

Statistical Analysis Plan: Post-hoc analysis of the CALORIES trial

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Role, Name and Position	Signature	Date
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Version control

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1.0	18/04/2017	N/A

Background

Varied and conflicting results have been reported previously regarding the relationship between the amount of energy and/or protein delivered to critically ill patients and their subsequent outcomes.

Among 2,772 mechanically ventilated patients in 167 critical care units across 37 countries, Alberda and colleagues reported that increasing calorie intake was associated with lower mortality (odds ratio 0.76 per 1,000 kcal/day increase, 95% CI 0.61 to 0.95) and increased number of ventilator free days (3.5 per 1,000 kcal/day increase, 95% CI 1.2 to 5.9).¹ This effect was observed in patients with a body mass index (BMI) <25 and ≥35, with no effect among patients with a BMI ≥25 and <35. Similar effects were observed for protein intake.

Among 475 patients mechanically ventilated for at least 8 days, Wei and colleagues reported that poor nutritional adequacy was associated with worse survival to six months (hazard ratio 1.7 for energy intake <50% vs ≥80% of target).² Among responders to the SF-36 questionnaire at three months following discharge (n=179), increasing nutritional adequacy was associated with higher scores on the Physical Functioning (7.3 per 25% increase in percentage of energy target received, 95% CI 1.4 to 13.2) and Role Physical (8.3, 2.7 to 14.0) domains. These associations were reduced and no longer statistically significant at six months (Physical Functioning 4.2, -1.3 to 9.6; Role Physical 3.2, -2.3 to 8.5; n=202).

Among 2,828 patients in a critical care unit for at least 4 days, Nicolo and colleagues reported an odds ratio of 0.68 (95% CI 0.50 to 0.91) for mortality associated with receipt of ≥80% of protein target, but no significant effect associated with receipt of ≥80% of energy target.³

Conversely, post-hoc analysis of the EPaNIC Trial found that lower doses of energy received (as a percentage of target) were associated with earlier discharge alive from the critical care unit.⁴

We aim to explore these relationships in a post-hoc analysis of the CALORIES trial.⁵

Objectives

To conduct a secondary analysis of data from the CALORIES trial to address the following research questions:

1. Is there a relationship between the dose of energy and protein received and the following outcomes:
 - a. mortality at 30 days, 90 days and 1 year;
 - b. days alive and free of advanced respiratory support to 30 days;
 - c. number of treated infectious complications per patient; and

- d. health utility (EQ-5D-5L) at 90 days and 1 year?
2. For the outcomes of mortality at 30 days and infectious complications, does this relationship vary according to:
 - a. route of delivery (enteral versus parenteral);
 - b. body mass index (BMI);
 - c. modified NUTRIC score⁶?
3. In the event that the optimum dose of energy is found to be in the region of 20-25 kcal/kg/day, is there an association between the number of days taken to achieve this target and the outcomes specified in objective 1, above?

Case selection

All patients recruited to the CALORIES trial, excluding:

- patients that withdrew from the trial;
- patients missing baseline data for weight or height;
- patients missing data for dose of energy/protein received;
- patients that received less than 96 hours of nutritional support

For analysis of the relationship between dose and outcome by route of delivery, only patients that received at least 96 hours of nutritional support via their allocated route (enteral or parenteral) will be included.

Handling of missing data

For each outcome measure, patients with missing data for that outcome will be excluded, except for health utility, for which multiply imputed datasets generated for the primary analysis of the CALORIES trial will be used.

Exposures

The dose of energy received (kcal/kg/day) will be defined as the total amount of energy received via any route (including energy received from propofol infusions) divided by the actual or estimated weight of the patient divided by the duration of nutritional support (in days, or fractions of days) up to 120 hours following the start of nutritional support.

The dose of protein received (g/kg/day) will be defined as the total amount of protein received from enteral or parenteral nutrition divided by the actual or estimated weight of the

patient divided by the duration of nutritional support (in days, or fractions of days) up to 120 hours following the start of nutritional support.

Number of days to achieve target will be defined as the first calendar day (00:00-23:59) from randomisation (day 0) onwards on which the patient received an energy dose of at least 20 kcal/kg.

Outcomes

All outcome variables will be defined as in the primary analysis of the CALORIES trial.

Analysis

Characteristics of the cohort

Age *mean (SD)*

Gender *n (%)*

BMI *mean (SD)* and *n (%)* by categories of <18.5, 18.5-24.9, 25.0-29.9, 30.0-39.9 and ≥ 40.0

APACHE II score *mean (SD)*

ICNARC Physiology Score *mean (SD)*

SOFA score *mean (SD)*

Modified NUTRIC score *mean (SD)* and *n (%)* with a score of 5-9 (high risk)

[Notes on calculation of NUTRIC score: IL-6 is not available; only severe comorbidities as recorded for APACHE II are available, therefore 1 point will be assigned for any severe comorbidity rather than for 2 or more comorbidities]

Dose of energy received *median (IQR)*

Dose of protein received *median (IQR)*

Distributions and correlations

Histograms showing the distribution of energy dose, protein dose and BMI

Correlation between energy dose and protein dose (scatter plot with linear fit and R^2)

Modelling

The relationship between energy and protein dose (restricted cubic spline with 4 knots) and the outcome measures will be assessed both individually and mutually adjusted, provided the variance inflation factors from including both in the model simultaneously is less than 10. The relationships will be assessed using hierarchical regression models – logistic regression for binary outcomes (mortality at 30 days, 90 day and 1 year), linear regression for continuous

outcomes (days alive and free of advanced respiratory support to 30 days, health utility at 90 days and 1 year) and Poisson regression for count outcomes (number of treated infectious complications per patient). The dose of energy and protein will be included in the regression models as continuous, non-linear variables, modelled using restricted cubic splines with 4 knots (at the 5th, 35th, 65th and 95th percentiles of the distribution). The regression models will additionally be adjusted for:

- age (restricted cubic splines with 4 knots);
- gender (female vs male);
- BMI (<18.5, 18.5-24.9, 25.0-29.9, 30.0-39.9 and ≥40.0);
- Modified NUTRIC score; and
- random effect of site.

The regression models will use robust variance estimators, clustered by site. The Poisson regression models will use normally distributed random effects (rather than the default Gamma distribution) to allow calculation of the predicted number of events, marginal with respect to the random effect.

The results of the regression models will be displayed graphically using marginal predicted means, varying the values of energy and protein dose and with all other covariates held at their observed values in the dataset.

Subgroup effects of route of delivery (enteral vs parenteral), BMI (<18.5, 18.5-24.9, 25.0-29.9, 30.0-39.9 and ≥40.0) and Modified NUTRIC score (low vs high risk) for the outcomes of 30-day mortality and number of infectious complications will be evaluated by introducing interaction terms between the subgroup categories and energy/protein dose into the hierarchical regression models.

In the event that the optimum energy dose is in the region of 20-25 kcal/kg/day, the association between number of days to achieve target and the outcomes, adjusted for energy and protein dose, will be assessed by introducing an additional (linear) covariate for number of days to achieve target into the hierarchical regression models for all outcomes.

References

¹ Alberda C, Gramlich L, Jones N, Jeejeebhoy K, Day AG, Dhaliwal R, Heyland DK. The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study. *Intensive Care Med* 2009; 35:1728-37.

² Wei X, Day AG, Ouellette-Kuntz H, Heyland DK. The association between nutritional adequacy and long-term outcomes in critically ill patients requiring prolonged mechanical ventilation: a multicenter cohort study. *Crit Care Med* 2015; 43:1569-79.

³ Nicolo M, Heyland DK, Chittams J, Sammarco T, Compher C. Clinical outcomes related to protein delivery in a critically ill population: a multicenter multinational observation study. *JPEN J Parenter Enteral Nutr* 2016; 40:45-51.

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- ⁴ Casaer MP, Wilmer A, Hermens G, Wouters PJ, Mesotten D, Van den Berghe G. Role of disease and macronutrient dose in the randomized controlled EPaNIC trial: a post hoc analysis. *Am J Respir Crit Care Med* 2013; 187:247-55.
- ⁵ Harvey S, Parrott F, Harrison DA, Bear DE, Segaran E, Beale R, Bellington G, Leonard R, Mythen MG, Rowan KM; CALORIES Trial Investigators. Trial of the route of early nutritional support in critically ill adults. *N Engl J Med* 2014; 371:1673-84.
- ⁶ Rahman A, Hasan RM, Agarwala R, Martin C, Day AG, Heyland DK. Identifying critically-ill patients who will benefit most from nutritional therapy: Further validation of the “modified NUTRIC” nutritional risk assessment tool. *Clin Nutr* 2016; 35:158-62.