SECTION 4: RECRUIT PARTICIPANTS

Contents

Participant Eligibility & Enrollment

Screening

Once your site registration has been approved and you have received your login credentials for REDCap, you should begin to screen for eligible patients (adults, ≥ 1 high nutrition risk factors and mechanically ventilated,) in the study. Repeat screening daily. Remember to document your screening in the Screening Log described in Section 3: Prepare and Promote.

Study ID Numbers

Please enter data on all patients screened that meet all the inclusion criteria.

Patients, with their data entered into REDCap will be assigned a unique study number by the system (e.g. 2454-35). For patients that are randomized, this study number will never change and will be used for the entire duration of the patient's participation in the study and should be used to label all patient CRFs, worksheets and records.

Inclusion Criteria

If eligible, they must be randomized to the trial within ***96h of admission to your ICU***.

1. **≥18 years old.**

2. **Requiring mechanical ventilation with actual or expected total duration > 48 hours from time of screening.**
   This includes ***any*** positive inspiratory pressure (excluding PEEP only) delivered via an endotracheal tube or a tracheostomy. ***Non-invasive*** methods of ventilation, such as high flow oxygen nasal cannula (OPTIFLOW), BI-PAP or mask-CPAP, **are not permitted**.

   The 48h window should be measured from the time of initiation of mechanical ventilation (i.e. intubation). A patient should either have ***already achieved*** at least 48h of mechanical ventilation or they are ***expected*** to achieve at least 48h from point of screening.

   If the patient received ≥ 48h of mechanical ventilation, but is extubated at the time of screening or has been actively weaned, please do not enroll the patient. We want patients that will remain in ICU requiring artificial nutrition for another 3-4 days minimum from the point of screening.

   If the patient was intubated outside of the hospital setting (e.g. by paramedics in the field or at another hospital), use the precise time of intubation from the medical notes. However, if such a time is not available, use the time of your hospital's admission to determine this criterion.

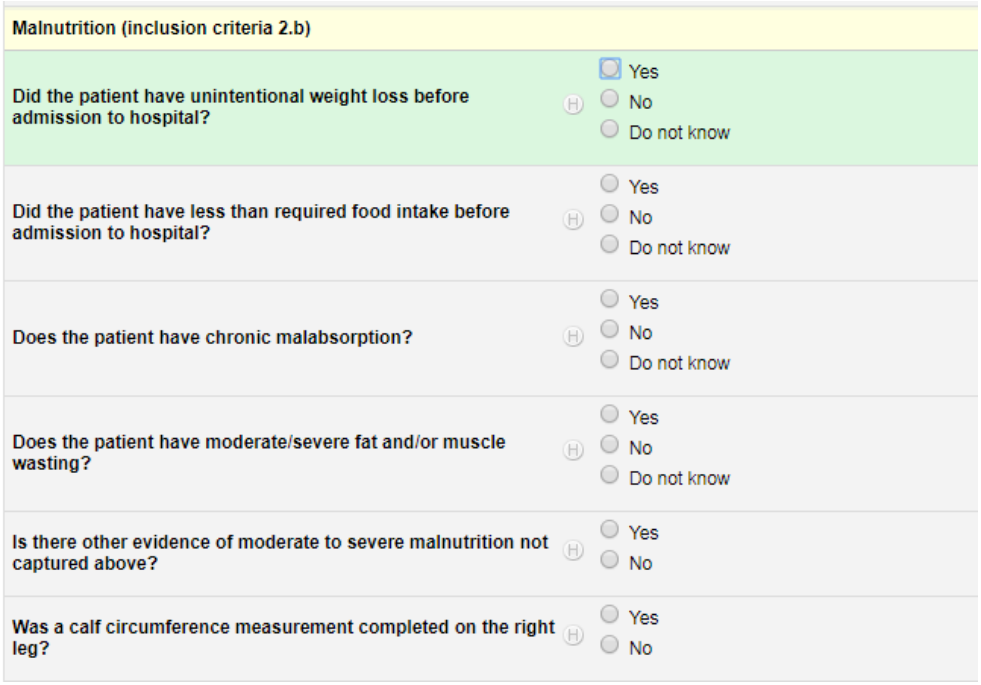
3. **Have one or more of the following risk factors that make them a high nutritional risk.**
   NOTE: Patients may have more than one nutritional risk factor and each patient will need to be assessed for the presence of nutritional risk criteria at some point (listed a-d below). If the patient is eligible on one of the criteria, say for example BMI, the rest of the data points can be

deferred till later. However, only one criterion of the following is required to meet these inclusion criteria to enable you to randomize the patient:

a. **Low (≤25) or high BMI (≥35)**

b. **Moderate to severe malnutrition (as defined by local assessments).**

We are not trying to be prescriptive as to how you document moderate-severe malnutrition. But rather, we will document the means by which sites are making this determination and capture the elements of the assessment. The data collection worksheet in REDCAP as shown below, you will be required to indicate 'yes' or 'no' or 'do not know' to all the following criteria:



Malnutrition (inclusion criteria 2.b)	
Did the patient have unintentional weight loss before admission to hospital?	○ Yes ○ No ○ Do not know
Did the patient have less than required food intake before admission to hospital?	○ Yes ○ No ○ Do not know
Does the patient have chronic malabsorption?	○ Yes ○ No ○ Do not know
Does the patient have moderate/severe fat and/or muscle wasting?	○ Yes ○ No ○ Do not know
Is there other evidence of moderate to severe malnutrition not captured above?	○ Yes ○ No
Was a calf circumference measurement completed on the right leg?	○ Yes ○ No

Refer to the ***Patient CRF and Instructions*** for detailed information regarding this aspect of data collection.

c. **Frailty (Clinical Frailty Scale of 5 or more, as determined by surrogate or next of kin).**

The Clinical Frailty Scale assessment tool, including instructions for use, are found in the ***Patient CRF and Instructions***, and can be downloaded from the study website.

d. **Sarcopenia (SARC-F score of 4 or more, as determined by surrogate or next of kin).**

The SARC-F assessment tool, including instructions for use, are found in the ***Patient CRF and Instructions***, and can be downloaded from the study website.

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

To aid the attending physician in making this determination, ask them what the probability (i.e. high, medium, low) of the patient being in the ICU for an additional 4 days (or 3 days if the study intervention can start on the day of screening).

- If the physician assessment is medium or high, they fulfill this particular high risk criterion.
- If the patient is considered low probability, then the patient does not fulfill this particular high risk criteria

NOTE: All randomized patients will have documented assessments completed for each of the 4 nutrition risk factors (i.e. inclusion criteria 3a-d). If you do not have sufficient time to assess all of these at the time of screening, but are able to confirm at least one is present, the remaining assessments will be completed post-randomization. See Section 5 and Patient CRF & Instructions for data collection details.

Exclusion Criteria

1. **> 96 continuous hours of mechanical ventilation before screening.**
   We want the study intervention to begin as early as possible in the patient's ICU admission. Therefore this criterion should be assessed as *> 96 continuous hours of mechanical ventilation from the point of ICU admission*. If the patient was intubated outside of the hospital setting (e.g. by paramedics in the field or at another hospital), use the precise time in the notes, if available.

2. **Expected death or withdrawal of life-sustaining treatments within 7 days from screening.**
   Patients who die or receive palliative therapy (have nutrition stopped) within days of randomization are not good study patients. They won't help us answer the study question. By this criterion, we mean a very high likelihood of death or withdrawal of life-sustaining treatments (if the patient has an isolated DNR, they can still be included). It may be difficult for some clinicians to make this judgment. Therefore, only patients with a 'high' probability (>50%) of not surviving the next 7 days should be excluded.

3. **Pregnant.**
   We don't know the safety of high protein on the fetus. Post-partum and lactating patients are permitted.

4. **The responsible clinician feels that the patient either needs low or high protein**
   If this is the case, we require an understanding of the clinician's reasons. From the options below, check all that apply.

   ❒ No longer critically ill
   ❒ New onset of ARDS
   ❒ Worsening renal function
   ❒ Improved renal function
   ❒ Starting dialysis
   ❒ New wound (non-surgical)
   ❒ New surgical wound
   ❒ Negative nitrogen balance
   ❒ Increased protein losses (eg. increased ostomy output, pleural fluid drainage, etc)
   ❒ BMI ≥30
   ❒ Improving hepatic failure
   ❒ Worsening hepatic failure
   ❒ Other, please specify: _____

5. **Patient requires parenteral nutrition only and site does not have products to reach the high protein dose group.**

Note: These exclusion criteria are assessed at the time of screening. If a patient is eligible for the trial and randomized, if then subsequently and unexpectedly meet an exclusion criteria (e.g. life-sustaining treatment is withdrawn), the patient is to continue in the trial and the nutrition should be managed as per clinical standards.

Eligibility Clarifications

Should hemodynamically unstable patients be enrolled in the study?

Hemodynamic instability is not an exclusion criterion. We want EFFORT patients to be as diverse as clinically feasible so that the data will be useful to general ICU care. There are no concerns enrolling patients who are receiving inotropes and/or vasopressors, though it may be difficult to achieve high protein goals vial the enteral route in these patients. However, the NUTRIEA-2 (Reignier J, Boisrame-Helms J, Brisard L, et al. Enteral versus parenteral early nutrition in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2). *Lancet.* 2018;391(10116):133-143) study demonstrated both the safety and value of using PN in this patient population.

How is the trial handling patients with renal failure (pre/post dialysis), liver cirrhosis and GI bleeding?

This is a pragmatic trial where we have very few exclusion criteria. We are trying to mirror clinical practice and yet not dictate any changes to clinical practice except the protein dosing. Ie don't specify renal or hepatic problems being a contraindication to study participation however, if the clinical team is not comfortable randomizing a patient with one of these conditions, you may exclude them based on your judgement. Exclusion criteria # 4 should be used in this instance as it relates to the clinician NOT having equipoise or having a strong opinion that a high or low dose of protein may NOT be in the patient's best interest.

If a patient on study develops renal failure and requires renal replacement therapy, again, we are not prescriptive as to how you manage the protein dosing except that we strongly encourage you to stay within the ranges set by your randomization schema. If clinicians feel strongly that deviating from this range is in the best interests of the patient, then try and return to the randomized dosing range as soon as possible.

It is important to stress that there are no RCT level of evidence to guide a protein dosing recommendation pre-dialysis or while on dialysis. Therefore, it is explicitly one of our apriori expressed subgroup analyses so we hope there will be enough patients randomized with AKI and/or receiving CRRT that we can see the effect of protein as an outcome in this patient population.

A low protein prescription (i.e. ≤ 1.2/kg/day) does not seem appropriate in some patient groups (e.g. polytrauma, massive surgery, some burns). Are we going to exclude these types of patients from the study?

These patients should be included in the study. This question highlights the importance of the EFFORT Trial. There is insufficient evidence to tell us what protein dose should be recommended to any ICU patient. *What RCT level of evidence is there that supports that assertion that burns, or trauma, or other patient groups need more protein?* Moreover, if you believe the story that protein suppresses autophagy and is associated with worse outcomes, you could be doing harm by continuing this practice. We hope we can include many burns and trauma patients in EFFORT so we can do an apriori specified subgroup analyses on these 'special' populations- which will be the largest randomized evaluation of protein doses in these patients!

If I have a patient that is randomized to the low dose protein arm, but I feel that they need more protein, can I withdraw them from the study?

No, you should not change the protein prescription because this will defeat the purpose of the trial. Don't enroll the patient if you don't have equipoise. But once a patient is enrolled, they can't be withdrawn from the trial (intention-to-treat analysis). Participating sites must do their best to respect the study assigned group.

If something happens clinically that does not enable you to stay within the group assignment, you will treat the patient as appropriate and the patient remains in the trial and data are collected.

Co-Enrollment

We are supportive of co-enrollment in non-industry sponsored or academic randomized trials and observational studies. However, patients should not be co-enrolled in any other nutrition-related trials. If there are questions about the suitability of co-enrollment, please contact the Project Leader.

How do I show my screening activity in REDCap?

All patients screened that at **a minimum fulfill all the inclusion criteria** should be entered into REDCap. The table below outlines the situations where a screened patient should be entered in REDCap.

Inclusion Criteria	Exclusion Criteria	Enter into REDCap?	Comments
Absent	Absent	No	
Present	Present	**Yes**	Excluded patient
Present	Absent	**Yes**	Randomized patient*

**For sites that are not using a waived consent, written consent must be obtained prior to randomization.*

For example, if you have screened a patient that is an adult, with a high BMI (≥ 35), but is not currently mechanically ventilated, they do not fulfill all of the inclusion criteria (i.e. the mechanical ventilation criteria are absent). ***This patient would <u>NOT</u> be entered into REDCap.***

For example, if you have a patient that is an adult who has been identified as having severe malnutrition (as defined by local assessments) and has been mechanically ventilated for the past 24h, and after speaking to the clinical team, it is anticipated that they will continue to be mechanically ventilated for another few days. ***This patient <u>should</u> be entered into REDCap.***

Informed Consent Procedures

Following the confirmation of participant eligibility with the site investigator, the site should proceed with consent procedures. The consent procedures to be followed will differ across participating regions. Sites must ***adhere to written consent procedures as approved by their ethics committee*** (i.e. IEC, IRB, REB).

Sites will either have ethics clearance to use waived consent or standard consent (i.e. written consent obtained from the substitute decision maker).

<u>Substitute-decision maker (SDM):</u> *is someone who has the responsibility for making decisions for a patient, who is not able to make his/her own health care decisions. You will see this term used in the information below.*

Consent Type: Waiver of Consent

- ☑ This must be pre-approved by your ethics board before registering for this trial.
- ☑ For enrolled patients, the family member or a substitute-decision maker (SDM) should be contacted where and when available to advise them regarding the fact that the patient is enrolled in a clinical trial.
- ☑ The information sheet is to be given to the family member/SDM and, once appropriate, the patient.
- ☑ Administer the Clinical Frailty Scale and SARC-F assessments to the family member/SDM at this time.

Consent Type: Standard Written Consent

- ☑ For sites that need to obtain consent, the ICF must be pre-approved by your ethics board before registering for the trial.
- ☑ Written consent from the family member/SDM must be obtained within the first 96h of ICU admission, in order to ensure the participant is randomized to the trial within the 96h timeframe.
- ☑ Administer the Clinical Frailty Scale and SARC-F assessments to the family member/SDM after written consent is obtained.

☑ If during the trial period (first 60 days from ICU admission) the patient regains the capacity to provide informed consent, the patient should be consented using the same ICF the family member/SDM signed. Refer to local policies for further details regarding capacity and re-consent procedures.

Randomization

Once the applicable consent process has been completed (i.e. waived consent or standard written consent), the site study team should proceed to randomize the participant.

Download the detailed instruction guide ***How to Randomize a Participant Using REDCap*** from the website.

Each study participant will be assigned to one (1) of the following study treatment arms:

High Protein Dose	Low Protein Dose
Participants randomized to the *high protein dose* treatment arm of the study will have a prescribed protein intake of *≥ 2.2g/kg/d*.	Participants randomized to the *low protein dose* treatment arm of the study will have a prescribed protein intake of *≤ 1.2g/kg/d*.

For all randomized *patients, the protein target should be followed daily until the first of:*

- ICU Discharge*
- Death
- Transition to oral feeds
- Day 28

**If a patient is discharged from the ICU and is then re-admitted to the ICU within 48 hrs, the study protein target should be resumed. This should continue until the first of the following options listed to the left occurs. Do not resume study protocol if > 48hrs.*

Participant Procedures

The following Schedule of Events table will give you a high level look at how to progress an enrolled participant through the study from the time of randomization until the Day 60 Follow-up.

Please refer to the:

- protocol outcomes section for the primary, secondary and exploratory outcomes explanations.
- CRF Instructions & Worksheet for detailed descriptions, instructions and data collection worksheets related to the data outlined in the table below.

Procedures	Screening/ Enrollment	Day 1 (ICU Adm)	ICU Days 1-12*	ICU days 13-28†	Day 60 from ICU admission
Review of Inclusion/Exclusion criteria	☑				
Randomization	☑				
Participant Characteristics Admission category, diagnosis, comorbidities, sex, age, height, weight, APACHE II, SOFA.		☑			
Enrollment Conditions present at the time of enrollment.		☑			
Nutrition Assessment Recent weight loss or food intake changes.		☑			
Nutrition Goals Protein and calorie goals.		☑			
Standard of Care Laboratory Measurements If collected for clinical reasons: Blood sugar, lowest phosphate, urea (BUN) and creatinine.			☑		
Daily Nutrition Data Type and amount of nutrition received (EN, PN), use of pro-kinetics, use of supplements.			☑	☑ *Protein intake only*	
Other Daily Data Vasopressors/inotropes received and renal replacement therapy.		☑	☑		
Outcomes information Duration of mechanical ventilation, renal replacement therapy, vasopressor use, length of ICU and hospital stay, ICU readmissions, and hospital mortality.					☑
Study Participation Complete					☑

*Collected daily until the first of ICU discharge, death or day 12.

†Collected daily until the first of ICU discharge, death, transition to oral feeds or day 28.