Confidential Study Protocol

The Effect of Higher Protein Dosing in Critically Ill Patients: A Multicenter Registry-based Randomized Trial

The EFFORT Trial and EFFORT US sub-study

Clinical trials.gov ID #~~NCT03160547~~

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1.0 THE NEED FOR A TRIAL

1.1 An overview of the problem to be addressed

Our prior work has demonstrated that increased provision of protein and calories to critically ill patients is associated with reduced infectious complications, more ventilator-free days, improved long-term physical recovery, and lower mortality. There is an argument to be made, from basic physiologic principles, animal studies, and clinical observations, that it is probably more important to provide adequate protein than calories. After a careful review of the published (albeit weak) evidence, experts concluded that critically ill patients should receive 2.0-2.5 g/kg/day of protein.[1] Receiving at least 80% of what is prescribed is associated with more optimal outcomes.[2]

Despite these recommendations, however, recent review of current International Nutrition Survey (INS, a registry with data collection done by volunteers around the world) data suggest that protein in critically ill patients is grossly under-prescribed and under-delivered. In 2014, on average, patients were prescribed 94 grams of protein per day or approximately 1.3 g/kg/day (interquartile range, 1.0-1.5 grams/kg/day, overall range, 0.5-3.8 g/kg/day).[3] Overall, patients treated at participating ICUs received approximately 55% of prescribed protein requirements with site averages ranging from 15-101%. We believe that one of the reasons that patients are under-dosed and protein is under-delivered is the lack of strong evidence supporting this treatment recommendation. We further believe that answering this question *re: the optimal dose of protein or the effect of high amounts of protein provided to critically ill patients* represents one of the most important research questions for our field today. Developing a pathway to obtain higher quality evidence to support the outcomes of higher doses of protein (should) represent both a top priority and challenge for our scientific community.

A registry-based randomized controlled trial (RRCT), which capitalizes on data collected routinely for other reasons, may offer our community a pathway forward to answer this important question.[4] With this approach, patients who are entered into an existing registry and meet pre-specified enrollment criteria can be randomized to a treatment; the screening, data capture, and outcomes measures are already collected by the existing registry. This strategy allows investigators to control costs, focus on patient recruitment, and benefit from the power of randomization to draw the strongest possible conclusions about causation. One notable example of the RRCT method is the TASTE trial examining the use of thrombus aspiration in ST-segment elevation myocardial infarction.[5] This study benefited from massive cost savings (relative to traditional RCT) and rapid recruitment, with investigators enrolling more than 7000 patients from 29 sites – about 60% of those who were eligible – in less than three years. By contrast, the conventionally ran TOTAL RCT asking the same question needed three times as many study sites and an extra year to enroll some 10,700 patients.[6] Reassuringly,

both TASTE and TOTAL arrived at the same conclusion, namely that thrombus aspiration did not confer a significant benefit.

We plan to combine the International Nutrition Survey with the power of randomization to accomplish this goal. The purpose of the current proposal is to provide the rationale for a large clinical trial where 4000 nutritionally-high risk patients are randomized to 2 different protein doses that demonstrate the value of higher protein supplementation in this type of patient, using the INS as a type of RRCT: The Effect of Higher Protein Dosing in Critically Ill Patients or the EFFORT Trial. In addition, we plan a sub-study where some patients enrolled in the parent EFFORT trial will also be included in a sub-study that uses ultrasound (US) of the quadriceps to evaluate the effect of these nutritional practices on muscle mass.

1.2 What are the principal research questions to be addressed by the EFFORT Trial?

Primary research question:

In critically ill patients with nutrition 'risk factors', what is the effect of prescribing a higher dose (≥2.2 grams/kg/day) of protein/amino acid administration compared to a low group prescribed ≤1.2 gram/kg/day on 60 day mortality?

Secondary Research questions:

In critically ill patients with nutrition 'risk factors', what is the effect of prescribing a higher dose (≥2.2 grams/kg/day) of protein/amino acid administration compared to patients prescribed ≤1.2 gram/kg/day on time to discharge alive from hospital?

In critically ill patients with nutrition 'risk factors', what is the effect of prescribing a higher dose (≥2.2 grams/kg/day) of protein/amino acid administration compared to patients prescribed ≤1.2 gram/kg/day on muscle quality and quantity measured by US of quadriceps?

Overall Hypothesis: Compared to receiving ~~lower~~ the usual dose of protein/amino acids, the administration of a higher dose of protein/amino acids (a consequence of having a higher prescription) to nutritionally high-risk critically ill patients will be associated with greater muscle mass, improved survival and a quicker rate of recovery.

1.3 Background Rationale and Systematic Review of the Literature

Critically ill patients receiving mechanical ventilation are at high risk of dying or developing complications that delay their recovery. Patients who develop sepsis, multi-organ failure, or require prolonged mechanical ventilation or immobility are at particular risk for developing weakness and other

neuromuscular abnormalities.[7,8] These impairments are associated with delayed liberation from mechanical ventilation, extended ICU and hospital stays, more healthcare-related hospital costs, a higher risk of death, and impaired physical functioning and quality of life in the months following an ICU admission.[7-9] These observations speak to the importance of developing new strategies to aid in the physical recovery of critically ill patients. Emerging evidence suggests that exogenous protein/amino acid supplementation has the potential to favorably impact protein balance and improve the recovery of critically ill patients. After a careful review of the published evidence, experts concluded that critically ill patients should receive up to 2.0-2.5 grams/kg/day of protein and receiving at least 80% of the protein that is prescribed is associated with optimal outcomes.[1,2]

Current Practice

How much are they actually receiving? In 2014, we conducted an International Nutrition Survey (INS) of actual clinical practice in 187 ICUs around the world involving almost 4000 patients (see Table 1). The methodology of this survey is published elsewhere.[10] In 2014, these survey data clearly demonstrated that ICU patients worldwide are receiving nowhere near current protein recommendations. On average, patients were prescribed 94 grams of protein per day or approximately 1.3 grams/kg/day (interquartile range, 1.0-1.5 grams/kg/day, overall range, 0.5-3.8 grams/kg/day). Even within a site, we observed tremendous variability in the protein prescription. Median prescription within a site was 1.2 gram/kg/day but the range went from 0.86 to 2.6. Overall, patients from these participating ICUs received approximately 55% of prescribed protein requirements with site averages ranging from 15-101%. When reviewing individual sites, 11 sites (5.9%) averaged providing more than 80% of prescribed protein amounts in all included patients and 13 sites (7.3%) of the 179 sites with high nutritional risk patients as determined by the NUTrition Risk in the Critically Ill score (NUTRIC, explained below) managed to provide more than 80% of prescribed amounts of protein to these high-risk patients. At a patient level, 634 (16.1%) of patients received more than 80% of prescribed protein amounts and only 296 (16.3%) of high NUTRIC Score patients received more than 80% of prescribed amount. Note that the percentage of patients receiving 80% of prescribed protein is the same in all patients and in nutritionally high-risk patients suggesting that practitioners are not discriminating between low and high-risk patients.

Overall, protein delivery was low with the majority of protein delivered coming from enteral nutrition (EN) formulas (82.5%), an additional 11.5% coming from parenteral amino acid sources and very little coming from enteral protein supplements (5.9%) or IV amino acids alone without IV glucose and/or lipids (13 patients, 0.1%). Of note, parenteral nutrition (PN) was used in only 14.2% of included patients, enteral protein supplements were used in only 21.0% of patients, and only 7 sites used a feeding protocol that optimized the delivery of EN (i.e., PEP uP Protocol). Is current practice providing adequate amounts of protein to critically ill patients?

Statistical analysis of the same INS database, as well as other existing nutritional databases, revealed a relationship between increased nutrition intake (either 30 grams/day more of protein and/or 1000 more calories per day) and improved clinical outcomes. For example, we have shown that for an additional 30 grams of protein per day or 1000 calories per day, critically ill patients have reduced infectious complications, shorter duration of mechanical ventilation, and reduced mortality.[2,11,12] Admittedly, the clinical inference we can make from these observational data is weak. But in the absence of stronger evidence from randomized trials, it is sufficient to inform clinical practice.

Some of the most exciting recent developments in the world of critical care nutrition are the emerging evidences that our nutritional practices may actually impact the physical recovery of critically ill patients. A recent study found that intravenous (IV) amino acids in ICU patients improved protein balance and stimulated an anabolic response.[13] This suggests that our nutritional strategies may be used to preserve muscle mass and muscle function although data supporting this assertion is just accumulating. Such data include a small RCT demonstrating that greater protein intake is associated with improved pulmonary function in ICU patients with chronic obstructive pulmonary disease (COPD).[14] In addition, Heyland and colleagues conducted a long-term follow up study of patients enrolled in a randomized trial and documented their physical function using the Short-form 36 health status measure at 3 and 6 months.[15] They demonstrated that for every 25% increase in nutritional intake, surviving patients had a higher physical function or better physical recovery that was statistically significant at 3 months. At 6 months, the improvements with better nutritional intake were still present and clinically important but lost statistical significance.

In another recent analysis using the same INS data, we demonstrated that meeting protein requirements seems to be more important than meeting caloric requirements. When we control for caloric intake, we still see a significant reduction in associated mortality when more than 80% of protein requirements are delivered compared to less than 80% (Odds Ratio [OR] for 60 day mortality, 0.68 and 95% Confidence Intervals [CI]: 0.50, 0.91). In contrast, when we control for protein administration, there is no incremental effect of increased caloric administration (OR 0.89; 95% CI 0.71, 1.12). Whilst the inference is weak from this statistical modelling, it is consistent with other observational studies that show an association between protein optimization and survival, but a negative or absent effect of caloric intake.[16,17]

In contrast to the prevailing data, some observational studies have reported that adverse patient outcomes were associated with higher protein intake. In an elegant cohort study that carefully examined muscle outcomes using imaging techniques, Puthucheary and colleagues concluded that increased protein delivery was associated with increased muscle wasting.[18] In a post-hoc analysis of The Early vs. Late PN trial[19,20], investigators showed an association with increased protein intake and lower likelihood of early ICU discharge.[20] These investigators go on to postulate the mechanism of harm, that

exogenous protein inhibits autophagy, a key cell survival strategy and recommend systematic underfeeding for the first 7 days of critical illness[21], including publishing such statements in high profile journals, such as the New England Journal of Medicine.[22] Finally, others have published an additional post-hoc analysis of a small randomized trial of aggressive nutritional interventions compared to usual care and demonstrated that the amount of protein received in the first week was associated with a significant increased risk of death.[23] Whilst these observations are hypothesis-generating analyses, they are significant in that they suggest a significant harm associated with increased protein and further contribute to the uncertainty about the role of protein in critical illness.

What do the RCTs demonstrate?

As part of our ongoing clinical practice guidelines effort, we systematically review the literature since 1980 looking for all RCTs related to critical care nutrition topics. To date, the data set is sparse. There are only 5 RCTs of ICU patients randomized to high versus ~~a lower~~ the usual protein intake. These trials are summarized in Table 1 in Appendix 1. The trials vary in sample size (20-470), methodological quality (7-10), year of publication (1985-2016) and the outcomes assessed. Because of the heterogeneity of outcome assessment and incomplete data sets, we were only able to aggregate the effect of higher protein dosing on mortality (Risk Ratio 0.89, 95%CI 0.66-1.19, P=0.42, see Figure 1 in Appendix 1). Thus the RCTs in the field, which are few and of varying quality and significance, do not settle the controversy about the optimal role of protein delivery.

Summary of Background Trials to Date

Despite provocative results from these observational analyses, and the intuitive nature of the hypothesis related to supporting metabolism with adequate nutritional substrates, large-scale randomized trials examining the effect of increased enteral nutrition (EN) intake have not provided supportive evidence. Why might that be? First, these trials have focused on increased amounts of calories, not protein. Protein dose was either kept the same[24] or not reported[25] but regardless, prescribed amounts were well below recommended amounts noted above. Second, not all clinically important outcomes were reported. Short-term mortality may not be the best outcome used to evaluate the effect of increased protein administration. In fact, we posit that measures of muscle mass or function or patient-based performance measures (such as the 6 minute walk test) may be more sensitive to differential amounts of protein intake. Of note, the EDEN study compared goal feeding with trophic feeding, and demonstrated no difference in short term outcomes; however, better fed patients had a trend towards improvements in long-term physical functional performance (6 minute walk test) at one year.[26] A large scale trial of supplemental parenteral nutrition in the context of a relative contraindication to enteral nutrition also showed a significant improvement in 60-day quality of life.[27] Yet, a large scale trial of IV amino acids infusing up to 2.0 gram/kg/day in over 400 ICU patients did not

result in any impact in patient-reported outcomes (mortality or quality of life).[28] How do we reconcile these conflicting observations?

Nutrition Risk Assessment in the Critically Ill

We propose that the conflict between observational and interventional studies can, in part, be resolved using our nascent understanding of nutrition risk assessment in the critically ill. Large-scale RCTs may have failed to demonstrate an impact of different amounts of nutrition intake because they enroll heterogeneous patient populations of varying nutritional risk, not all of whom will respond to optimal nutrition intake. We posit that not all critically ill patients are the same in terms of their nutritional risk. The evidence for this assertion comes from studies that demonstrate a differential treatment effect of artificial nutrition in different subgroups of ICU patients.[11,29,30]

So how do we begin to approach determining 'nutritional risk' in the critical care setting? Conceptually, nutrition status in ICU patients will be a function of both undernourishment and inflammation, both of which occur in the acute and chronic setting. Using this conceptual model, we developed and validated the NUTRIC score which was designed to identify critically ill patients that would have the greatest benefit from optimizing nutrition intake.[31] The NUTRIC score considers the patient's age, Acute Physiology And Chronic Health Evaluation (APACHE) II Score, Sequential Organ Failure Assessment (SOFA) Score, number of comorbidities, time in hospital prior to ICU admission, and interleukin-6 levels in developing an understanding of which patients will benefit the most from artificial nutrition therapy (See Table 2). The NUTRIC score is also now validated without the IL-6 level.[32] In three distinct analyses from three separate databases, we have shown that patients with high NUTRIC scores are less likely to die if they received closer-to-goal calories or protein, when compared to low NUTRIC score patients where there is no relationship between nutrition intake and outcome.[31-33] In addition, the NUTRIC score has been validated by independent investigators in Asian, Brazilian and Portuguese populations.[34-36] In contrast, Arabi and colleagues recently published a post-hoc analysis of the PERMIT trial, where patients were randomized to different levels of caloric intake and they analyzed the effect with high vs. low NUTRIC groups of patients.[24,37] Consistent with the overall results of the PERMIT trial[24], they did not demonstrate any differential effect of caloric intake in high vs. low NUTRIC patients. While the analysis was underpowered (as evidenced by very wide confidence intervals around point estimates), we point out that protein intake was the same in all patient groups and as noted above, protein intake is probably more important than caloric intake.

Clearly definitive proof from prospective RCTs evaluating different levels of protein intake in nutritionally high-risk patients is lacking. Moreover, based on the arguments for and against higher dose of protein administration, there is clinical equipoise or uncertainty about the optimal dose of protein in

ICU patients. Hence, we believe a trial, such as the EFFORT trial, that evaluates the effect of high protein intake in high nutritional risk critically ill patients is warranted.

US of Quadriceps

Ultrasonography is an accessible, non-invasive, portable and user-friendly tool that is gaining popularity in the ICU and can be used to quantify structural and physical characteristics of skeletal muscle at the bedside. Diverse ultrasound protocols have been developed and applied in an ICU setting to quantify muscle thickness, cross sectional area of the rectus femoris, and other measures of muscle quality (echogenicity, pennation angle, fiber length).[38] These measures have largely been shown to be reliable in critically ill patient populations and have some degree of validity as they predict for total body skeletal muscle and more distal functional outcomes.[39-41] In this trial, we will use an US protocol that we have developed and are using in our other research projects that can be found on our website, www.criticalcarenutrition.com/EFFORT. These measures will be taken locally at baseline (within 24 hrs of randomization), ~~day~~ 10 days post randomization and just prior to hospital discharge and sent securely via the internet to a central storage facility where they will be read by experts.

1.4 How will the results of this trial be used?

Positive, neutral, or negative, the results of the EFFORT study will inform the clinical practice in ICU settings around the world. If positive, because of the pragmatic, multicentre nature of this trial, results will be broadly applicable to all critically ill patients worldwide. If the results are negative, we need to ensure that patients no longer receive high-dose protein/amino acid admixtures. If the trials are neutral or show no overall effect on mortality or time-to-discharge alive, this will prompt our clinical research community to explore the effect of high protein on specific subpopulations or on other outcomes (such as functional outcomes).

As it relates to critical care nutrition practice in general, we have a long history of practice-changing initiatives. We have a process of synthesizing (in the form of evidence-based clinical practice guidelines[42]) and disseminating best practice ideas (in the form of web-based repository of tools and information [see www.criticalcarenutrition.com]). In addition, we have conducted several large cluster RCTs[43-45] to introduce system-changing practices in ICUs in North America and several large scale quality improvement audits of practice to define current practice.[46,47]

Over the past several years, we have discussed this program of research with leaders of the American Society of Parenteral and Enteral Nutrition (ASPEN) and this specific protocol at the annual Clinical Nutrition Week with society leaders, researchers, and the clinical nutrition community at large. We have formally partnered with ASPEN to further facilitate both our recruitment initiatives and,

importantly, our knowledge translation initiatives. These efforts will increase the likelihood of the uptake of EFFORT results across the world.

2.0 THE PROPOSED TRIAL

2.1 What is the proposed trial design?

We propose a large, multicenter, pragmatic, volunteer-driven, registry-based, patient randomized, clinical trial of 4000 nutritionally high-risk critically ill patients. Given the large sample size across numerous participating units, we have adopted a pragmatic philosophy in developing this trial protocol.

2.2 What are the planned trial interventions?

Currently, protein prescriptions for critically ill patients range from 0.5-3.8 g/kg/d and at a site level, from 0.8-2.6 gm/kg/day. There is an insufficient evidentiary basis to establish which level of protein administration is right for which patient population. We will take usual practices and create 2 groups randomizing eligible patients to a ~~lower~~ usual prescription (≤1.2 g/kg/d) or to a higher prescribed protein/amino acid intake (≥2.2 g/kg/d). In both groups, targets will be set using pre-ICU dry actual weight. For patients with BMI >30, ideal body weight based on a BMI of 25 will be used.

Moreover, although this trial is not about caloric dose, we want to encourage participating clinicians to be conservative in meeting energy targets and avoid overfeeding. Caloric goals should be the same in both groups. We will endorse the guidelines for energy targets set forth by ASPEN/SCCM, especially as it pertains to the obese patient.[48] For non-obese patients, we suggest that their caloric prescription be around 20-25 kcal/kg/day using a simple weight based formula. If the site chooses to use more sophisticated equations or indirect calorimetry, that is permissible. For obese patients, if indirect calorimetry is used, the goal of the nutritional prescription should be to provide energy not to exceed 65%–70% of measured requirements. If indirect calorimetry is unavailable or not used, consistent with the American guidelines, we suggest using the weight-based equation 11–14 kcal/kg actual body weight per day for patients with BMI in the range of 30–50 and 22–25 kcal/kg ideal body weight per day for patients with BMI >50.

In both groups, targets will be achieved through any combination of enteral nutrition (high protein content in high group if available), protein supplements, and parenteral nutrition or amino acids only (as clinically available). The only difference between the 2 groups is the protein targets that are set. Similar efforts should be used in both groups to achieve at least 80% of these targets. The remainder of care provided to eligible patients will be at the discretion of ICU providers.

2.3 What are the proposed arrangements for allocating participants to trial groups?

Patients will be screened, evaluated, and randomized into this trial within 96 hours of admission to the ICU. We will apply for a waiver of consent (see below) or in those ICUs where informed consent is required, this will be obtained within 96 hours following admission and prior to randomization. The site representative[1] will log on to the web-based randomization system at the Clinical Evaluation Research Unit (http://www.ceru.ca/) at Kingston General Hospital to randomize patients. The system will confirm eligibility prior to allowing randomization. The system will then provide the site representative with the treatment assignment (either low dose protein group or high dose protein group) along with a reminder of the caloric targets to be used in this trial. The randomization system, which has proven reliable in several prior RCTs, has a robust audit trail, and will maintain concealment of future allocations.

The randomization system will use a computer generated randomization schedule allocating patients 1:1 to either low dose or high dose protein by the method of permuted blocks of random undisclosed size within strata. Randomization will be stratified by site. Given the large pragmatic nature of the trial, we will not stratify by additional factors.

2.4 What are the proposed methods for protecting against other sources of bias?

Given the nature of this pragmatic trial, it will not be possible to blind clinicians with the exception that future allocations will be concealed, as explained above. However, we expect patients to be unaware of their treatment assignment. Consistent with the pragmatic stance of this protocol and, in an effort to maximize generalizability of the trials' findings, we will not make efforts to standardize other key co-interventions aside from providing guidance on caloric dosing. However, we will capture key nutrition process of care issues in our minimalistic data collection strategies (See Section 2.7).

2.5 What are the planned Inclusion/Exclusion criteria?

We plan to enroll 4000 critically ill mechanically ventilated adult patients (≥18 years old) expected to remain mechanically ventilated for an additional 48 hours from screening and have one or more of the following risk factors that make them at high nutritional risk:

1. Low (≤25) or High BMI (≥35)

[1] We use this term "site representative" to represent the clinician taking responsibility for enrolling this patient and doing their nutritional assessment and prescription. In most settings, this will be a dietitian but in some setting this could be a physician or a nurse.

2. Moderate to severe malnutrition (as defined by local assessments). We will document the means by which sites are making this determination and capture the elements of the assessment (history of weight loss, history of reduced oral intake, etc.).

3. Frailty (Clinical Frailty Scale 5 or more from proxy)

4. Sarcopenia- (SARC-F score of 4 or more from proxy)

5. From point of screening, projected duration of mechanical ventilation >4 days

We considered using the NUTRIC score as an entry criteria but it is difficult to use 'real –time' and would be a barrier to enrollment. Hence, we will collect the data to calculate a NUTRIC score retrospectively and conduct an *a priori* subgroup analysis on high vs. low NUTRIC patients. Extremes of BMI[11], moderate-severe malnutrition (as defined by nutrition history variables[49], Subjective Global Assessment[50] , or other standardly accepted tools), and prolong ICU stay[51] are well known additional clinical characteristics that place a patient at 'higher' nutritional risk. In addition, there is emerging literature that patients with low muscle mass, or sarcopenia, may be an additional high risk patient population.[52] However, it is currently impractical to do body compositional analysis of mechanically ventilated critically ill patients and bed-side imaging techniques may not have sufficient reliability or validity.[40] Nevertheless, there is a questionnaire that can be used to define sarcopenia[53] and another questionnaire used to identify frailty (the Clinical Frailty Scale[54]), which correlates with low muscularity or sarcopenia. Both of these questionnaires can be answered by proxies at baseline in just a few minutes. We will capture the presence or absence of all of these nutritional risk variables but to be eligible, patients must have at least one present at baseline.

We considered whether to include or exclude various subgroups of patients who might have higher protein requirements (renal failure, burns, trauma, obesity, for example) or lower requirements (liver disease, older patients, for example) but since the evidence for dosing these subpopulations is uncertain and provider beliefs on what is best are variable, we reasoned to not exclude them but to allow participating clinicians to exclude any patient they feel would be possibly harmed if they were randomized to a high or ~~lower~~ usual dose of protein (in other words, where clinical equipoise does not exist). Additional exclusion criteria and the reason for them are outlined in the Table below. Clinicians at participating sites will review these eligibility criteria before enrolling patients into the trial.

Table 1. Inclusion and Exclusion Criteria for Study Entry

Inclusion Criteria	Exclusion Criteria	Rationale for Exclusion
1. ≥18 years old	1. >96 continuous hours of mechanical ventilation before screening	Intervention is likely most effective when delivered early

2. Nutritionally 'high-risk" (meeting one of above criteria) 3. Requiring mechanical ventilation with actual or expected total duration of mechanical ventilation >48 hours		
	2. Expected death or withdrawal of life-sustaining treatments within 7 days from screening	Patients unlikely to receive benefit
	3. Pregnant	Unknown effects on fetus
	4. The responsible clinician feels that the patient either needs low or high protein	Uncertainty doesn't exist; patient safety issues
	5. Patient requires parenteral nutrition only and site does not have products to reach the high protein dose group.	Site will be unable to reach high protein dose prescription.

2.6 What is the proposed duration of treatment period?

Patients will remain on the assigned study intervention for the entire duration of their ICU stay. If enrolled patients leave the ICU and return later during that hospitalization, the same treatment group will be applied.

2.7 Data Collection

As per our usual practices for the INS, we will use a secure web-based data collection tool to capture all relevant de-identified data. Site representatives will be asked to enter the characteristics of their hospital and ICU plus general aspects of nutrition practice (e.g. use of feeding protocol or algorithms). For randomized patients, they will be asked to extract data on the personal characteristics and clinical condition of patients from the patient charts. These data points include: admission category (surgical vs. medical), diagnosis, comorbidities, sex, age, height, weight, baseline APACHE II score, SOFA score. In addition, we will extract data on the nutrition care provided such as: nutrition prescription (protein and calories), recent weight loss or food intake changes, type of nutrition, received, amount of nutrition received (protein and calories), blood sugar levels, insulin total units/day lowest phosphate level, highest triglycerides, urea and creatinine, use of pro-kinetics, and use of supplements. This daily data will be for 12 days except protein intake, which will continue for duration of ICU stay (maximum of 28 days) or until death or transition to oral feeds. Finally, duration of mechanical ventilation, length of ICU and hospital stay, ICU readmissions, and hospital mortality will also be recorded.

2.8 What is the proposed duration of follow-up?

As per usual clinical routines, patient clinical status will be monitored daily during the ICU stay. Once discharged from intensive care unit, patients will no longer be followed daily but hospital

outcomes will be abstracted from the chart. The maximal duration of follow up for patients in this trial is 60 days or hospital discharge, whichever comes first. For patients remaining in hospital at 60 days, outcomes will be censored at that point.

2.9 What are the proposed primary and secondary outcome measures?

The **primary outcome** for this trial is 60-day mortality. We justify this endpoint as the primary outcome because of the following reasons: 1) Mortality is a clinically meaningful endpoint; 2) our prior studies have shown 60-day mortality is influenced by amount of protein intake[2,11,33]; and 3) longer-term outcomes and outcomes related to functional recovery, as important as they are, are not practical given the nature of this pragmatic, volunteer driven protocol.

The secondary outcome is time to discharge alive from hospital. Time to discharge alive is an important secondary outcome that is a composite of mortality and length of stay. This composite is similar to "ventilator- free days", which is a widely accepted and commonly used outcome in intensive care research.[25,55] As stated in the background of this trial, we expect higher amounts of protein to reduce infection, reduce mortality and shorten length of stay. These treatment effects will all be captured in a 'time to discharge alive' endpoint.

Tertiary outcomes include nutritional adequacy, hospital mortality, readmission to ICU and hospital, and duration of mechanical ventilation, ICU stay and hospital stay.

Sub study outcomes

The primary outcome of the ultrasound sub study is to evaluate the effect of parent EFFORT protein doses on muscle mass and quality using ultrasound of the quadriceps.

To assess this, patients ~~For patients in the US sub-study, they~~ will undergo the US measures at baseline (within 24 hours of randomization, ~~day~~ 10 days post randomization (if still in hospital) and just prior to hospital discharge. In the event that hospital discharge is prior to day 10, the day 10 measure will not be done. To ensure standardization and quality in the measures, we have created high quality training materials and will have US films sent centrally to abstract all measurements. In the first 10 patients enrolled in the US sub-study, participating sites will conduct a run-in phase where their submitted data will be evaluated for quality and reliability (both intra and inter-rater reliability) to ensure subsequent measures are of high quality. Nutritional and clinical data for these patients will be included in the parent EFFORT trial but the US measures may be omitted if quality is poor.

2.10 What is the proposed sample size and what is the justification for the assumptions underlying the power calculation?

We aim to enroll 4000 patients in this trial examining the impact of different protein dosing strategies on 60-day mortality. From 2007-2014, the average 60-day mortality for all patients included in the INS (>20,000 subjects) was 25%. We expect a higher rate given we are selecting out patients with nutrition risk factors, which may increase their mortality as well. So for the sample size calculation, we assume a 30% 60-day mortality in the ~~lower~~ usual dose group. Given the pragmatic nature of this RCT, we feel we have to acknowledge that the signal, relative to the noise, will be reduced. Hence, we need to have a sample size large enough to detect these smaller treatment effects. On the other hand, given the
volunteer nature of the trial and that there are no study funds to support efforts in this trial, we have to be realistic in our expectations of our collaborating colleagues. **We plan to enroll 2000 patients per group which will achieve 80% power to detect a 4% absolute risk reduction (13.3% relative risk reduction) from 30% to 26% using Pearson's chi-squared test at alpha=0.05.** Table in Appendix 2 shows the 'n' per arm under various assumptions and demonstrates that the sample size will be adequate to maintain >80% power to detect a 15% RRR over a plausible range of baseline rates. With an overall sample of 4000 patients, we would have 90% power to detect an improvement in time to discharge alive if the odds of a random person in the treatment arm having an earlier discharge time was 1.13 times the odds of a person in the control arm. To put this sample size in perspective, every year we host the INS, we get >200 ICUs worldwide contribute around 4000 patients per cycle. We feel this sample size is both realistic, given the large-scale, multinational, pragmatic nature of trial and yet is grounded in adequate scientific and statistical principles. Based on our prior experience with the International Nutrition Survey we expect loss to follow-up for the primary and secondary outcome to be trivial.

It is difficult to estimate a sample size required for the US sub-study as we lack a solid understanding of the minimally clinically important difference. Nevertheless, based on the study by Puthucheary[18], CSA of the rectus femoris decreased by 17.72% (95% C I -21.15 to -14.29) at day 10 in the ICU without any intervention. We postulate that our intervention may possibly prevented 25% of the reduction of RFC SA at day 10 (17.72/4=4.43%). With an calculated SD of 7.63, the effect size, d=4.43/7.63 = 0.58, the sample size with 2-tailed independent t-test at 90% power and alpha 0.05 is 64 per group. To account for potential drop out, where we don't have a follow up scan available (30-40%), we aim to enroll a minimum of 100 patients per group. However, given the voluntary nature of this sub-study, we will enroll more patients into this sub-study if possible. We aim to create a much larger database of US measures that can be used to correlate US measures to more distal, clinically-important outcomes.

2.11 What is the planned recruitment rate?

In prior INSs, participating sites have needed 5-8 months to recruit a minimum of 20 eligible patients. However, those patients were identified retrospectively (those adult mechanically ventilated patients that remained in ICU for more than 72 hours). In EFFORT, site representatives will have to identify potentially eligible patients prospectively. Moreover, we have modified the inclusion/exclusion

criteria such that only a select number of previously eligible patients may be eligible. We expect it to take much longer for sites to identify qualifying nutritionally high-risk mechanically ventilated critically ill patients. Hence, we estimate a site recruiting 0.5-1.0 patients per month or 6-12 patients per year. With a minimum of 30 patients required per site, we will allow for 3 years of recruitment. We will plan for 12 months of start-up activities and 12 months of close out activities, including a few extra months to accommodate delays, data cleaning, and manuscript preparation. Thus the total duration of this trial is 5 years.

2.12 Are there likely to be any problems with compliance? and 2.14 What is the likely rate of loss to follow up?

Over the past several years, we have conducted several INSs in over 700 distinct ICUs around the world. We have established study procedures manuals, very good compliance with data collection and almost no missing data on our primary outcome, 60-day mortality (assuming that patients discharged from hospital alive are counted as alive at 60 days). Since the rest of our secondary outcomes are hospital-related outcomes, we expect to have virtually no missing data on these key secondary endpoints.

2.13 How many centers will participate?

Consistent with our recruiting practices for the INS, ICUs from around the world will be invited to participate via our website (www.criticalcarenutrition.com) and through established communication channels with ASPEN and their international partners. Any ICU can register to participate but they will be screened for suitability. At the time of registration, participants must be knowledgeable about critical care nutrition (submit their CV or other documentation); have Good Clinical Practice (or similar) training (submit their training certificate); confirm their site has overall equipoise and is willing to abide by the randomization schema; confirm they use some form of a standardized feeding protocol (specific nature of the protocol not important; just that they have protocolized their approach to artificial nutrition); confirm they have access to a range of commercial products (high protein enteral nutrition, protein supplements, and parenteral nutrition or amino acids); have obtained local ethics approval (upload documentation) and provide an electronic signature that they will be committed to enrolling a minimum of 30 eligible patients in 2-3 years. Overall, we expect between 100-150 sites worldwide to join this collaborative with a smaller proportion joining the US sub-study.

2.14 What is the proposed type of analyses?

The **primary** analysis of 60-day mortality will be compared between arms using Pearson's chi-square test for two independent proportions. A secondary analysis will employ the generalized mixed effects model with a random site effect. This will provide a within site interpretation of effect, will allow

us to explore between site heterogeneity and will meet regulatory guidance suggesting that site be incorporated in a sensitivity analysis if it is not used for the primary analysis.[56-58]

The **secondary** outcome of this study is time to live discharge from hospital where death is considered a competing risk that precludes live discharge. We will report the cumulative incidence function by arm and formally test for differences between arms using Gray's test as implemented in SAS/STAT 14.1 (or later).[59] We expect minimal loss to follow up prior to hospital discharge, but if loss to follow up does occur due to hospital transfer or other reasons, patients will be censored at the last time known to be in the hospital. A secondary analysis will use a shared frailty model to incorporate site as a random effect.[60] The methods used for the primary (excluding the interim analyses) and secondary outcome will be applied to the binary and time-to-event **tertiary** outcomes respectively. In accordance with the intent-to-treat principle, the primary analysis will include all patients in the arm to which they were randomized regardless of study compliance. However, a priori, we plan an efficacy analysis in which we will only include patients treated as per protocol. That is, they remained on artificial nutrition for at least 4 calendar days and achieved at least 80% of their prescription in the high dose group, received no more than 1.2 grams/kg/day in the low dose group and received not more than 110% of energy requirement. Based on our substantial prior experience with this population we expect minimal missing data. However, details of missing data will be provided and if we have more than 1% missing we will perform a sensitivity analysis using a graphical pattern mixture tipping point approach demonstrating the treatment effect over the possible range of missing outcomes.[61,62]

Measurements of muscle mass will be made centrally by analysts blinded to clinical characteristics and randomisation. RFCSA will be measured off-line by a single investigator using ImageJ (National Institute of Health, USA). Derived RFCSA will be taken as the average of three consecutive measurements within 10% of one another. Muscle Linear Depth will be taken as the average of three consecutive measurements within 10% of one another. Muscle echogenicity will be determined by the same investigators using greyscale histogram analyses on Image J.

2.15 What is the frequency of analysis?

We plan to conduct one formal interim analysis with early stopping guideline after the 60 day mortality status is known for 2000 patients. We propose to apply the alpha spending approach of Lan and DeMets with O'Brien-Fleming type boundaries to the primary outcome.[63,64] This interim analysis would suggest stopping the study early if a two-side p-value of 0.003. To maintain the overall type I error rate of the study at 0.05, we will perform the final analysis at a nominal alpha of 0.049. This interim analysis has a trivial (less than 1%) effect on the overall power of the study. Using this rule and assuming a 30% mortality rate in the low dose arm, the study would be stopped at the interim if a 6% absolute difference in mortality was observed between arms.

2.16 Are there any planned subgroup analyses?

We will perform a pre-specified subgroup analysis based on baseline NUTRIC score, as previously explained. In addition, we plan to evaluate the treatment effect within subpopulations of our enrolled patients (age (based on median), sepsis, burns, trauma, acute kidney injury or use of RRT, severity of illness [median APACHE] and BMI>30), depending on the numbers of patients in each of these subgroups. Finally, we will consider the effect of each of the multiple nutrition risk factors, both individually and in combination on the magnitude of the treatment effect. The statistical significance of apparent effect modification will be assessed by testing a treatment by covariate interaction term using logistic regression for mortality and Cox PH model accounting for competing risk of death for time to discharge alive.[65] Due to the increased risk of type I and type II error, subgroup specific inferences will be considered exploratory and hypothesis generating. Subgroup specific effects will be presented by forest plots.

2.17 Ethics

This registry based RCT will be testing two practices within the range of usual or standard care. Currently, protein prescriptions for critically ill patients range from 0.5-3.8 g/kg/d and at a site level, from 0.8-2.6 g/kg/day (median 1.2 g/kg/day). There is an insufficient evidentiary basis to establish which level of protein administration is right for which patient population. Some have argued that until one level of protein administration is proven to be beneficial, randomization is the most ethical approach that will provide the correct answer sooner compared to allowing current practice, with tremendous variability and uncertainty, to continue. We will take usual practices and create 2 groups randomizing eligible patients to a ~~lower~~ usual prescription (≤1.2 g/kg/d) or to a higher prescribed protein prescription (≥2.2 g/kg/d). The remainder of care provided to eligible patients will be at the discretion of ICU providers.

To ensure adequate safety of trial participants, the EFFORT trial has the following features:

- No modifications to usual ICU care other than fixing the dose of protein intake (by randomization), from the wide range of existing doses in current practice, will be used.
- For individual patients, because of their individual characteristics, if a clinician believes the patients must receive either high or low protein, they will be excluded from the trial. No experimental products will be tested.
- Credentialed clinicians with expertise in directing the feeding of critically ill patients will monitor and provide usual nutritional care.
- No tissue or blood specimens will be collected for the RCT.

- Although data collection for the purposes of medical records will be prospective, for the purposes of this trial, data collection will be retrospective and abstracted from the medical record (no contact with patient or family for the purposes of this trial will be required). Please note, dietitians, as part of their standard of care will be attempting to contact families to obtain nutrition risk factor information from proxies.

- Trained ICU clinicians, volunteering to participate in data collection, will enter de-identified data into a secure, password-protected web site using a study identification code.

- Participating sites will not receive payment or incentives of any kind beyond an end-of-trial benchmarking report detailing the site's mean delivery of goal protein intake against the entire sample's mean.

- A unique patient ID number will be assigned to patients. No direct patient identifiers will be disclosed to the registry site or in any publications or presentation

We consider this parent trial to be low risk and impractical for clinicians to obtain fully informed consent and thus, where permitted, will be applying to local Institutional Review Boards for a waiver of informed consent. This request is consistent with the evolution of modern medicine where clinical research is embedded into "learning health care systems", a system designed to improve the effectiveness and safety of health care by creating a system that *'continuously learns to be better'*. The learning comes through research. This creates a tension between moral imperatives. Some authors have developed an ethical framework for evaluating the ethics of research activities embedded within health care systems[66] and concluded, along with others[67], that, in some pragmatic, comparative-effectiveness RCTs, the fact of randomization need not be disclosed to patients and no express informed consent is required.[68,69] These investigators argued that this approach is unnecessarily prohibitive and, in some situations, exposes vulnerable patients to unnecessary risks. By maintaining the status quo, unproven and potentially inferior interventions continue to be delivered due to a lack of better alternative. Others object to this idea of a 'no-consent' model and offer up an "Integrated Consent" model.[70] They object to the 'no-consent' model because it bypasses the patients' rights to information, involvement, and to weigh in on preference sensitive decisions. However, for mechanically ventilated, critically ill patients, often sedated and unconscious, these issues are not relevant nor dependent on patient preferences. Their solution, to use an "integrated consent model', relies heavily on verbal conversations at the point of decision-making, where a clinician would be discussing the options, risks, benefits and outcomes associated with different treatment options and obtain verbal consent to the randomization process. Again, this clinical process is not relevant to the decision about which dose to prescribe a critically ill patient. These clinical decisions are not made in discussion with patients nor their

surrogates. In the EFFORT trial, we simply aim to replace the clinician variability in practice with a randomization schema.

Given the safety characteristics of this trial described above, this trial presents no greater risk than typical management of feeding in ICU patients today. The ranges of protein prescribed are within the standard of care, the protein supplementation used is approved and currently used in practice, and there is significant equipoise amongst clinicians as to the best practice. If for a given patient, equipoise does not exist, the patient will be excluded from participation. It is important to point out that data collected for this study will mirror data collected for the International Nutrition Survey, a multicenter, multinational quality improvement collaborative, which has been granted a waiver of consent for more than a decade for >250 ICUs across the US and >500 ICUs worldwide. Data are all collected from standard hospital records and there are no study-specific procedures EXCEPT the randomization function explained above. Simply adding a randomization function to these patients in which equipoise exists does not increase risk and is consistent with 'minimal risk.' Certainly, there is precedent in the critical care literature that other such registry trials[71-73] conducted in critically ill patients using existing datasets and cluster RCTs of other nutrition interventions[39-41] have been granted a waiver of informed consent.

The other reason to justify a waiver of informed consent is that protein administration is time sensitive. In order to be most effective, protein administration needs to occur as soon as possible after initiation of mechanical ventilation. To be consistent with clinical practice guidelines, there should be no delays from the time the patient is assessed to when nutrition therapy is initiated. Delays in initiating optimal protein therapy may result in sub-optimal patient outcomes. Moreover, there is no funding, nor research resources available for this RCT. It will be driven by dietitians (or other health care professionals) who volunteer their time to randomize their patients early in ICU stay and collect the data retrospectively when the patient has been discharged or dies within that hospitalization. Without funds to access research resources, conducting this trial will be impractical. Requiring informed consent will mean the trial is impractical in many settings and if some clinicians are motivated and able to obtain informed consent, it will surely be on a select patient population enrolled in this trial as not all patients will have families available to discuss the matter within the time frame for enrollment (within 96 hours of admission to ICU). Lack of family availability and clinical ability to take the time to do this task will result in a very select and biased patient population enrolled, which will severely limit the generalizability of what is meant to be a 'real practice, pragmatic study.' With all enrolled patients, we aim to contact family members, where and when available, to advise them regarding the fact that their family member is enrolled in a clinical trial and provide them with an information sheet (See Appendix 3). If at that point, they refuse to have their family member involved in the trial, they will be withdrawn.

In other health care jurisdictions where this practice is not allowed or necessary (such as in some countries in Europe where they can use third party health care professionals to provide consent, these approaches will be used according to local health care regulations. We have included an ICF template in Appendix 4 for such settings. In the event a patient is enrolled in the US sub-study, we anticipate, because of the extra clinical procedures, that we will be required to consent surrogate decision-makers and have included a version of the ICF that includes the US procedure, to be used where applicable (see Appendix 4).

Given the nature of this trial of 2 different protein dosing strategies with the usual care practice in critically ill patients and that no pharmaceutical or investigational device are being studied, we are not reporting adverse or serious adverse clinical events. As many deaths are expected in this study population and since we are capturing deaths as our primary endpoint, we will not report these events. Loss of confidentiality represents a risk of this study and we will report any loss of confidentiality event to local REB/IRBs. We expect some local ethics boards will have different reporting requirements for their local sites and will instruct sites to follow local reporting policies to their local REB/IRB where necessary. We have constituted a Data Monitoring Committee who will provide a third-party assessment of all interim analyses and an assessment of the scientific literature as it evolves over the duration of the trial (See Appendix 5).

3.0 TRIAL MANAGEMENT

3.1.1 Day-to-day management of the trial:

The Clinical Evaluation Research Unit (CERU, see www.ceru.ca), under the Direction of Dr. Daren Heyland, will be the coordinating center for this trial (see Appendix 6 for description of CERU). This research unit has considerable experience with conducting large scale, multicenter, multinational trials, including 2 trials published in the New England Journal of Medicine.[74,75] As the Methods Center, CERU will be responsible for the coordination of all aspects of the trial including activities related to Start-up, Implementation, Data Management, Data Monitoring, Data Analysis, and the close out phase of the trial. Mr. Andrew Day, senior biostatistician at CERU, will be responsible for the statistical analysis of this trial.

3.2 Trial Organization and Committees

All CERU staff will be supervised by Dr. Daren Heyland and they will form the Executive Committee which will be responsible for the day-to-day management of the trial. In partnership with Dr. Charlene Compher and other ASPEN Board Members, we have recruited a multidisciplinary group of critical care nutrition experts to provide guidance, advice, and oversight. Collectively with the Executive committee, they will form the Steering Committee that will provide specific scientific and operational

input on a regular basis (see Appendix 5 for listing of Executive and Steering Committee members). As needed, we also plan to constitute a Stakeholder Committee to obtain input from a broader group of stakeholders (such as regional or national nutrition societies, basic scientists, key opinion leaders, industry liaisons, etc.).

3.3 Funding

There is no specific funding associated with this trial. There will be no transfer of funds between sites, the coordinating center (CERU) or ASPEN. At CERU, Dr. Heyland will use existing resources to support the data collection/management infrastructure and analysis. Sites are expected to volunteer their time and use local resources to conduct the study. As with past INS projects, sites that enrol 30 or more patients in the RRCT will also receive a bench-marked report highlighting their nutrition performance compared to the performance of other sites in the database.

4.0 SIGNIFICANCE

This study has both the potential to answer a high-priority clinical question and also transform the way we do research in clinical nutrition. It further represents a unique collaboration between ASPEN, its global partners, and the Clinical Evaluation Research Unit, a methodological support center based in Kingston, Ontario, Canada and managed by Dr. Daren Heyland. Without the need for additional funding, CERU can coordinate this trial and by relying on motivated health care professionals around the world to contribute data, like they do in the INS. We have the potential to conduct a large scale pragmatic trial. If successful, this type of collaboration sets an important precedent for how our community may approach additional research questions related to clinical nutrition.

Appendix 1: RCTs of High vs Low Protein and Amino acids

Study	Population	Methods (score)	*Intervention*	Mortality # (%)		Infections # (%)		Mechanical Ventilation	
				High protein	Low Protein	High protein	Low Protein	High protein	Low Protein
1) Clifton 1985**	Head injured patients comatose for 24 hrs N=20	C.Random: not sure ITT: yes Blinding: no (8)	22% pro, 38 % CHO, 41 % fat, 1.5 Kcal/ml (Traumacal) vs. 14 % pro, 50 % CHO, 36 % fat, 2.0 Kcal/ml (Magnacal) Isocaloric, 29 gm Nitrogen vs.17.6 gms Nitrogen	**3-month** 1/10 (10)	**3-month** 1/10 (10)	3/10 (30)	2/10 (20)	NR	NR
2) Scheinkestel 2003**	Critically ill ventilated pts on 6 days CRRT for renal failure N=50	C.Random: yes ITT: yes Blinding: no (9)	1.5 g/kg/d protein x2 days, 2.0 g/kg/d protein x2 days and 2.5 g/kg/d protein x2 days while receiving CRRT vs 2.0 g/kg/d protein x6 days while receiving CRRT	**ICU** 9/40 (23)	**ICU** 4/10 (40)	NR	NR	NR	NR
3) Rugeles 2013	Medical adult ICU patients N=80	C.Random: yes ITT: no Blinding: double (7)	Hypocaloric hyperproteic (15 kcal/kg, 1.7 g/kg/d) x 7 days vs standard (25 kcal/kg, 20% calories from protein).	**28 day**[2]* 11/40 (28)	**28 day**[1]* 12/40 (29)	NR[1]**	NR[1]**	8.5 ± 4.6	9.7 ± 4.9

[2] Response from author: 28 day mortality, Hyperproteic: 28%, Control: 29%. Other mortality by group: NR. Number of patients who developed infections, by group: NR

4) Doig 2015	Medical ICU adult patients N=474	C.Random: yes ITT: yes Blinding: no (10)	IV aa infusion (Synthamin, Baxter, 100g/L) providing a max 100 g aa/day. IV aa infusion was titrated to provide 2 g/kg/d of aa from all nutrition sources.	**ICU** 28/239 (11.7) **Hospital** 37/239 (15.5) **90-day** 42/236 (17.8)	**ICU** 30/235 (12.8) **Hospital** 43/235 (18.3) 90-day 47/235 (20)	NR[3]**	NR[2]**	7.33 (7.0-7.68) Mean ± SD**	7.26 (6.94-7.61) Mean ± SD**
5) Ferrie 2016	Medical/Surgical ICU adult patients N=120	C.Random: yes ITT: yes (modified) Blinding: double (10)	Patients on PN randomized to receive a higher aa vs lower aa solution with a goal of 1.2 vs 0.8 g/kg/d aa from EN and PN.	**ICU** 8/59 (14) **Hospital** 12/59 (20) **6 month** 15/59 (25)	**ICU** 6/60 (10) **Hospital** 9/60 (15) **6 month** 9/60 (15)	31/59 (53)	34/60 (57)	2.0 (1.0–3.0) 3.68 ± 6.17[4]*	2.0 (1.0–5.0) 5.87 ± 14.27[3]*

[3] Response from author: NR

[4] Response from author: Days mechanically ventilated, low aa: mean 5.87 (SD 14.27), higher aa: mean 3.68 (SD 6.17)

Study	LOS High protein Low Protein	Physical and QOL Outcomes High protein Low Protein	Nutrition parameters High protein Low Protein
1) Clifton 1985**	NR	NR	**Calories (kcal/kg/d)** 51 48 **Grams nitrogen/day** 0.42 0.24
2) Scheinkestel 2003**	NR	NR	**Calories per day** 2063 2095 **Nitrogen balance** -0.56 -4,5
3) Rugeles 2013	**ICU** 9.5 ± 5.5 days 10.4 ± 5.0 days **Hospital[5]*** 19.5 ± 6.5 days 20.5 ± 5.0 days	NR	**Calories (kcal/kg/d)** 12 14 **Protein (g/kg/d)** 1.4 0.76
4) Doig 2015	**ICU** 11.6 (10.8 to 12.5) 10.7 (10.0 to 11.5) Mean ± SD[6]** **Hospital** 26.0 (24.2 to 28.0) 24.8 (23.0 to 26.6) Mean ± SD[5]**	**RAND-36 General Health, mean (SD)** 50.5 (27.2) (n=192) 52.8 (25.9) (n=180) P=0.41 **ECOG, mean (SD)** 1.31 (1.0) (n=192) 1.18 (1.0) (n=181) P=0.21 Diff (95% CI): -0.13 (-0.34 to 0.07) **RAND-36 Physical, mean (SD)** 47.7 (33.7) (n=192) 53.2 (33.0) (n=180)	**Protein**** Significantly more protein during first 7 ICU days in intervention group

[5]Response from author: Hospital length of stay, Hyperproteic: 19.5 +-6.5; Control: 20.5 +- 5.0

[6] Response from author: mean and SD not available.

		P=0.11 Diff (95% CI): 5.5 (-1.31 to 12.3)	
5) Ferrie 2016	**ICU** 5.0 (3.0–8.0) 6.0 (3.8–10.0) 7.36 ± 7.85[7]* 5.87 ± 14.27[6]* **Hospital** 25.0 (16.8–41.3) 27.5 (18.8–55.8) 38.31 ± 35.90[6]* 41.75 ± 37.36[6]*	**Hand grip strength at ICU d/c, kg** 18.5 ± 10.4 15.8 ± 10.3, P=0.054 **% Expected Value** 51 45 **Hand grip strength at day 7, kg** 22.1 ± 10.1 18.5 ± 11.8, P=0.025 **% Expected Value** 62 52 **Fatigue Score at day 7** 5.4 ± 2.2 6.2 ± 2.2, P=0.045 **Sum of 3 muscle sites on u/s at day 7, cm** 8.4 ± 1.0 7.9 ± 1.1, P=0.02 **Forearm muscle thickness on u/s at day 7, cm** 3.2 ± 0.4 2.8 ± 0.4, P=<0.0001 **Biceps muscle thickness on u/s at day 7, cm** 2.5 ± 0.6 2.4 ± 0.4, P=0.21 **Thigh muscle area on u/s at day 7, cm^2** 6.8 ± 2.1 5.8 ± 1.9, P=0.02 **Leg circumference at day 7, cm** 35.9 ± 4.3 35.9 ± 4.4, P=0.98	**Kcal/kg/d in first 3 study days** 23.5 ± 3.9 26.0 ± 3.8 **Kcal/kg/d in first 7 study days** 23.1 ± 3.9 24.9 ± 4.2 **grams/kg/d in first 3 study days** 1.17 ± 0.21 0.87 ± 1.17 **grams/kg/d in first 7 study days** 1.09 ± 0.22 0.90 ± 0.21

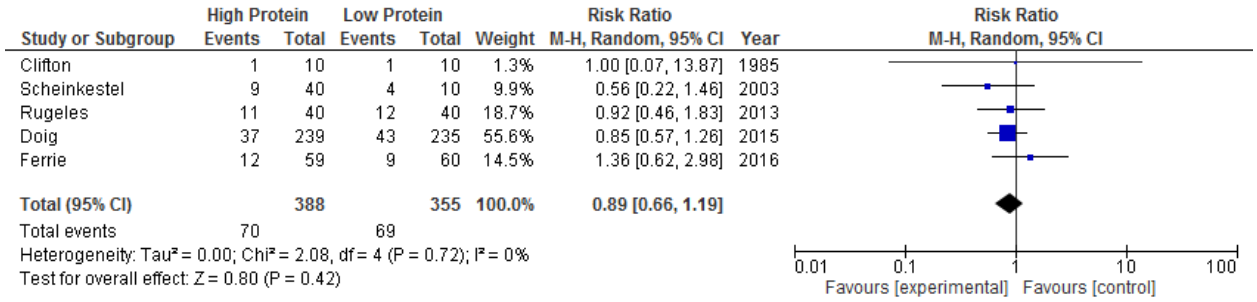
***Data/information was obtained directly from the author

**Unable to obtain further data directly from the author

[7] Response from author: ICU LOS, low aa: mean 5.87 (SD 14.75), higher aa: mean 7.36 (SD 7.85). Hospital LOS, low aa: mean 41.75 (SD 14.75), higher aa: mean 7.36 (SD 7.85).

NR, not reported; LOS, length of stay; ICU, intensive care unit; ITT, intention to treat; C. random, concealed randomization; QOL, quality of life; u/s, ultrasound; d/c, discharge; SD, standard deviation; kg, kilograms; cm, centimeter; aa, amino acid; EN, enteral nutrition; PN, parenteral nutrition;

Overall Mortality



Appendix 2: Sample Size Justification

Relative Risk Reduction (1-RR) @	Control Group Event Rate (60-day Mortality)								
	25%			30%			35%		
	ARR	80% Power	90% Power	*ARR*	80% Power	90% Power	*ARR*	80% Power	90% Power
10%	2.50%	4, 548	6,087	3.00%	3,554	4,757	3.5%	2,844	3,806
15%	3.75%	1,984	2,655	4.50%	1,554	2,079	5.25%	1,247	1,668
20%	*5.00%*	1,094	1,465	*6.00%*	859	1,149	*7.00%*	691	924
25%	*6.25%*	686	918	*7.50%*	540	722	*8.75%*	435	582
30%	*7.50%*	466	624	*9.00%*	367	491	*10.50%*	297	397

ARR, absolute risk reduction; RR, relative risk;

Appendix 3: Information Sheet Template

The Effect of Higher Protein Dosing in Critically Ill Patients:
A Multicenter Registry-based Randomized Trial: The EFFORT Trial

Why is this research being done?

As part of the patient's usual care in the Intensive Care Unit (ICU), an ICU nutrition specialist will do a check the nutritional status of the patient and create a nutrition plan. Providing protein and calories to critically ill patients is associated with less infectious complications, more days off the ventilator, improved long-term physical recovery, and lower death rates. The recommendations for how much protein a patient should receive vary from lower amounts to quite high amounts. We do not know the right dose of protein to provide critically ill patients so we are doing a research project where nutrition specialists are randomly told to prescribe a higher or a lower dose of protein. Other than the amount of protein patients receive, all patients will continue to receive usual care. This research study may help to clarify what the ideal amount of protein is for a critically ill patient. We expect to include 4000 patients worldwide and approximately 30 patients from your ICU in this study.

How will my personal health information be protected?

Information from the patient's medical record will be collected by the researchers to look at if the higher or lower amounts of protein cause better patient outcomes. The researchers will only collect the information they need for the study from the hospital record. All information collected will be kept confidential and will not be shared with anyone outside the study unless required by law. Only de-identified or anonymized information that is collected about the patient (called study data) will be sent electronically to the Clinical Evaluation Research Unit (CERU) in Kingston, Ontario, Canada for analysis. The research team at [Hospital name] and at CERU and the Research Ethics Board will have access to the study data. The patient's name, birthdate, address, or other information that may directly identify you will not be used. The electronic records received by CERU will only contain a unique participant code. You will not be named in any reports, publications or presentations that may come from this study. The study records will be retained for [5 years as per local policy].

What are the risks and benefits of this study?

The protein critically ill patients will receive in this trial does not differ from usual care, so we do not foresee any new risks with participating. There may be risks that are currently unexpected. Receiving lower or higher amounts of protein may be beneficial. Future patients will benefit once we know the optimal amount of protein to provide critically ill patients.

Will this study cost me anything? Will I be paid?

Participating in this study will not cost you any money and you will not be paid for your participation.

What if I have questions?

You may direct your questions or concerns to the on-site study nutrition specialist and/or the doctor who sees you in the ICU for your nutrition. Further questions can be addressed by the Site Investigator, [Name], at [Telephone number] or [Email address].

If you have any questions about your rights as a research participant, please call the Chair of the Research Ethics Board, [Name], at [Phone number].

Appendix 4: Informed Consent Form Template

Informed Consent Form for Participation in a Research Study

Study Title: The Effect of Higher Protein Dosing in Critically Ill Patients: A Multicenter Registry-based Randomized Trial and US Sub-study

Sponsor's Study ID: The EFFORT Trial

Study Doctor: *insert name, department and telephone or pager number*

Sponsor: Dr. Daren Heyland, MD, FRCPC, MSc

Emergency Contact Number (24 hours / 7 days a week): _____

Non-Emergency contact numbers are noted at the end of this document under the section heading "Contacts".

INTRODUCTION

As a Substitute Decision Maker, you are being asked to provide informed consent on behalf of a person who is unable to provide consent for him/herself. Throughout this form, "you" means the person you are representing. You are being invited to participate in a research project. Current treatments available to you are only available because previous patients like you participated in clinical trials. Future advances are dependent on participation in clinical trials. You are invited to participate in this trial because you are a critically ill patient at high nutrition risk. This consent form provides you with information to help you make an informed choice. Please read this document carefully and ask any questions you may have. All your questions should be answered to your satisfaction before you decide whether to participate in this research study. The study staff will tell you about the study timelines for making your decision.

Taking part in this study is voluntary. Deciding not to take part or deciding to leave the study later will not result in any penalty or affect current or future health care.

WHAT IS THE BACKGROUND INFORMATION FOR THIS STUDY?

Critically ill mechanically ventilated patients are not able to consume a regular diet. Normally, a dietitian or other health care professional will assess the critically ill patient and determine their requirements and provide protein and calories through a feeding tube or intravenous (IV) as part of their usual care. However, there is a wide range of doses of protein provided and we do not know the optimal or best amount of protein to feed critically ill patients.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to compare the effects on you and your recovery of 2 different protein doses, both of which are commonly used for critically ill patients. In addition, we will use an ultrasound of the upper leg to evaluate the effects of these nutritional practices on muscles mass.

WHAT OTHER CHOICES ARE THERE?

If you choose not take part in this study, nutrition care will be provided to you as part of the usual care in your ICU.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

It is anticipated that about 4000 people will take part in this study, from at least 100 ICUs located around the world. We expect to enroll at least 30 patients locally.

WHAT WILL HAPPEN DURING THIS STUDY?

If you decide to participate then you will be "randomized" into one of the two groups described below. Randomization means that you are put into a group by chance (like flipping a coin). There is no way to predict which group you will be assigned to. You will have an equal chance of being placed in either group. Neither you, the study staff, nor the study doctors can choose what group you will be in. The study doctor and study staff will know which group you are in. As a participant, you will not have any responsibilities in this study.

WHAT IS THE STUDY INTERVENTION?

Group 1: Usual ICU care plus a protein dose of ≥2.2 g/kg/day. If you are randomized to this group, your protein dose will be met by providing protein through tube feeding, protein supplements and/or IV protein, as determined by the doctors and/or dietitian.

Group 2: Usual ICU care plus a protein dose of ≤1.2 g/kg/day. If you are randomized to this group, your protein dose will be met by providing protein through tube feeding, protein supplements and/or IV protein, as determined by the doctors and/or dietitian.

The study intervention will continue for your entire time in ICU while you are receiving tube feeding and/or IV nutrition. There are no other changes to your usual care, just the amount of protein prescribed.

WHAT ARE THE STUDY PROCEDURES?

Non-Experimental Procedures

1. You will confirm this agreement by signing this consent form.
2. While you are in ICU, the clinical team will visit you daily and review your medical record to assess your medical condition.
3. The clinical team will record information about your past medical history, nutrition, and recovery during your stay in ICU.

4. The results from the blood tests that are routinely done while you are recovering in the ICU will be recorded for this study.
5. An ultrasound will be done on your upper leg at the start of the study, ~~around Day~~ 10 days post randomization, ~~of hospital stay~~, and just prior to hospital discharge.

Experimental Procedures

1. You will be prescribed a protein dose based on your study group assignment.
2. You will undergo ultrasound of the thigh muscles with 24 hours of enrollment, day 10 and just prior to hospital discharge.

WHAT ARE THE RESPONSIBILITIES OF STUDY PARTICIPANTS?

If you choose to participate in this study, you will be expected to:

- Provide consent to participate.

HOW LONG WILL PARTICIPANTS BE IN THE STUDY?

The study will last until you are discharged from hospital.

CAN PARTICIPANTS CHOOSE TO LEAVE THE STUDY?

Participation in research is voluntary. You can choose to end your participation in this research (called withdrawal) at any time without having to provide a reason. This will not affect their medical care in any way. Information that was recorded before you withdrew will be used by the researchers for the purposes of the study, but no information will be collected or sent to the sponsor after you withdraw your permission. If you choose to withdraw from the study, you are encouraged to contact the study doctor or study staff.

CAN PARTICIPATION IN THIS STUDY END EARLY?

You will be informed, in a timely manner, of any new information which may affect your willingness to have your family member continue taking part in this study. The clinical team may stop your participation in the study early, and without your consent, for reasons such as:

- You are unable to tolerate the study intervention
- The study doctor no longer feels this is the best option for you
- The Sponsor decides to stop the study

If this happens, it may mean that you would not receive the study intervention for the full period described in this consent form. If you are removed from this study, the study doctor will discuss the reasons with you.

WHAT ARE THE RISKS OR HARMS OF PARTICIPATING IN THIS STUDY?

We do not expect any greater risk compared to usual care. There are no risks associated with the ultrasound as it is a safe, non-invasive type of imaging.

There may be other risks that are currently unforeseeable.

WHAT ARE THE REPRODUCTIVE RISKS?

Protein dosing for critically ill pregnant women or children has not been tested, therefore, you may not take part in this research study if you are pregnant. Post-partum and lactating patients may participate.

WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?

If you agree to take part in this study, the experimental intervention may or may not be of direct benefit to you. We anticipate a higher amount of protein may improve survival and recovery but we currently do not know for sure and that is why we are doing this trial.

HOW WILL PARTICIPANT INFORMATION BE KEPT CONFIDENTIAL?

If you decide to participate in this study, the study doctors and study staff will only collect the information they need for this study from the medical record. Records identifying you at this centre will be kept confidential and, to the extent permitted by the applicable laws, will not be disclosed or made publicly available, except as described in this consent document.

Authorized representatives of the following organizations may look at your original (identifiable) medical/clinical study records at the site where these records are held, to check that the information collected for the study is correct and follows proper laws and guidelines.

- Dr. Daren Heyland, the Sponsor of this study, and the study staff coordinating the study
- The research ethics board who oversees the ethical conduct of this study in Ontario
- *insert research site name*, to oversee the ethical conduct of research at this location

Information that is collected about you for the study (called study data) may also be sent to the organizations listed above. The de-identified ultrasound images will be sent to a storage facility in Aachen Germany. Representatives of Clinical Trials Ontario, a not-for-profit organization, may see study data that is sent to the research ethics board for this study. Your name, address, or other information that may directly identify you will not be used. The records received by these organizations may contain

your unique participant code, sex, age, and ~~admission and discharge dates~~duration of stay. It would be highly unlikely that this type of recorded information would lead to identifying a study participant without the corresponding patient health information, which is never collected or input to the study's secure electronic data capture system, and later used by researchers.

If the results of this study are published, your identity will remain confidential. It is expected that the information collected during this study will be published in the medical literature and that the de-identified data collected from this study – that is, the information that does not directly identify you may be used in additional studies and by other researchers, as determined by the Sponsor.~~may be used in additional study questions as determined by the sponsor. Even though the likelihood that someone may identify you from the study data is very small, it can never be completely eliminated~~.

A copy of the consent form that you sign to enter the study may be included in your health record/hospital chart.

WILL INFORMATION ABOUT THIS STUDY BE AVAILABLE ONLINE?

A description of this clinical trial will be available on http://www.clinicaltrials.gov. This website will not include information that can identify you. You can search this website at any time.

WHAT IS THE COST TO PARTICIPANTS? ARE STUDY PARTICIPANTS PAID?

Participation in this study will not involve any additional costs to you or your private health care insurance. You will not be paid for taking part in this study.

WHAT ARE THE RIGHTS OF PARTICIPANTS IN A RESEARCH STUDY?

You will be told, in a timely manner, about new information that may be relevant to your willingness to stay in this study. Your rights to privacy are legally protected by federal and provincial laws that require safeguards to ensure that your privacy is respected. By signing this form you do not give up any of your legal rights against the study doctor, sponsor or involved institutions for compensation, nor does this form relieve the study doctor, sponsor or their agents of their legal and professional responsibilities.

You will be given a copy of this signed and dated consent form prior to participating in this study.

WHOM DO PARTICIPANTS CONTACT FOR QUESTIONS?

If you have questions about taking part in this study, contact the study doctor [Name] at [Telephone].

If you have any concerns about your rights as a research participant please contact the Board of Record – Dr. Albert Clark, Chair of the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics at 1-844-535-2988.

SIGNATURES

- All of my questions have been answered,
- I understand the information within this informed consent form,
- I allow access to my medical records as explained in this consent form,
- I do not give up any of my legal rights by signing this consent form,
- I agree, or agree to allow the person I am responsible for, to take part in this study.

_____	_____	_____
Signature of Participant/ Substitute Decision-Maker	PRINTED NAME	Date
_____	_____	_____
Signature of Person Conducting the Consent Discussion	PRINTED NAME & ROLE	Date

Complete the following section once the patient is able to consent to participate in the study:

- All of my questions have been answered,
- I understand the information within this informed consent form,
- I allow access to my medical records as explained in this consent form,
- I do not give up any of my legal rights by signing this consent form,
- I agree to take part in this study.

_____	_____	_____
Signature of Patient	PRINTED NAME	Date
_____	_____	_____
Signature of Person Conducting the Consent Discussion	PRINTED NAME & ROLE	Date

Complete the following section only if the participant is unable to read or requires an oral translation:

- The informed consent form was accurately explained to, and apparently understood by, the participant/substitute decision maker, and
- Informed consent was freely given by the participant/substitute decision maker

_____	_____	_____
Signature of Impartial Witness/Translator	PRINTED NAME	Date

Appendix 5: EFFORT Committee Structure

Data Monitoring Committee

Name	Title	Country	Institution
Timothy Sentongo	DMC Chair	USA	University of Chicago
Jennifer Jin	Member	Canada	Royal Alexandra Hospital
Stéphane Ahern	Member	Canada	University of Montreal
Greg Samsa	Member	USA	Duke University School of Medicine

Steering and Executive Committee

Name	Title	Country	Institution
Daren Heyland*	CERU Director, MD	Canada	Clinical Evaluation Research Unit
Jennifer Korol*	Project Leader	Canada	Clinical Evaluation Research Unit
Charlene Compher*	PhD, RD	USA	University of Pennsylvania
Nilesh Mehta	MD	USA	Boston Children's Hospital
Todd Rice*	MD, MSc	USA	Vanderbilt University
Gordon Sacks	PharmD	USA	Auburn University
Heidi Nixdorf	RD	Canada	Credit Valley Hospital
Vera Jovanovic	RD	Canada	Trillium Health Partners – Mississauga Hospital
Danielle Bear	RD	UK	St. Thomas' Hospital
Jayshil Patel	MD	USA	Froedtert Hospital and the Medical College of Wisconsin

***Members of Executive Committee**

Appendix 6: The Clinical Evaluation Research Unit (CERU)

Description of CERU

The coordinating centre for this trial is located at the Clinical Evaluation Research Unit (CERU) at the Kingston General Hospital, Ontario, Canada. Founded in 1998, the mission of CERU is to improve the care of acutely ill patients through knowledge generation, synthesis, and translation in a manner that will translate into improved clinical outcomes for sick patients and improved efficiencies to our health care systems. As such, CERU consists of a staff with experience and resources to support the successful completion of all phases of the design, conduct, monitoring, and interpretation of multicenter clinical studies. Dr Daren Heyland, the Director of CERU, is a Professor of Medicine and Epidemiology at Queen's University, Kingston, Ontario, Canada. He is trained in Internal Medicine, Critical Care Medicine, and Clinical Epidemiology. He has a variety of research interests which include 3 Canadian Institutes of Health Research (CIHR) funded programs of research and has conducted multicenter trials in the areas of nutrition, infection, and end of life care. Overall, Dr. Heyland has published approximately 310 peer-reviewed papers, raised more than $109 million in external grant support including more than $54 million from CIHR, and given > 300 international presentations.

CERU is staffed with several members that have considerable experience in all phases of clinical studies. Along with Dr Heyland, the Senior Project Leaders at CERU will take overall responsibility for the day-to-day conduct of the trial, development of the study protocol and comprehensive study procedures, execution of contracts, administration/oversight of study funds, training and liaising with the sites, monitoring data quality, arranging all trial meetings, reporting the progress of the trial to the participating sites and the steering committee, and supervision of all trial staff. The data manager will be responsible for all aspects of data collection and processing, while the statistician at CERU is responsible for all aspects of the data analysis and reporting of data. The applications developer will implement the web-based data entry/query/monitoring/reporting system for efficient conduct of the trial, including randomization, automatic CRF monitoring, data validation and cleaning.

Description of Electronic Data Capture System

CERU's proprietary central randomization system (CRS) is a modular web-based tool used to monitor patient enrollment, accrual and/or randomization. The CRS uses customizable PHP modules and a MySQL database backend to accommodate a wide variety of study designs. This flexible architecture reduces start-up costs by providing a solid framework on which to base a particular study.

CERU uses REDCap[64] as an electronic data capture system for capturing, managing, and reporting clinical research data for trials. The electronic data capture system provides state of the art capability in all aspects of clinical trials data management, assisting both investigators and CERU with the conduct of a

clinical trial. Through a simple, full-featured interface, investigators and research coordinators, etc. can enter and clean clinical data, monitor trial progress, and track source document verification. The REDCap system will run on the SOLARIS 10 operating system and the data will be hosted on a MySQL server database.

The above mentioned servers/applications run on a Sun Microsystems tower server with 4

Gigabytes of ram, 8 core running at 1900 Mhz (2 physical CPU's) and 127 Gigabytes of disk space on a 3.5" 15,000 RPM hard drive. Also CERU has 2 identical Sun Microsystems servers, each runs dual core 2,200 Mhz CPU's with 250 Gigabytes of disk space (each) on 3.5" 7,200 RPM and 4 Gigabytes of RAM. These servers are located at the High Performance Computing Facility (HPCVL) at Queen's University. This facility is a state of the art data center with strict security controls in place; no visitors are allowed into the server room without previous authorization from HPCVL management. The servers are located in a climate controlled room where humidity and temperature are kept at an optimum level to prevent equipment damage and reduce the risk of fire.

Accessing the servers from the CERU offices is done via Virtual Private Network. HPCVL provides an encrypted connection to their network to ensure only authorized users can access the servers. The permissions to connect to the virtual private network are granted by HPCVL at the request of CERU's IT staff.

End users will access the CRS and REDCap using a Secure Socket Layer connection (SSL) and secure passwords provided by CERU's IT staff. Access to the CRS and REDCap is only possible with previous authorization by CERU IT staff.

All data pertaining to the research participant are transmitted to CERU in an anonymized fashion. At the time of data entry participants will be identified in the CRS and REDCap with a unique identifier (i.e. enrollment or randomization number).

All these resources are compliant with Good Clinical Practice and other regulatory authorities worldwide.

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