PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Impact of Early Low-Calorie Low-Protein versus Standard-Calorie Standard-Protein Feeding on Outcomes of Ventilated Adults with Shock: Design and Conduct of a Randomised, Controlled, Multicentre, Open-Label, Parallel-Group Trial (NUTRIREA-3)
AUTHORS	Reignier, Jean; Le Gouge, Amélie; Lascarrou, Jean-Baptiste; annane, djillali; Argaud, Laurent Argaud; Hourmant, Yannick; Asfar, Pierre; Badie, Julio; Nay, Mai-Anh; Botoc, Nicolae-Vlad; Brisard, Laurent; Bui, Hoang-Nam; Chatellier, Delphine; Chauvelot, Louis; Combes, Alain; Cracco, Christophe; Darmon, Michael; Das, Vincent; Debarre, Matthieu; Delbove, Agathe; Devaquet, Jérôme; Voicu, Sebastian; Aissaoui-Balanant, Nadia; Dumont, Louis-Marie; Oziel, Johanna; Gontier, Olivier; Groyer, Samuel; Guidet, Bertrand; Jaber, S.; Lambiotte, Fabien; Leroy, Christophe; Letocart, Philippe; Madeux, Benjamin; Maizel, Julien; Martinet, Olivier; Martino, Frédéric; Mercier, Emmanuelle; Mira, Jean-Paul; Nseir, Saad; Picard, Walter; Piton, G; Plantefeve, Gaetan; Quenot, Jean-Pierre; Renault, Anne; Guérin, Laurent; Richecoeur, Jack; Rigaud, Jean Philippe; Schneider, Francis; Silva, Daniel; Sirodot, Michel; Souweine, Bertrand; Reizine, Florian; Tamion, Fabienne; Terzi, Nicolas; Thévenin, Didier; Thiéry, Guillaume; Thieulot-Rolin, Nathalie; Timsit, Jean-François; Tinturier, François; Tirot, Patrice; Vanderlinden, Thierry; Vinatier, Isabelle; Vinsonneau, Christophe; Maugars, Diane; Giraudeau, Bruno

VERSION 1 – REVIEW

REVIEWER	Casaer, Michael UZ Leuven Campus Gasthuisberg Hospital Pharmacy
REVIEW RETURNED	14-Jan-2021

GENERAL COMMENTS	Jean Reignier and co-investigators provide a detailed protocol of the NUTRIREA-3 trial, evaluating low energy and protein intake versus standard intake in ventilated patients receiving vasopressors. The protocol is well written and methodologically sound, reflecting the important experience of the PI and the research group in setting up large multi-center RCT's in ICU. Hopefully, my comments can contribute to further improving the paper and in clarifying some issues, avoiding confusion. I have two major comments: - Why is the randomized intervention stopped and left at the discretion of the attending physician as soon the patient is weaned from the ventilator? I an era where post-extubation non-invasive respiratory support including high flow nasal oxygen gains importance, I wouldn't consider the removal of the endotracheal tube as the end of critical illness. So, nutritional management in

	patients at this stage remains an important question. Particularly as such patients rarely feed adequately by mouth due to muscle weakness, swallowing disorders, etcetera… Please explain the rationale for this choice. - In the statistics, some detail regarding how the time to event analyses will be conducted is missing for ICU-discharge (independency) and mortality. Will the authors rely on Kaplan Meier curves compared based on log-rank, Breslow, or other statistics? Or will these events be evaluated in an adjusted Cox proportional hazard analysis? In the latter case, could the authors define the variables that will be considered for adjustment as continuous or dichotomized parameter and how the decision will be taken to include them or not? Are there any predefined subgroups? This kind of detail is what makes pre-published protocols and analysis plans more informative than the information provided in the trial registries. (I consider this information crucial and thus selected "major revision" while all my other comments are minor issues) Some minor comments; Line 12 page 8 Abstract: Introduction “Recent data challenge the wisdom of providing standard amounts of calories and protein” I would suggest “Recent data challenge the appropriateness of providing standard amounts of calories and protein” Line 17, same page “key mechanism in muscle protection during critical illness.” I would suggest “key mechanism in safeguarding cellular integrity, among others in the muscle, during critical illness.” Page 14 line 24 “We used two strong patient-centered primary outcomes, i.e., 90-day mortality and ICU dependency, and we evaluated important secondary outcomes, including long-term function, in keeping with recommendations about studies on of nutritional support in critically ill patients.” Line 17 page 11 “Prescribing nutritional support in the critically ill is the result of a” shouldn’t that be “the prescription of nutritional support”? perhaps I’m wrong… Page 11 line 40 ““Recent data challenge the wisdom of providing standard amounts of calories and protein” I would suggest, again “Recent data challenge the appropriateness of providing standard amounts of calories and protein” Page 11 line 56 “muscle protection” too narrow “key mechanism in safeguarding cellular integrity, among others in the muscle, during critical illness.” Page 12 line 5 – 10. Consider discussing the Target RCT1 Page 14 line 19 “The designated feeding strategy will be initiated as soon as possible after randomization (in all patients, within 24 hours after intubation or ICU admission in patients with MV started before admission) and continued until extubation and withdrawal of vasoactive support, or death, or day 7, whichever occurs first” See my major comment, does critical illness and the need for nutritional support stop when a patient is extubated?

	Page 14 line 33 “based on body weight” the authors provide more detail in the next paragraph on how this weight is corrected in the obese and <18.5 BMI patients. Upon first reading, I thought weight would go into the calculation “as such” particularly problematic when Please refer to this important information in line 14 to avoid erroneous interpretations. Page 15 line 12 “Randomised controlled trials showed that feeding route during the acute phase had no impact on major clinical outcomes of critically ill patients (32, 33).” I think this should be “Randomized controlled trials showed that feeding route during the acute phase had no impact on major clinical outcomes of critically ill patients when iso-caloric nutrition was provided in both arms “(32, 33). This was also the conclusion from an older meta-analysis2 and is the crucial difference between NUTRIREA-2 & CALORIES versus EPaNIC, EAT-ICU or TICACOS-1. I also wonder whether this important reflection is not rather something to be discussed in the introduction? Page 15 line 56 “after extubation” vide supra Page 16 line 12 “Iso-osmotic iso-caloric normal-protein polymeric preparations are used during the first week, ….” Iso-osmotic and iso-caloric refers to same dose as in another group or another preparation, but here I don’t see this other group, iso-caloric to nutrition in the other participating centers? Certainly not iso-caloric to the other study arm? Please clarify. Page 17 nutritional management, glucose control will be left at the discretion of the attending physicians? Will the insulin doses and glucose metrics be registered and in how much detail? Will the eventual glucose control protocols in different centers be collected? I guess we all treat hyperglycemia at some point? Page 18 line 37 “Secondary outcomes: Daily mean values during the first week, throughout the time on IMV and from weaning off MV to readiness for ICU discharge of the following: number of calories (in Kcal) delivered enterally and/or parenterally ratio (as a %) of prescribed over delivered calories – Proportion of patients who achieved their calorie target from day 0 to day 7 – Daily mean values from day 0 to day 7 and during MV of the following: protein supply (g) given enterally and/or parenterally volume of fluids (in mL) received (daily mean from day 0 to day 7 and during MV)” I wouldn’t call these outcomes, they are part of the intervention so I would rather call them “operational parameters” or “study conduct or measures of protocol adherence…” Page 22 power calculation The anticipated impact on survival appears rather optimistic to me, the 1.5 day difference in time to ICU discharge alive is very reasonable. Page 24 Primary endpoints, see my general comments please provide some more information on the survival statistics to be applied for the time-to-event –analyses. Will they be adjusted (I think this is most appropriate for effect size estimates) which pre-randomization baseline characteristics will be considered and how will they be treated, continuous, dichotomized?

	Page 25 please provide some detail on the glucose metrics that will be collected and analyzed during the study intervention. 1. Chapman M, Peake SL, Bellomo R, et al. Energy-Dense versus Routine Enteral Nutrition in the Critically Ill. N Engl J Med 2018;379:1823-34. 2. Elke G, van Zanten AR, Lemieux M, et al. Enteral versus parenteral nutrition in critically ill patients: an updated systematic review and meta-analysis of randomized controlled trials. Crit Care 2016;20:117. I uploaded the same review report for your convenience in formated version

REVIEWER	Hoffman, Leah University of Oklahoma, Nutritional Sciences
REVIEW RETURNED	15-Feb-2021

GENERAL COMMENTS	This is clearly an excellent article detailing the protocol for the NUTRIREA-3 trial. This publication will answer many questions that would be raised in the minds of clinicians reading the subsequent paper with the results. The methodology throughout the trial is sound, both from a scientific perspective and from a realistic clinical perspective. There are only a few points for clarification I would like to see: -- Page 15/40, line 3 in describing the kilocalorie and protein goals for obesity and using a BMI of 30 -- Do you have a reference for this method, or is it clinical practices at the participating hospitals? I'm familiar with using a BMI of 25 as an ideal body weight and in calculations, but not 30. -- Page 15/50, line ~20 -- The attending team chooses the route to meet energy and protein goals. I suspect that the Standard group will require more use of parenteral nutrition in order to meet goals (based on the well-known and almost universal underfeeding via the enteral route that the vast majority of hospitals worldwide encounter). Do you anticipate this a priori, and do you plan to account for it in any way? -- Page 17/40, line 54 -- please clarify: enteral nutrition will NOT be stopped for diarrhea? You so elegantly described your protocol related to concerns about gastric residual volume; including similar details regarding diarrhea (another common reason that clinicians slow or stop enteral feeding) would be welcome. -- Page 18/40, line 17 -- Not a clarification, just a compliment on accounting not for actual date of ICU discharge but readiness for ICU discharge as an outcome. -- Page 21/40 -- I appreciate the inclusion of functional outcomes via the quality of life questionnaires as late follow-up with these patients. Do you plan to include any direct measures of muscle mass as an outcome? The introduction mentions autophagy as a potential mechanism to preserve muscle mass; including measurements of how muscle mass changes throughout the trial could provide additional data to support that hypothesis. Again, this is overall an excellent paper. I look forward to seeing it in print and even more so to the final results, which could have a major impact on how we feed critically ill patients in the intensive care unit.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Prof. Michael Casaer, UZ Leuven Campus Gasthuisberg Hospital Pharmacy

Comments to the Author:

Jean Reignier and co-investigators provide a detailed protocol of the NUTRIREA-3 trial, evaluating low energy and protein intake versus standard intake in ventilated patients receiving vasopressors. The protocol is well written and methodologically sound, reflecting the important experience of the PI and the research group in setting up large multi-center RCT's in ICU. Hopefully, my comments can contribute to further improving the paper and in clarifying some issues, avoiding confusion.

I have two major comments:

Why is the randomized intervention stopped and left at the discretion of the attending physician as soon the patient is weaned from the ventilator? I an era where post-extubation non-invasive respiratory support including high flow nasal oxygen gains importance, I wouldn't consider the removal of the endotracheal tube as the end of critical illness. So, nutritional management in patients at this stage remains an important question. Particularly as such patients rarely feed adequately by mouth due to muscle weakness, swallowing disorders, etcetera… Please explain the rationale for this choice.

Response: As stated in the manuscript, our goal was to focus on an intervention involving nutritional support during the acute phase of the critical illness. This focus on the acute phase is in accordance with the recent RCTs on nutritional support in the critically ill. However, the definition of the acute phase is unclear. In the recent European guidelines, the acute phase was defined as the first week of the ICU stay and was followed by the rehabilitation or late phase from day 8 onwards. This timeline does not take into account the course of the acute illness, which may resolve far more quickly. Thus, in the NUTRIREA3 trial, we use a clinical and more pragmatic definition of the acute phase as the period from intubation (or ICU admission in patients with MV started before admission) until extubation and withdrawal of vasoactive support, or day 7, whichever occurs first. ("Interventions"

section). A similar design and follow-up was used in the NUTRIREA2 trial. The randomised intervention is applied during the acute phase. In the current trial, the calorie target is increased to 30 Kcal/kg/d after the acute phase.

As stated in the introduction section of the manuscript, the trial focusses on a well-defined group of severely ill ICU patients requiring at least MV and vasoactive drugs. These patients typically have poor outcomes with long ICU stays, high frequencies of ICU-acquired weakness and infections, and high mortality. The randomised intervention is stopped only when the patient is weaned from the ventilator and from the vasoactive drugs before day 8. Such a rapidly favourable course is associated with a good functional and vital prognosis, even in patients previously admitted to the ICU for a severe acute illness requiring mechanical ventilation and vasopressor therapy. Imposing artificial nutrition and strict calorie and protein goals seems inappropriate for those patients. No data are available for such a strategy. This is why nutrition, and if necessary, nutritional support, are left at the discretion of the attending physician in the NUTRIREA3 study.

In the statistics, some detail regarding how the time to event analyses will be conducted is missing for ICU-discharge (independency) and mortality. Will the authors rely on Kaplan Meier curves compared based on log-rank, Breslow, or other statistics? Or will these events be evaluated in an adjusted Cox proportional hazard analysis? In the latter case, could the authors define the variables that will be considered for adjustment as continuous or dichotomized parameter and how the decision will be taken to include them or not? Are there any predefined subgroups? This kind of detail is what makes pre-published protocols and analysis plans more informative than the information provided in the trial registries. (I consider this information crucial and thus selected "major revision" while all my other comments are minor issues)

Response: No adjustment or subgroup analysis is planned. Time-to-event analyses will be performed using the Fine and Gray model. This information has been added to the manuscript (“Statistical analysis” section).

Some minor comments;

Line 12 page 8 Abstract: Introduction "Recent data challenge the wisdom of providing standard amounts of calories and protein" I would suggest "Recent data challenge the appropriateness of providing standard amounts of calories and protein"

Response: We agree with Professor Casaer and have modified the sentence as requested.

Line 17, same page "key mechanism in muscle protection during critical illness." I would suggest "key mechanism in safeguarding cellular integrity, among others in the muscle, during critical illness."

Response: The sentence has been modified as requested.

Page 14 line 24 "We used two strong patient-centered primary outcomes, i.e., 90-day mortality and ICU dependency, and we evaluated important secondary outcomes, including long-term function, in keeping with recommendations about studies on of nutritional support in critically ill patients."

Response: The mistakes have been corrected.

Line 17 page 11 "Prescribing nutritional support in the critically ill is the result of a" shouldn't that be "the prescription of nutritional support"? perhaps I'm wrong…

Response: The original sentence is correct.

Page 11 line 40 ""Recent data challenge the wisdom of providing standard amounts of calories and protein" I would suggest, again "Recent data challenge the appropriateness of providing standard amounts of calories and protein"

Response: The sentence has been modified as requested.

Page 11 line 56 “muscle protection” too narrow “key mechanism in safeguarding cellular integrity, among others in the muscle, during critical illness.”

Response: The sentence has been modified as requested.

Page 12 line 5 – 10. Consider discussing the Target RCT1

Response: The TARGET trial is now discussed in the revised manuscript.

Page 14 line 19 “The designated feeding strategy will be initiated as soon as possible after randomization (in all patients, within 24 hours after intubation or ICU admission in patients with MV started before admission) and continued until extubation and withdrawal of vasoactive support, or death, or day 7, whichever occurs first” See my major comment, does critical illness and the need for nutritional support stop when a patient is extubated?

Response: Please, see our response to the first major comment.

Page 14 line 33 “based on body weight” the authors provide more detail in the next paragraph on how this weight is corrected in the obese and <18.5 BMI patients. Upon first reading, I thought weight would go into the calculation “as such” particularly problematic when Please refer to this important information in line 14 to avoid erroneous interpretations.

Response: As requested by Prof. Casaer, the sentences about the calculation of calories and proteins goals have been transferred from the “Nutritional support protocol” section to the “Interventions” section.

Page 15 line 12 "Randomised controlled trials showed that feeding route during the acute phase had no impact on major clinical outcomes of critically ill patients (32, 33)." I think this should be "Randomized controlled trials showed that feeding route during the acute phase had no impact on major clinical outcomes of critically ill patients when iso-caloric nutrition was provided in both arms "(32, 33). This was also the conclusion from an older meta-analysis2 and is the crucial difference between NUTRIREA-2 & CALORIES versus EPaNIC, EAT-ICU or TICACOS-1.

I also wonder whether this important reflection is not rather something to be discussed in the introduction?

Response: The sentence has been modified as requested. We agree that the question of the route of feeding in the critically ill is still a matter of debate, despite the results of two large RCTs showing no impact of the enteral vs. the parenteral route on patient outcomes. However, this question is not the subject of the NUTRIREA3 trial, and the sentence "Randomised controlled trials…in both arms" is intended simply to explain why "physicians will be free, each day, to choose the best feeding route, according to clinical considerations, to ensure that the calorie target is achieved". Thus, we prefer to leave the sentence in this section.

Page 15 line 56 "after extubation" vide supra

Response: Please, see our response to the first major comment.

Page 16 line 12 "Iso-osmotic iso-caloric normal-protein polymeric preparations are used during the first week, …." Iso-osmotic and iso-caloric refers to same dose as in another group or another preparation, but here I don't see this other group, iso-caloric to nutrition in the other participating centers? Certainly not iso-caloric to the other study arm? Please clarify.

Response: These iso-osmotic iso-caloric normal-protein polymeric solutions are used in both groups. This point is now clarified in the revised manuscript. The sentence is "Iso-osmotic iso-caloric normal-protein polymeric preparations are used during the first week in both groups…". The

difference in calorie and protein intake between the two arms is achieved by administering different amounts of the same preparation.

Page 17 nutritional management, glucose control will be left at the discretion of the attending physicians? Will the insulin doses and glucose metrics be registered and in how much detail? Will the eventual glucose control protocols in different centers be collected? I guess we all treat hyperglycemia at some point?

Response: We agree with Prof. Casaer that blood glucose control is an important issue in the care of the critically ill. A section entitled “Blood glucose control” has been added in the revised manuscript, page 18.

Page 18 line 37 “Secondary outcomes: Daily mean values during the first week, throughout the time on IMV and from weaning off MV to readiness for ICU discharge of the following: number of calories (in Kcal) delivered enterally and/or parenterally ratio (as a %) of prescribed over delivered calories – Proportion of patients who achieved their calorie target from day 0 to day 7 – Daily mean values from day 0 to day 7 and during MV of the following: protein supply (g) given enterally and/or parenterally volume of fluids (in mL) received (daily mean from day 0 to day 7 and during MV)”

I wouldn’t call these outcomes, they are part of the intervention so I would rather call them “operational parameters” or “study conduct or measures of protocol adherence…”

Response: We respectfully disagree with Prof. Casaer here. The points listed here are *observed* values, as opposed to values prescribed by the *protocol*, i.e., as opposed to the description of the intervention. Not all patients will be able to receive the desired amount of calories, for instance. These variables therefore constitute outcomes.

Page 22 power calculation. The anticipated impact on survival appears rather optimistic to me, the 1.5 day difference in time to ICU discharge alive is very reasonable.

Response: The 43% day-90 mortality rate used for the standard group was reported in the NUTRIREA 2 trial that used similar inclusion/exclusion criteria. A 5% absolute decrease in day-90 mortality (from 43% in the standard group to 38% in the low group) is quite low and seems realistic. Please, note that an 8% absolute decrease (from 25% to 17%) was used in the PERMIT trial to estimate the sample size.

Page 24 Primary endpoints, see my general comments please provide some more information on the survival statistics to be applied for the time-to-event –analyses. Will they be adjusted (I think this is most appropriate for effect size estimates) which pre-randomization baseline characteristics will be considered and how will they be treated, continuous, dichotomized?

Response: Additional details on the statistics are now provided in the revised manuscript.

Page 25 please provide some detail on the glucose metrics that will be collected and analyzed during the study intervention.

Response: A “Blood glucose section” has been added to the revised manuscript. It states that the monitoring and blood glucose-control and insulin-therapy protocols used in each centre will be followed. Thus, we will not impose a timeline for blood glucose monitoring. As stated in the “secondary outcomes” section, outcomes involving blood glucose control will be “changes in daily maximum blood glucose levels, proportion of patients with hypoglycaemia, and total insulin dose received daily from day 0 to day 7”. Additionally, we will compare the number of days on insulin treatment from day 0 to readiness for ICU discharge between the two groups.

1. Chapman M, Peake SL, Bellomo R, et al. Energy-Dense versus Routine Enteral Nutrition in the Critically Ill. N Engl J Med 2018;379:1823-34.

2. Elke G, van Zanten AR, Lemieux M, et al. Enteral versus parenteral nutrition in critically ill patients: an updated systematic review and meta-analysis of randomized controlled trials. Crit Care 2016;20:117.

I uploaded the same review report for your convenience in formated version

Reviewer: 2

Dr. Leah Hoffman, University of Oklahoma

Comments to the Author:

This is clearly an excellent article detailing the protocol for the NUTRIREA-3 trial. This publication will answer many questions that would be raised in the minds of clinicians reading the subsequent paper with the results. The methodology throughout the trial is sound, both from a scientific perspective and from a realistic clinical perspective. There are only a few points for clarification I would like to see:

Page 15/40, line 3 in describing the kilocalorie and protein goals for obesity and using a BMI of 30. Do you have a reference for this method, or is it clinical practices at the participating hospitals? I'm familiar with using a BMI of 25 as an ideal body weight and in calculations, but not 30.

Response: We are pleased that Dr Hoffman found merit in our work. We used the World Health Organization (WHO) definition of obesity and overweight: “body mass index (BMI) over 25 is considered overweight, and over 30 is obese” (https://www.who.int/health-topics/obesity#tab=tab_1). The 30 cut-off value was used in previous studies by the NUTRIREA group (Reignier, Lancet 2018; Reignier, JAMA 2013) and in RCTs by other groups (Arabi, NEJM 2015).

Page 15/50, line ~20 -- The attending team chooses the route to meet energy and protein goals. I suspect that the Standard group will require more use of parenteral nutrition in order to meet goals (based on the well-known and almost universal underfeeding via the enteral route that the vast majority of hospitals worldwide encounter). Do you anticipate this a priori, and do you plan to account for it in any way?

Response: As stated in the manuscript, the attending team is left free to choose the feeding route, given that two large RCTs showed no difference in outcomes of patients fed via the enteral route vs. the parenteral route. We are confident that the choice of the feeding route will not influence the results of the trial, notably our primary outcomes of day-90 mortality and time to ICU discharge readiness. Thus, we did not plan for a specific statistical analysis of this point.

Page 17/40, line 54 -- please clarify: enteral nutrition will NOT be stopped for diarrhea? You so elegantly described your protocol related to concerns about gastric residual volume; including similar details regarding diarrhea (another common reason that clinicians slow or stop enteral feeding) would be welcome.

Response: We apologise for the lack of clarity and have added information on this point. If stopping prokinetics and any other agents that accelerate bowel transit is ineffective and a stool test for *Clostridium difficile* toxin is negative, the enteral preparation is changed. If the diarrhoea persists nevertheless, the rate of enteral feeding is decreased until the diarrhoea resolves then increased gradually to the desired level.

Page 18/40, line 17 - Not a clarification, just a compliment on accounting not for actual date of ICU discharge but readiness for ICU discharge as an outcome.

Response: Thank you.

Page 21/40 - I appreciate the inclusion of functional outcomes via the quality of life questionnaires as late follow-up with these patients. Do you plan to include any direct measures of muscle mass as an outcome? The introduction mentions autophagy as a potential mechanism to preserve muscle mass; including measurements of how muscle mass changes throughout the trial could provide additional data to support that hypothesis.

Response: We agree that direct measures of muscle mass would have been interesting. However, we did not plan to include such measurements. Overall, we are confident that the primary and secondary outcomes will provide highly reliable data that will permit definitive conclusions, thereby improving the care of the critically ill. Moreover, the trial protocol in its current version already involves multiple measurements and a massive amount of work for all those conducting the trial.

Again, this is overall an excellent paper. I look forward to seeing it in print and even more so to the final results, which could have a major impact on how we feed critically ill patients in the intensive care unit.

Response: Thank you.

VERSION 2 – REVIEW

REVIEWER	Casaer, Michael UZ Leuven Campus Gasthuisberg Hospital Pharmacy
REVIEW RETURNED	02-Apr-2021

GENERAL COMMENTS	I thank the authors for the consideration given to my comments! For evaluation of the impact of the intervention on glucose control and glucose homeostasis I would suggest to compare blood glucose concentrations sampled at a fixed hour on every study day in both arms (e.g. average daily morning glucose on day 1 to 14 by study arm).