# SECTION 3: PREPARE & PROMOTE

## Contents

# Promotion of the Study Locally

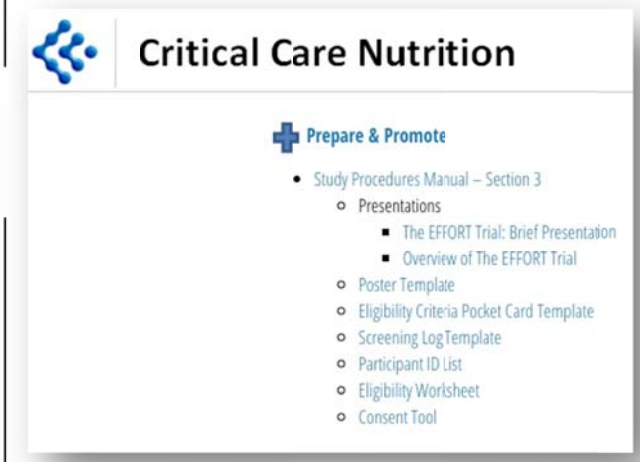
## Engagement of Clinical Staff

Each participating ICU will have a different organizational system and process for introducing a new study to clinical staff. The EFFORT study leaders should take some time to consider their communication strategy and which clinician groups should be engaged.

For example, if the study is running in a surgical ICU, the study leaders should consider engaging the surgeons to get their buy-in regarding the study as the care for any enrolled patient will likely be collaboration between the surgeon and ICU clinicians.

We have developed some tools that study leaders can use as part of their local EFFORT communication strategy.

### In Servicing (Training) Staff




We have created training materials and support documents for the EFFORT study leaders to in service clinical staff. ICUs may download these tools from our website.

***PowerPoint Presentations*** **-** These slide decks may be used to conduct in service training of clinical staff as well as new study team members. They are available for download from the website.

- The ***EFFORT Trial Brief Presentation*** – This presentation may be used to engage the ICU team and succinctly explain the purpose of the trial.
- ***Overview of The EFFORT Trial*** – This presentation is longer and may be suitable for local implementation purposes as the study team sees fit.

***NIBBLE –*** A nutritional memo (posted on our website) which addresses the issue of clinical equipoise. ***"Should We Have Equipoise (or Clinical Uncertainty) About How Much Protein to Provide to Critically Ill Patients?" This NIBBLE should be shared with clinicians (Doctors and Dietitians) working in participating ICUs so that they are comfortable with randomizing patients into this trial.***

***Poster*** **-** A Poster template is available for sites to post around their ICU to create study awareness amongst the staff. Please note that use of this poster may require local ethics approval. If you are not sure whether this should be submitted for approval prior to use, please contact your ethics committee. They are available for download from the website.

***Eligibility Criteria Pocket Cards*** **-** A template for pocket size study eligibility criteria cards is available for sites to use and distribute to their attending physicians, residents and nursing staff. They are available for download from the website.

## *Addressing Clinical Staff Questions & Concerns*

**Are we blinded to the study intervention? If a patient is randomly assigned to the low protein dose group (i.e. ≤ 1.2g/kg/d); can I give them more protein if I think that the patient needs more protein?**

This is not a blinded study.

The clinical team should not change the protein prescription, if you do, that will defeat the purpose of the trial. *Remember, to register for the trial you had to confirm that your ICU (including the clinicians) have clinical equipoise to the study treatment arms. If however, for a particular patient, you don't have equipoise, they should not be enrolled. If something happens clinically that does not enable you to stay within the group assignment, we will have to live with this. But the patient remains in the trial and data are to be collected.

**We have a very hard time feeding our patients the majority of their prescribed needs. If patients are unable to meet 80% of their goal, are they eliminated from the study?**

There is no penalty if patient did not reach at least 80% of the protein goal daily; however, we expect that sites, based on their clinical experience, be able to provide the protein goal to patients allocated to each arm of study. We have built in a daily nutritional adequacy tool into the data collection system to help sites monitor their adherence to the study intervention and nutrition goals. This tool will allow you to clearly see how well you are complying with the treatment protocol and make changes to improve your adherence.

**What do I do if my ICU does not normally feed protein at high levels found in the high protein dose arm (i.e. ≥ 2.2g/kg/d)?**

We expect that most participating ICUs will have their standard approach to providing protein to their patients and that their 'normal practice' will not be to target >2.2 grams/kg/day in all patients. Some may target 1.2 gram/kg/day or 1.5 gram/kg/day. However, the guidelines support anywhere from 1.2-2.0 grams/kg/day, experts recommend up to 2.5 grams/kg/day, and our observations of real practice observe some patients getting anywhere from 0.5 to 3.5 gram/kg/day. *Remember, for ICUs to

participate, they have to agree that we don't know what the right amount is and they must be willing to alter their 'standard' approach so that they follow the randomization scheme: that patients randomized to the high dose get 2.2grams/kg/day (or at last 80% of that) and those randomized to the low group get 1.2 grams/kg/day (or at least 80% of that and not any more).

**Protein prescription in amounts of ≤ 1.2/kg/day is not rational in some groups of patients such as poly trauma, massive surgery, and some burns. Are patients with higher protein needs going to be excluded from the study?**

The reason we are doing this trial is that we have 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. By the way, we hope we can include many burns and trauma patients so we can do an *a priori* subgroup analyses on these 'special' populations, which will be the largest randomized evaluation of protein doses in these patients!

**How is the trial handling patients with renal failure pre and post dialysis, and how is it handling patients with liver cirrhosis with 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. There is an important exclusion criteria that relates to the clinician NOT having equipoise or where the clinician feels strongly that a high (or low) dose protein may NOT be in the patient's best interest (i.e. that patient would be excluded). Renal or hepatic problems are not a contraindication to participation but if the clinical team is not comfortable randomizing such patients, you may exclude them based on your judgement.

With regards to renal failure, there is a rationale that high dose amino acids/protein may be helpful in AKI w/o RRT and there is a recent post hoc analysis that suggests it may be harmful. See below excerpt from the NIBBLE https://www.criticalcarenutrition.com/resources/nibbles -Issue 21 which summarizes the situation.

*Outcomes in renal failure:*

- Nephroprotect was a multicenter RCT comparing provision of IVAA at a dose of up to 2.0g/kg/day to standard care. As stated earlier, this study represents the strongest evidence against a higher protein dose. The rationale of the Nephroprotect study was built on the following observations:
    - Animal models have demonstrated that an increase in renal blood flow in response to a short-term amino acid infusion can protect the kidney from acute ischemic insults. [25]
    - Several observational studies and one RCT document improved nitrogen balance in dialysis patients receiving higher amounts of amino acids.[26,27,28,29,30]

- A single center RCT (n=53) in critically ill patients demonstrated that a short-term infusion of IVAA led to faster recovery from severe acute renal failure, particularly in those with oliguric renal failure, in those who received dialysis, and in those who developed sepsis.[31]
- Another single center trial (n=14) compared 2 doses of IVAA in critically ill patients with non-oliguric renal failure (creatinine clearance below 50 mL/min), and those receiving a higher AA dose were more likely to preserve the effect of diuresis and required less furosemide to achieve negative fluid balance.[32]
- A subgroup analysis of a cluster RCT of 27 ICUs evaluating nutrition guidelines identified 242 critically ill patients at high risk of renal dysfunction at study entry and found those with greater protein dose were less likely to require RRT.[33,34]

• A post-hoc, hypothesis-generating, subgroup analysis of the same trial suggested a survival advantage to those patients with normal renal function who received the supplementary IVAA compared to usual care (21/179 [11.7%] vs. 37/189 [19.6%]), but also suggested potential harm (lower survival) in those with renal dysfunction at baseline (17/60 [28.3%] vs. 7/46 [15.2%]).[35] The later observation was not significant in the adjusted analysis (covariate-adjusted risk difference, –0.6%; 95% CI, –16.2 to 15.2; p = 0.95). However, we note several limitations to this post hoc analysis: 1) Subgroup numbers are small and event rates low, so results are unstable or fragile; 2) There is inconsistency among study outcomes (only mortality showed a significant difference between groups; but quality of life and physical function measures tended to be worse with treatment); and 3) Given the underlying rationale for the Nephroprotect study, that IV AA were intended to improve the outcome of patients with renal dysfunction, there is a lack of compelling biological plausibility for this sub-group finding. Nevertheless, it remains a published hypothesis that IVAA supplementation may increase harm in patients with renal failure (or may save lives in patient with normal kidney function).

In the end, we don't know which the right answer is. We feel the only ethical answer is to have our patients participate in an RCT so we can get to the answer. We are capturing kidney function status in the EFFORT database and intend in doing a subgroup analysis if there are enough patients with AKI in the trial.

# Preparing to Begin Patient Recruitment

## Clinical Supplies & Nutrition Products

There are no supplies provided to the sites for this trial. ***Sites will use nutrition products available at their institution, as clinically indicated, to achieve the appropriate protein dose in accordance with the study group assignment.***

Refer to the next section "Recruit Participants" for examples of nutrition products that can be used to achieve the study group assignment.

## Organizing Study Paperwork

Each site must ensure that they maintain data (i.e. source documents) and records that are organized and retrievable for each study participant. This documentation should clearly note the screening, consent and study procedures performed and data collected for each participant.

### Screening Packages

Tools are available to ICUs to document screening, consent and enrolment procedures followed for each patient. It is recommended that screening packages are prepared before recruitment activities start.

Having packages pre-assembled and ready for use will make the process more efficient for the local study team.

It is recommended that each screening package contain the following documents:

- ✓ Eligibility Worksheet
- ✓ Ethics Approved:
  - o Consent Form (if ethics approval requires a standard consent)
  - o Patient Information Form (if ethics approval allows for waived consent)
- ✓ Consent Tool

Detailed information regarding the use of these tools is found in the next section "Recruit."

### Enrolled Patient Packages

Once a patient is enrolled in EFFORT, over the course of their participation you will be creating and collecting study records to support the data you are collecting. A best practice recommendation is that you create an individual study file for each patient.

Participating ICUs may use any existing practices related to maintaining individual patient study records however, if an ICU does not already have procedures in place to do this they may create a patient study file as suggested in the image on the left.


The purpose of each of the documents as noted in the suggested index to the left, as well as the worksheet templates are explained in the next section "Recruit."

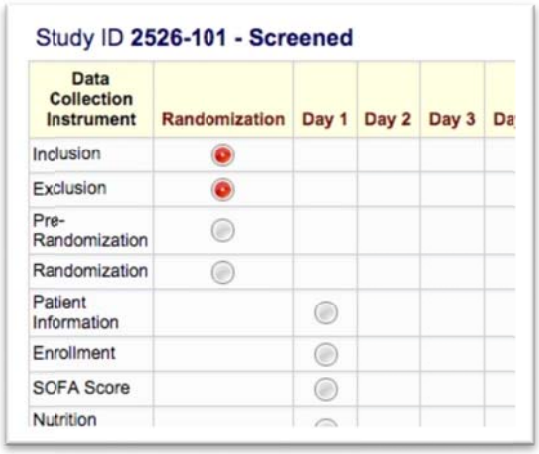
## How to Keep Track of Screened and Enrolled Patients from your ICU

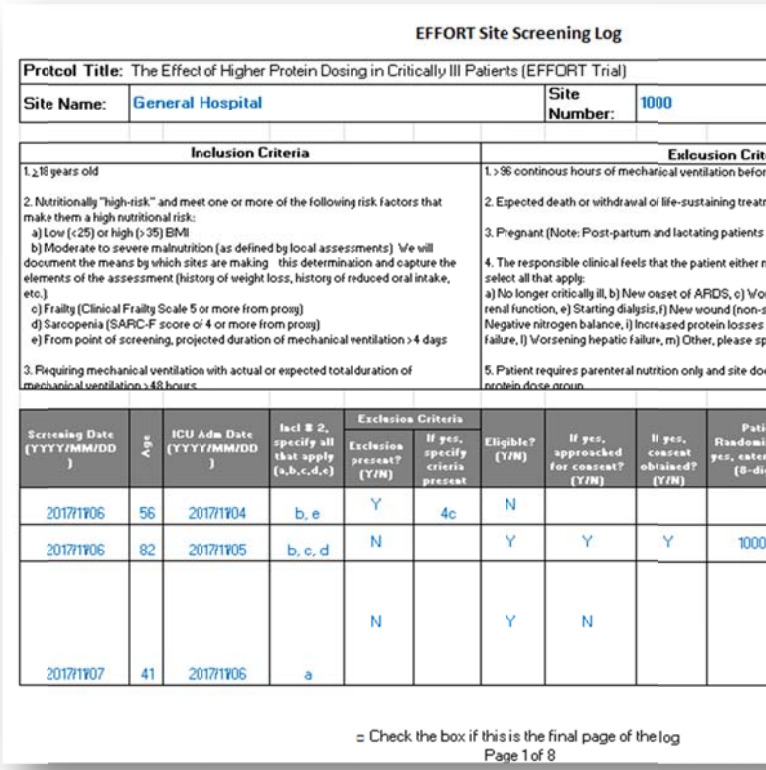
To make sure you are following Good Clinical Practice (GCP), an essential activity is to maintain records and tracking documents about the types of patients that have been screened for the study. If they are found to be eligible for the study, also keep records about their consent (if applicable) and enrolment.

### Screening Logs

The purpose of keeping a screening log document is to record patients who entered pre-trial screening. It also serves to chronologically document the enrollment of eligible patients. And finally, it can be used to assist the site in updating their screening data in REDCap.

**Screen shot of the EFFORT Trial Screening Log**





EFFORT Site Screening Log

Protcol Title: The Effect of Higher Protein Dosing in Critically Ill Patients (EFFORT Trial)

Site Name: General Hospital | Site Number: 1000

| Inclusion Criteria | Exclusion Crit |
|---|---|
| 1. ≥18 years old<br><br>2. Nutritionally "high-risk" and meet one or more of the following risk factors that make them a high nutritional risk:<br>a) Low (<25) or high (>35) BMI<br>b) 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.)<br>c) Frailty (Clinical Frailty Scale 5 or more from proxy)<br>d) Sarcopenia (SARC-F score of 4 or more from proxy)<br>e) From point of screening, projected duration of mechanical ventilation >4 days<br><br>3. Requiring mechanical ventilation with actual or expected total duration of mechanical ventilation >48 hours | 1. >96 continous hours of mechanical ventilation befor<br><br>2. Expected death or withdrawal of life-sustaining treatr<br><br>3. Pregnant (Note: Post-partum and lactating patients<br><br>4. The responsible clinical feels that the patient either r select all that apply:<br>a) No longer critically ill, b) New onset of ARDS, c) Wo renal function, e) Starting dialysis, f) New wound (non-s Negative nitrogen balance, i) Increased protein losses failure, l) Worsening hepatic failure, m) Other, please sp<br><br>5. Patient requires parenteral nutrition only and site do protein dose group |

| Screening Date (YYYY/MM/DD) | Age | ICU Adm Date (YYYY/MM/DD) | Incl # 2, specify all that apply (a,b,c,d,e) | Exclusion Criteria: Exclusion present? (Y/N) | Exclusion Criteria: If yes, specify criteria present | Eligible? (Y/N) | If yes, approached for consent? (Y/N) | If yes, consent obtained? (Y/N) | Pati Randomi yes, ente (8-di |
|---|---|---|---|---|---|---|---|---|---|
| 2017/11/06 | 56 | 2017/11/04 | b, e | Y | 4c | N | | | |
| 2017/11/06 | 82 | 2017/11/05 | b, c, d | N | | Y | Y | Y | 1000 |
| 2017/11/07 | 41 | 2017/11/06 | a | N | | Y | N | | |

= Check the box if this is the final page of the log

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The ***Screening Log*** template can be downloaded from the website.

1. **Record all patients that meet <u>all inclusion criteria.</u>** (NOTE: If they do not meet all inclusion criteria, then you do not need to enter them into the log).
    a. Patients must meet <u>all</u> inclusion criteria to be eligible for the study.
    b. A patient is <u>not</u> eligible for the study if they meet any of the exclusion criteria.
    c. Where possible and appropriate, patient eligibility should be confirmed with a physician before randomizing.
    d. Patients must be randomized in the trial within 96 hours of their ICU admission.

2. Record the unique ID number assigned to the patient in REDCap on the Screening Log.

ID number = 2526-101

*Refer to SECTION 4: Recruit, for details on entering patients into REDCap to obtain the unique study ID number.*

3. If a patient has had several admissions to the ICU, use the **most recent** admission.
    a. Once a patient is randomized, they cannot be randomized again. For example, if you enrolled and collected data on a patient, they are discharged and leave the hospital. Then one week later they are admitted again. You cannot enroll this patient a second time.
    b. If a patient you are collecting data on is discharged from the ICU to the ward and is readmitted to the ICU within 48 hours consider, for the purposes of data collection, we treat this as if the patient never left the ICU. Collect data for the hours they were not in the ICU as best as possible, and continue collecting data on them once they return to the ICU.

4. This document may be maintained electronically or the template may be printed and 'wet ink' entries made as needed.

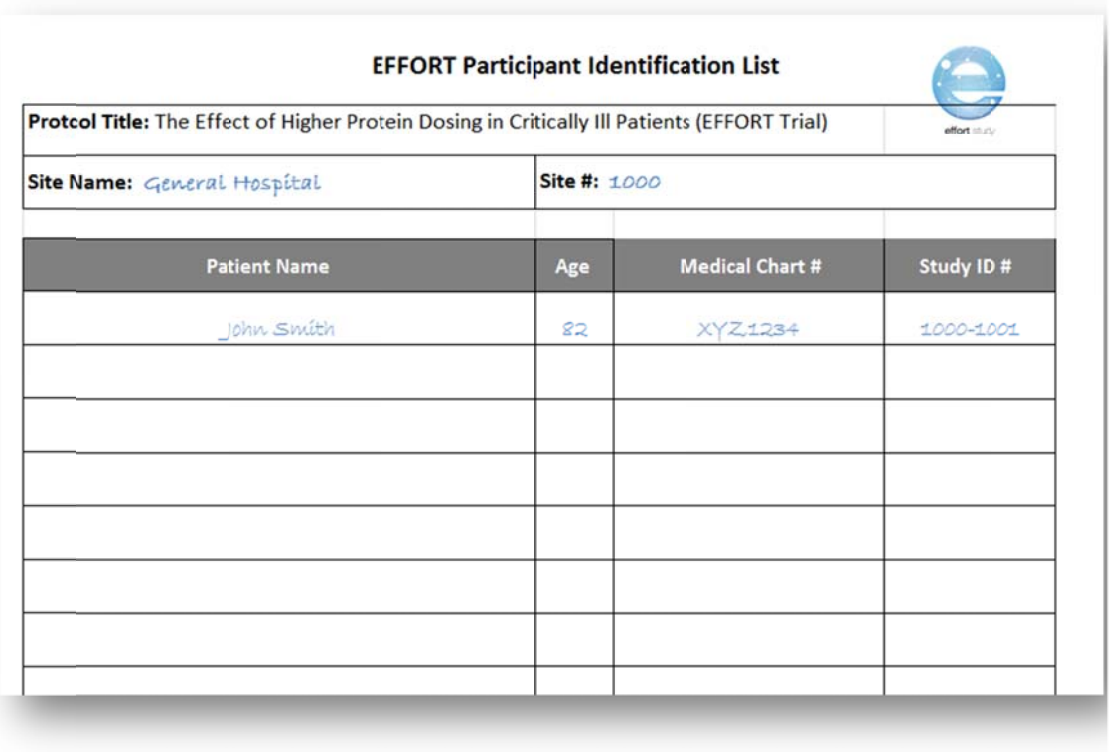
Please keep the Screening Log to help track down which patient corresponds to which patient ID number in case we have data queries at a later date, or if your site is selected for source verification. Use additional pages of the Screening Log as necessary.

### *Participant ID List*

The purpose of the Patient ID List is to permit the identification of all participants enrolled in the trial in case follow-up is required.

***This log contains personally identifying information and must be kept confidential. Do not send to the coordinating centre or Project Leader.***

**Screen shot of the EFFORT Trial Patient ID List**



**EFFORT Participant Identification List**

**Protcol Title:** The Effect of Higher Protein Dosing in Critically Ill Patients (EFFORT Trial)

**Site Name:** General Hospital | **Site #:** 1000

| Patient Name | Age | Medical Chart # | Study ID # |
|---|---|---|---|
| John Smith | 82 | XYZ1234 | 1000-1001 |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |

The ***Patient ID List*** can be downloaded from the website.

1. Record patients only who are <u>randomized</u> to the study on this log.

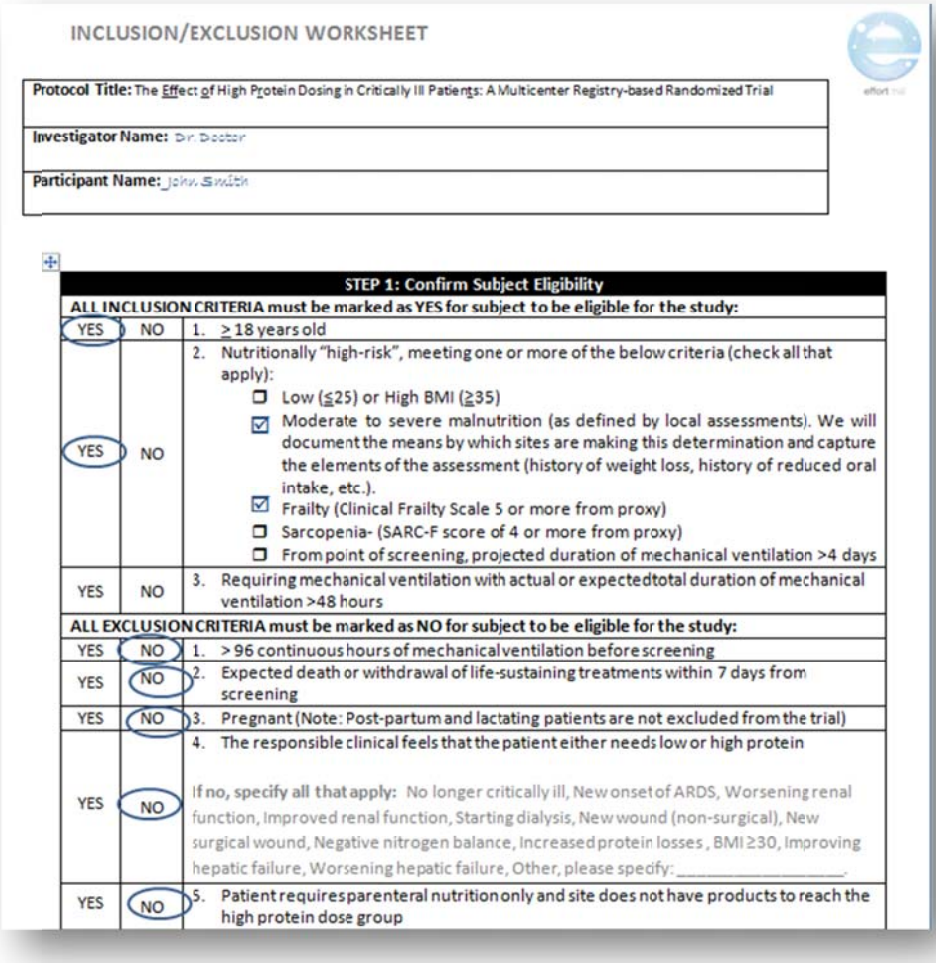
2. This document may be maintained electronically or the template may be printed and. and 'wet ink' entries made as needed.

## Documenting Eligibility and Consent

### Eligibility Worksheet

An important aspect of Good Clinical Practice is to ensure that there are records which accurately document the screening, consent and randomization processes being conducted. Use of the Eligibility Worksheet represents best practice for documenting these activities.

**Screen shot of EFFORT Eligibility Worksheet**



INCLUSION/EXCLUSION WORKSHEET

**Protocol Title:** The Effect of High Protein Dosing in Critically Ill Patients: A Multicenter Registry-based Randomized Trial

**Investigator Name:** Dr. Doctor

**Participant Name:** John Smith

| STEP 1: Confirm Subject Eligibility | | |
|---|---|---|
| **ALL INCLUSION CRITERIA must be marked as YES for subject to be eligible for the study:** | | |
| YES | NO | 1. ≥ 18 years old |
| YES | NO | 2. Nutritionally "high-risk", meeting one or more of the below criteria (check all that apply):<br>☐ Low (≤25) or High BMI (≥35)<br>☑ 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.).<br>☑ Frailty (Clinical Frailty Scale 5 or more from proxy)<br>☐ Sarcopenia- (SARC-F score of 4 or more from proxy)<br>☐ From point of screening, projected duration of mechanical ventilation >4 days |
| YES | NO | 3. Requiring mechanical ventilation with actual or expected total duration of mechanical ventilation >48 hours |
| **ALL EXCLUSION CRITERIA must be marked as NO for subject to be eligible for the study:** | | |
| YES | NO | 1. > 96 continuous hours of mechanical ventilation before screening |
| YES | NO | 2. Expected death or withdrawal of life-sustaining treatments within 7 days from screening |
| YES | NO | 3. Pregnant (Note: Post-partum and lactating patients are not excluded from the trial) |
| YES | NO | 4. The responsible clinical feels that the patient either needs low or high protein<br>If no, specify 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, BMI ≥30, Improving hepatic failure, Worsening hepatic failure, Other, please specify: _____ |
| YES | NO | 5. Patient requires parenteral nutrition only and site does not have products to reach the high protein dose group |

The ***Eligibility Worksheet*** can be downloaded from the website.

1. For each patient randomized to the EFFORT Trial, an Eligibility Worksheet should be completed and filed with the patient study documents.
2. Each step in completing this form is to be completed as follows:
    a. ***STEP 1*** – Confirm the patient's eligibility by reviewing and documenting the presence of all inclusion criteria and the absence of all exclusion criteria.
    b. ***STEP 2*** – If the patient is eligible for the study proceed to engage with a physician to ensure it is medically appropriate to enroll the patient into the study. Either a site investigator or an attending physician responsible for the care of the patient can be consulted.
    c. ***STEP 3*** – When applicable (i.e. standard consent is required by the local ethics committee) consent activities should be documented.
    d. ***STEP 4*** – Once consent has been obtained (if applicable) proceed to enter the patient's screening information into REDCap and Randomize the patient.

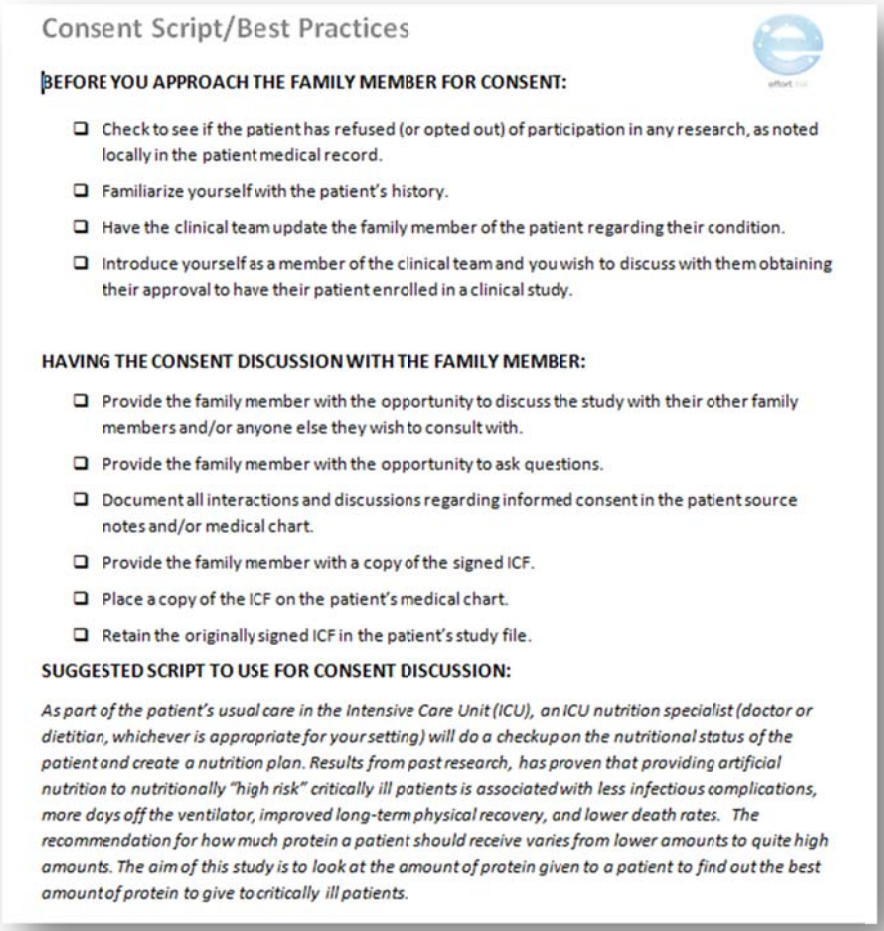
e. ***STEP 5*** – This worksheet must be signed off and dated by the individual who conducted the screening, consent and enrollment of this patient.

## Consent Tool

If your ethics committee requires written informed consent for this study, this tool may assist the sites with the consent dialogue with a patient's family member by providing a suggested script for describing the EFFORT Trial. As well, it outlines the steps that should be followed when performing activities related to consent.

This tool may be modified by the site to ensure adherence to local practice and policies.

**Screen shot of Consent Tool**



Consent Script/Best Practices

**BEFORE YOU APPROACH THE FAMILY MEMBER FOR CONSENT:**

- ❑ Check to see if the patient has refused (or opted out) of participation in any research, as noted locally in the patient medical record.
- ❑ Familiarize yourself with the patient's history.
- ❑ Have the clinical team update the family member of the patient regarding their condition.
- ❑ Introduce yourself as a member of the clinical team and you wish to discuss with them obtaining their approval to have their patient enrolled in a clinical study.

**HAVING THE CONSENT DISCUSSION WITH THE FAMILY MEMBER:**

- ❑ Provide the family member with the opportunity to discuss the study with their other family members and/or anyone else they wish to consult with.
- ❑ Provide the family member with the opportunity to ask questions.
- ❑ Document all interactions and discussions regarding informed consent in the patient source notes and/or medical chart.
- ❑ Provide the family member with a copy of the signed ICF.
- ❑ Place a copy of the ICF on the patient's medical chart.
- ❑ Retain the originally signed ICF in the patient's study file.

**SUGGESTED SCRIPT TO USE FOR CONSENT DISCUSSION:**

*As part of the patient's usual care in the Intensive Care Unit (ICU), an ICU nutrition specialist (doctor or dietitian, whichever is appropriate for your setting) will do a checkup on the nutritional status of the patient and create a nutrition plan. Results from past research, has proven that providing artificial nutrition to nutritionally "high risk" critically ill patients is associated with less infectious complications, more days off the ventilator, improved long-term physical recovery, and lower death rates. The recommendation for how much protein a patient should receive varies from lower amounts to quite high amounts. The aim of this study is to look at the amount of protein given to a patient to find out the best amount of protein to give to critically ill patients.*

The ***Consent Tool*** can be downloaded from the website.

## Are you Ready to Start Recruiting Patients?

Now that you have completed the EFFORT promotion and preparation activities let's see if you are ready to start recruiting patients.

*Review the items below to see how ready your ICU is to begin patient recruitment activities for the EFFORT Trial.*

- ❒ Have you prepared the Screening Log template for local use?
- ❒ Have you prepared the Participant ID List template for local use?
- ❒ Create screening packets (e.g. consent form/information sheet, Eligibility Worksheet, Consent Tool, etc.) so you can 'grab and go' when you have a potentially eligible patient.
    - o Ensure the consent form/information sheet approved by your ethics committee is the version used.
- ❒ Create multiple copies of enrolled participant study files (e.g. blank copies of data collection worksheets, etc.) so you can 'grab and go' when you have an enrolled participant.
- ❒ Review and become familiar with the procedures outlined in Sections "Recruit" and "Data Collection and Entry"
    - o Review How to Randomize a Participant Using REDCap from the "Recruit" section.

**Good luck!**

Please don't hesitate to contact the National Coordinator or Project Leader with any questions you might have as you begin your recruitment activities.