, Ella Segaran, Jermaine Tan (previous members: Ruth Canter, Louise Clement, Sarah Corlett, Krishna Patel, Rachael Scott)

Steering committee

Michael Stroud (Chair), Peter Emery, Alastair Forbes, Peter Gibb, Carys Jones, Hugh Montgomery, Janet Myers, Michael Mythen, Kathryn Rowan, Dewi Williams

Data monitoring and ethics committee

Elizabeth Allen (Chair), Peter Andrews, Steve Webb

Principal sites and investigators

Addenbrooke's Hospital (Dr Jacobus Preller), Bradford Royal Infirmary (Dr Stephen Fletcher), Bristol Royal Infirmary (Dr Jeremy Bewley), Dorset County Hospital (Dr Andrew Ball), Furness General Hospital (Dr Andrezj Szymczakowski), Kettering General Hospital (Dr Philip Watt), King's College Hospital (Dr Phil Hopkins), Medway Maritime Hospital (Dr Paul Hayden), Musgrove Park Hospital (Dr Richard Innes), New Cross Hospital (Dr Shameer Gopal), Norfolk and Norwich University Hospital (Dr Stephen Hutchinson), Northern General Hospital (Dr Sarah Irving), Poole Hospital (Dr Henrik Reschreiter), Queen Alexandra Hospital (Dr David Pogson), Royal Hampshire County Hospital (Dr Arthur Goldsmith), Royal Shrewsbury Hospital (Dr Robin Hollands), Royal Surrey County Hospital (Dr Ben Creagh-Brown), Southampton General Hospital (Dr Susan Tanser), Southend University Hospital (Dr David Higgins), St Mary's Hospital London (Dr Richard Leonard), St Richard's Hospital (Dr Mike Margarson), St Thomas' Hospital (Dr Richard Beale), The Ipswich Hospital (Dr Robert Lewis), The Queen Elizabeth Hospital, King's Lynn (Dr Parvez Moondi), The Royal Blackburn Hospital (Dr Anton Krige), University College Hospital (Dr David Brealey), University Hospital Lewisham (Dr Marthin Mostert), University Hospital of North Staffordshire (Dr Bryan Carr), Stafford Hospital (Dr Moses Chikungwa), Royal Free Hospital (Dr Daniel Martin), Papworth Hospital (Dr Stephen Webb), Blackpool Victoria Hospital (Dr Jason Cupitt), The Princess Alexandra Hospital (Dr Dev Dutta)