Supplementary Online Content


**eMethods.** Additional Methods and Results (Inclusion Criteria, Exclusion Criteria, Gastrointestinal Intolerances, Supplement Administration, Ventilator Procedures, Weaning, Commencement of Weaning, Spontaneous Breathing Trial Procedure and Assessment for Unassisted Breathing, Decision to Remove Ventilatory Support, Definition of Unassisted Breathing, Completion of Ventilator Procedures, Removal from the Ventilator Management Protocol, Conservative Fluid Management Approach, Plasma Fatty Acid Levels, Plasma Cytokines, Urine Leukotrienes and Isoprostanes, Efficacy and Futility Stopping Rules

**eTable.** Daily Calories Delivered by Enteral Feedings by Study Group

**eFigure 1.** Percent of Total Plasma Fatty Acids for Arachidonic Acid (AA) and Eicosapentanoic Acid (EPA)

**eFigure 2a.** Plasma IL-6 and IL-8 Levels

**eFigure 2b.** Plasma Leukotriene E4 (LTE4) Levels

**eFigure 2c.** Urinary F2- and F3-Isoprostanate Levels

**eFigure 3a.** Mean Serum Glucose Levels

**eFigure 3b.** Mean Morning Insulin Drip Rates

**eFigure 4.** Vasopressor Use by Day
eMethods

Inclusion Criteria

Patients were eligible for inclusion if they met all of the below criteria. Criteria 1-3 must have been present within a 24-hour time period:

Acute onset (defined below) of:

1. \( \text{PaO}_2 / \text{FiO}_2 \leq 300 \). If altitude > 1000m, then \( \text{PaO}_2 / \text{FiO}_2 \leq 300 \times (\text{PB}/760) \)

2. Bilateral infiltrates consistent with pulmonary edema on frontal chest radiograph. The infiltrates could be patchy, diffuse, homogeneous, or asymmetric

3. Requirement for positive pressure ventilation via endotracheal tube, and

4. No clinical evidence of left-sided cardiac failure to account for bilateral pulmonary infiltrates.

5. Intention of primary medical team to provide enteral nutrition to the patient

The 48-hour enrollment time window began when criteria 1-3 were met. If a patient met the first three inclusion criteria but had a PAOP (Pulmonary Arterial Wedge Pressure) greater than 18 mmHg, then the first four criteria had to persist for more than 12 hours after the PAOP had declined to \( \leq 18 \) mmHg, and still be within the 48-hour enrollment window.

“Acute onset” was defined as the duration of the hypoxemia criterion (#1) and the chest radiograph criterion (#2) must have been present for \( \leq 28 \) days at the time of randomization. Opacities considered “consistent with pulmonary edema” included any opacities not fully explained by mass, atelectasis, or effusion or opacities known to be chronic (greater than 28 days). Vascular redistribution, indistinct vessels, and indistinct heart borders alone were not considered “consistent with pulmonary edema” and thus did not count as qualifying opacities for this study.

Exclusion Criteria

1) Age < 13 years
2) Greater than 48 hours since all inclusion criteria met
3) Neuromuscular disease that impairs ability to ventilate without assistance, such as:
   a) cervical spinal cord injury at level C5 or higher
   b) amyotrophic lateral sclerosis
   c) Guillain-Barré Syndrome
   d) myasthenia gravis
   e) Kyphoscoliosis or chest wall deformity resulting in severe exercise restriction, secondary polycythemia, or respirator dependence
4) Pregnant or breast-feeding
5) Severe chronic respiratory disease, demonstrated by any of:
   a) \( \text{FEV}_1 < 20 \text{ ml/kg PBW} \)
   b) \( \text{FEV1/VC} < 50\% \) predicted
   c) Chronic hypercapnea with \( \text{PaCO}_2 > 45 \text{ mm Hg} \)
   d) Chronic hypoxemia with \( \text{PaO}_2 < 55 \text{ mm Hg on FiO}_2 = 0.21 \)
   e) Radiographic x-ray evidence of any chronic over-inflation or chronic interstitial infiltration
   f) Hospitalization within the past 6 months for respiratory failure
g) Chronic restrictive, obstructive, neuromuscular, chest wall, or pulmonary vascular disease resulting in severe exercise restriction, secondary polycythemia, severe pulmonary hypertension with mean PAP > 40 mm Hg, or respirator dependency

6) Burns greater than 40% total body surface area

7) Malignancy or other irreversible disease or condition for which 6-month mortality is estimated to be greater than 50%:
   a) Poorly controlled neoplasms
   b) Known HIV positive with known end stage process and known CD4 count < 50 / mm$^3$
   c) Prior cardiac arrest requiring cardiopulmonary resuscitation without fully demonstrated neurologic recovery
   d) New York Heart Association Class IV exercise restriction
   e) Chronic condition making patient respirator dependent

8) Allogeneic bone marrow transplant in the last 5 years

9) Patient, surrogate, or physician not committed to full support (Exception: a patient was not excluded if he/she would receive all supportive care except for attempts at resuscitation from cardiac arrest).

10) Severe chronic liver disease (Child-Pugh Score of 11-15)$^e$

11) Diffuse alveolar hemorrhage from vasculitis.

12) Morbid obesity (> 1kg/cm body weight)

13) No consent/inability to obtain consent

14) Unwillingness or inability to utilize the ARDS network 6 ml / kg PBW lung protective ventilation protocol

15) Moribund patient not expected to survive 24 hours

16) No intent to obtain central venous access for monitoring intravascular pressures.

17) Greater than 72 hours since initiation of mechanical ventilation

18) Refractory shock, defined by any of the following:
   a) Dopamine infusion at rate ≥ 15 mcg / kg / min
   b) Dobutamine infusion at rate ≥ 15 mcg / kg / min
   c) Epinephrine or Norepinephrine infusion at rate ≥ 30 mcg / min
   d) Phenylephrine infusion at rate ≥ 50 mcg / min
   e) Milrinone infusion at rate ≥ 0.5 mcg / kg / min
   f) Vasopressin infusion at rate > 0.04 U / min
   g) Intra-aortic Balloon Pump

19) Unable to obtain enteral access

20) Presence of partial or complete mechanical bowel obstruction, or ischemia, or infarction

21) Current TPN use or intent to use TPN within 7 days

22) Severe malnutrition with BMI < 18.5 or loss of > 30% total body weight in the previous 6 months

23) Laparotomy expected within 7 days

24) Unable to raise head of bed 30 degrees

25) Short-bowel syndrome or absence of gastrointestinal tract

26) Presence of high-output (> 500 cc/day) enterocutaneous fistula

27) INR > 5.0 or platelet count < 30,000 / mm$^3$ or history of bleeding disorder

28) Intracranial hemorrhage within the previous month

29) Allergy to enteral formula, n-3 fatty acids, gamma-linolenic acid, vitamin E, vitamin C, beta-carotene, taurine, or L-carnitine

30) Requirement for, or physician insistence on, enteral formula supplemented with n-3 fatty acids (ex: Oxepa®, Impact®) or providing n-3 fatty acid, GLA, or anti-oxidant supplementation
Gastrointestinal Intolerances
The action taken if a patient had one of the following gastrointestinal intolerances was
standardized. However, the patient’s primary medical team determined whether or not the
patient fulfilled the criteria for meeting the definition of the specific gastrointestinal intolerance.

The gastric residual volume (GRV) was the amount of gastric contents able to be withdrawn
from the gastric tube using a 60 cc syringe. If the patient had a post-pyloric feeding tube, gastric
residuals were measured only if a separate gastric port on the feeding tube or a separate gastric
tube was in place. If two gastric residuals exceeded 400 cc, the feeds were held and feeding rate
decreased. GRV in patients receiving post-pyloric feeding were only considered significant if they
exceeded 400 cc and contained tube feeding formula. The aspiration of gastric juice in patients fed
through post-pyloric tubes was not considered gastric residual for the purpose of adjusting tube
feeding rates unless it contained enteral formula. The use of pro-kinetic agents and/or advancing
the distal location of the feeding tube to a postpyloric position was suggested in patients
experiencing more than one episode of elevated gastric residual volume.

Abdominal distention or cramping was defined as the presence of a tense abdomen, rigidity,
guarding or rebound on exam. Aspiration was defined as the presence of food in the lungs. This
was determined by the primary medical team, but included visualization of enteral feeds in the
endotracheal tube or enteral formula suctioned from the endotracheal tube. Regurgitation was
defined as the presence of enteral feeds in the oropharynx or nasopharynx on routine oral care.
Vomiting was defined as the forceful expulsion of gastric contents from the oropharynx or
nasopharynx. Diarrhea was defined as more than 3 liquid bowel movements totaling more than an
estimated 500 cc in a 24-hour period. The treatment of diarrhea was determined by the patient’s
primary medical team and included discontinuation of laxatives and/or pro-kinetics, initiation of anti-
diarrheals, treatment for C. difficile infection, or addition of fiber to the diet. The treatment did not
include decreasing the enteral feeding rate unless the primary medical team felt that the patient’s
health was at risk because of the severity or nature of the diarrhea. Constipation was defined as
the absence of a bowel movement requiring a specific intervention
(i.e. enema, laxative, disimpaction, etc.) at the discretion of the primary medical team. The
treatment was determined by the patient’s primary medical team, but did not include decreasing
the enteral feeding rate unless the primary medical team felt that the patient’s health was at risk
because of the severity or nature of the constipation.

Supplement Administration
N-3 or matching control supplement was delivered in 2 oz (60 cc) sterile, plastic bottles to the
investigational pharmacy at each hospital. The investigational pharmacy delivered two plastic
bottles (2 x 60 cc) of supplement every 12 hours to the patient’s location for administration,
beginning at the time of randomization. Two 60 cc bottles were utilized for each administration (4
bottles or 240 cc each day). The bedside nurse was instructed to give the entire 120 cc of
supplement at one time through the enteral feeding tube. The feeding tube was then flushed with
60 cc of sterile water after the supplement was given to ensure delivery of the entire volume.

The gastric contents were not removed for at least two hours after study supplement
administration. If a study dosing time was missed, the supplement was administered as soon as
possible after the missed dosing time, unless it was more than six hours late in which case the
dose was skipped. The next scheduled dose and all subsequent doses were continued on the
original every 12-hour schedule.

N-3 or control supplement was administered even when enteral feedings were being held. The
exception to this was in cases when enteral feedings were being held because of vomiting. In
these situations, the supplement was held until six hours after the last episode of vomiting. All subsequent doses continued on the original every 12-hour schedule.

In the event of regurgitation, aspiration, or vomiting of the supplement, no attempt was made to replace expelled contents but the episode was recorded on the case report form as a gastrointestinal intolerance event.

Due to a theoretical risk of bleeding from n-3 fatty acids, study supplement was held when patients’ INR exceeded 5.0 or platelets were less than 30,000/mm³ and discontinued entirely in patients who developed intracranial hemorrhage.

**Ventilator Procedures**

A simplified version of the ARDS Network lung protective lower tidal volume strategy was initiated within 1 hour of randomization and used throughout this trial:

1. Tidal Volume (Vt) Goal: 6 ml / kg PBW
   - Predicted body weight (PBW) is calculated from age, gender, and height (heel to crown) according to the following equations:
     
     **Males:** PBW (kg) = 50 + 2.3 [height (inches) – 60]  
     **Females:** PBW (kg) = 45.5 + 2.3 [eight (inches) – 60]

2. Any mode of ventilation capable of delivering the prescribed Vt (6ml/kg PBW, +/- 2ml/kg) could be used, provided the Vt target was monitored and adjusted appropriately. During APRV, Vt was defined as the sum of the volume that results from the ventilator pressure-release and an estimation of the average spontaneous Vt.

3. Measure and record inspiratory plateau pressure (Pplat) according to ICU routine (at least every four hours and after changes in Vt and PEEP recommended)

4. If Pplat > 30 cm H₂O, reduce Vt to 5 ml / kg and then to 4 ml / kg PBW if necessary to decrease Pplat to ≤ 30 cm H₂O.

5. If Vt < 6 ml / kg PBW and Pplat < 25 cm H₂O, raise Vt by 1 ml / kg PBW to a maximum of 6 ml / kg.

6. If "severe dyspnea" (more than 3 double breaths per minute or airway pressure remains at or below PEEP level during inspiration), then raise Vt to 7 or 8 ml / kg PBW if Pplat remains below 30 cm H₂O. If Pplat exceeds 30 cm H₂O with Vt of 7 or 8 ml / kg PBW, then revert to lower Vt and consider more sedation.

7. If pH < 7.15, Vt may be raised and Pplat limit suspended (not required).

8. Oxygenation target: 55 mmHg < PaO₂ < 80 mm Hg or 88% < SpO₂ < 95%. When both PaO₂ and SpO₂ are available simultaneously, the PaO₂ criterion will take precedence.

9. Minimum PEEP = 5 cm H₂O

10. Adjust FiO₂ or PEEP upward within 5 minutes of consistent measurements below the oxygenation target range

11. Adjust FiO₂ or PEEP downward within 30 minutes of consistent measurements above the oxygenation target range.

12. There are no requirements for maintaining a specific PEEP to FiO₂ ratio. The lower PEEP / higher FiO₂ table represents a consensus approach developed by ARDS Network investigators. The higher PEEP / lower FiO₂ table (ALVEOLI) yielded equivalent results in a randomized trial and would be acceptable and perhaps preferable in patients who...
appear to respond with substantial increase in arterial oxygenation in the transition from lower to higher PEEP.

### Lower ELV/Higher FiO₂ Treatment Group

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### Higher ELV/Lower FiO₂ Study Group

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</table>

(Levels of PEEP in these FiO₂ / PEEP scales represent levels set on the ventilator, not levels of total-PEEP, auto-PEEP, or intrinsic-PEEP.)

13. No specific rules for respiratory rate, but incremental increase in the RR to maximum set rate of 35 if pH < 7.30.

14. No specific rules about I:E. Recommend that duration of Inspiration be ≤ duration of Expiration.

15. Bicarbonate is allowed (neither encouraged nor discouraged) if pH < 7.30.

Changes in more than one ventilator setting driven by measurements of PaO₂, pH, and Pplat may be performed simultaneously, if necessary.

**Weaning**

**Commencement of Weaning**

Patients were assessed for the following weaning readiness criteria each day between 06:00 and 10:00. If a patient procedure, test, or other extenuating circumstance prevented assessment for these criteria between 06:00 and 10:00, then the assessment and initiation of subsequent weaning procedures could be delayed for up to six hours.

(a) At least 12 hours since enrollment in the trial.

(b) FiO₂ ≤ 0.40 and PEEP ≤ 8 cm H₂O or FiO₂ ≤ 0.50 and PEEP = 5 cm H₂O

(c) Values of both PEEP and FiO₂ ≤ values from same time the previous day

(d) Not receiving neuromuscular blocking agents and without neuromuscular blockade

(e) Patient exhibiting inspiratory efforts. If no efforts were evident at baseline, ventilator set rate was decreased to 50% of baseline level for up to five minutes to detect inspiratory efforts.

(f) Systolic arterial pressure ≥ 90 mm Hg without vasopressor support (≤ 5 mcg / kg / min dopamine or dobutamine will not be considered a vasopressor).

**Spontaneous Breathing Trial Procedure and Assessment for Unassisted Breathing**

If criteria a-f above were met, then a trial of up to 120 minutes of spontaneous breathing with FiO₂ ≤ 0.5 was initiated using any of the following approaches:

1. Pressure support ≤ 5 cm H₂O, PEEP ≤ 5 cm H₂O
2. CPAP ≤ 5 cm H₂O
3. T-piece
4. Tracheostomy mask

Tolerance of the breathing trial was monitored using the following:

1. $\text{SpO}_2 \geq 90\%$ and / or $\text{PaO}_2 \geq 60 \text{ mmHg}$
2. Mean spontaneous tidal volume $\geq 4 \text{ ml} / \text{ kg PBW}$ (if measured)
3. Respiratory Rate $\leq 35 / \text{ min}$
4. $\text{pH} \geq 7.30$ (if measured)
5. No respiratory distress (defined as 2 or more of the following):
   a. Heart rate $\geq 120\%$ of the 06:00 rate ($\leq 5 \text{ min at } > 120\% \text{ may be tolerated}$)
   b. Marked use of accessory muscles
   c. Abdominal paradox
   d. Diaphoresis
   e. Marked subjective dyspnea.

If any of the goals 1-5 were not met, the patient was returned to the previous ventilator settings or to PS + 10 cm H$_2$O with Positive End-expiratory Pressure and FiO$_2$ = previous settings and reassessed for weaning the next morning.

The clinical team may decide to change mode of support during spontaneous breathing (PS = 5, CPAP, tracheostomy mask, or T-piece) at any time.

**Decision to remove ventilatory support**

For intubated patients, if tolerance criteria for spontaneous breathing trial (1-5 above) were met for at least 30 minutes, the clinical team could decide to extubate. However, the spontaneous breathing trial could be extended for up to 120 minutes if tolerance remained in question. If any of criteria 1-5 were not met during unassisted breathing (or 120 minutes passed without clear tolerance), then the ventilator settings that were in use before the attempt to wean were restored and the patient was reassessed for weaning the following day.

**Definition of Unassisted Breathing**

(a) Extubated with face mask, nasal prong oxygen, or room air, OR
(b) T-tube breathing, OR
(c) Tracheostomy mask breathing, OR
(d) CPAP $\leq 5$ without PS or IMV assistance

**Completion of Ventilator Procedures**

Patients were considered to have completed the study ventilator procedures if any of the following conditions occur:

a. Death
b. Hospital discharge
c. Alive 28 days after enrollment

If a patient required positive pressure ventilation after a period of unassisted breathing, the study ventilator procedures resumed unless the patient was discharged from the hospital or $> 28$ days elapsed since enrollment.
Removal from the Ventilator Management Protocol
Patients could be removed from the 6 ml / kg Vt ventilation requirement if they developed neurologic conditions where hypercapnea would be contraindicated (e.g., intracranial bleeding, GCS < 8, cerebral edema, mass effect [midline shift on CT scan], papilledema, intracranial pressure monitoring, fixed pupils).

Conservative Fluid Management Approach
This fluid protocol was initiated within four hours of randomization and continued until UAB or study day seven, whichever occurred first.

1. Discontinue maintenance fluids.
2. Continue medications and nutrition.
3. Manage electrolytes and blood products per usual practice.
4. For shock, use any combination of fluid boluses# and vasopressor(s) to achieve MAP ≥ 60 mmHg as fast as possible. Wean vasopressors as quickly as tolerated beginning four hours after blood pressure has stabilized.
5. Withhold diuretic therapy in renal failure § and until 12 hours after last fluid bolus or vasopressor given.

<table>
<thead>
<tr>
<th>CVP (recommended)</th>
<th>PAOP (optional)</th>
<th>MAP &gt; 60 mm Hg AND off vasopressors for &gt; 12 hours</th>
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</thead>
<tbody>
<tr>
<td>&gt;8</td>
<td>&gt; 12</td>
<td>Furosemide* Reassess in 1 hour</td>
</tr>
<tr>
<td>4-8</td>
<td>8-12</td>
<td>Give fluid bolus as fast as possible* Reassess in 1 hour</td>
</tr>
<tr>
<td>&lt; 4</td>
<td>&lt; 8</td>
<td>No intervention Reassess in 4 hours</td>
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</table>

§ Renal failure is defined as dialysis dependence, oliguria with serum creatinine > 3mg/dl, or oliguria with serum creatinine 0-3 mg/dL with urinary indices indicative of acute renal failure.
# Recommended fluid bolus= 15 mL / kg crystalloid (round to nearest 250 mL) or 1 Unit packed red cells or 25 grams albumin
* Recommended Furosemide dosing = begin with 20 mg bolus or 3 mg / hr infusion or last known effective dose. Double each subsequent dose until goal achieved (oliguria reversal or intravascular pressure target) or maximum infusion rate of 24 mg / hr or 160 mg bolus reached. Do not exceed 620 mg / day. Also, if patient has heart failure, consider treatment with dobutamine.

Plasma Fatty Acid Levels
Plasma was collected for measuring DHA, EPA and AA levels at days zero, three, six, and 12 from the first 30 patients receiving the control and the first 30 patients receiving the n-3 supplement. Plasma obtained from one, 5 ml EDTA anti-coagulated blood sample was placed immediately after centrifugation into one 2 ml aliquot in specified tubes and frozen at –70°C. The specimens were sent on dry ice to the central repository where they were maintained at -70°C until specimens from
all of the 60 patients had been received. They were then sent to University of Washington for quantitative analysis of fatty acid composition using gas chromatography. When they met after 100 patients were enrolled, the DSMB evaluated these plasma EPA, DHA, and arachidonic acid levels and the ratio of n-3 to n-6 fatty acids in the blood on day three in these 60 patients to ensure the dose and enteral administration resulted in an increase in plasma levels of n-3 fatty acids.

**Plasma Cytokines**

Blood for cytokines was collected at baseline and on days three and six. Plasma obtained from two, 10 ml EDTA anti-coagulated blood samples was divided immediately after centrifugation into four equal 2 ml aliquots in specified tubes and frozen at −70°C. Periodically throughout the study, plasma samples were sent from each site on dry ice to a central repository where they were stored until study completion. Upon study completion, 0.5 mL of plasma from each sample was sent to Vanderbilt University for analysis of IL-6, IL-8, and IL-10 levels using commercially available ELISA kits with multi-plexed assays using x-map technology via the Luminex100 system.

**Urine Leukotrienes and Isoprostanes**

On days zero, three, and six, 8 mL of urine was obtained from patients and divided into four aliquots of 2 ml each in specified tubes and frozen at −70°C. Periodically, each site sent urine samples on dry ice to the central repository where they remained stored frozen at −70°C. At the end of the study, 3 mL of the urine was sent to Vanderbilt University for leukotriene and isoprostane analysis. Leukotrienes E4 and E5 were analyzed from 1.5mL of urine at each time point using ultraperformance liquid chromatography followed by electrospray ionization-mass spectrometry. F2- and F3-isoprostanes were analyzed from 1.5mL of urine on days zero and six using thin-layer chromatography followed by gas chromatography mass spectrometry.

**Efficacy and Futility Stopping Rules**

The maximum sample size was planned to be 1000 patients. The study was monitored using a flexible group sequential design with stopping rules for both efficacy and futility. The reported confidence intervals on the treatment difference were adjusted for the group sequential design using the method of Jennison & Turnbull.e4

In order to allow flexibility we used alpha and beta spending boundaries as described by DeMets and Ware (z<sub>l</sub>=2.277, delta=1.663, zu=2.025, m=4, mu=3.3837).e5 Factors were considered as one sided with a separate upper efficacy boundary and lower futility boundary.

In this method of interim monitoring we specified a function a(t) and b(t) called the alpha and beta spending functions. The function a(t) gave the amount of the p-value that was “spent” by a given time “t” in the study, where time runs from 0 at study start to 1 when all patients have been entered. It represented the probability under the null hypothesis that the trial would stop for efficacy at or before time t. The function b(t) was the type II error that was “spent” by the interim monitoring plan to allow futility stopping. It represented the probability under the alternative hypothesis that the study would stop for futility at or before time t or that at the last look, the efficacy boundary would not be exceeded.

The table below shows the alpha-spending boundary a(t) where t is the proportion of patients accrued at that DSMB meeting. In the table we assumed 5 meetings at t= 0.10, 0.25, 0.50, 0.75 and 1.0. This function a(t) was extended to a smooth function of t using a cubic spline and at each DSMB meeting the actual stopping boundary was calculated so that the probability of stopping at or before that meeting was a(t). Similarly the futility boundary was defined by the beta-spending function b(t). The number b(t) represented the cumulative probability that the results would be below the futility stopping boundary given the alternative hypothesis of a 2.25 day
increase in VFD with a standard deviation of 10.5. At each DSMB meeting a futility stopping boundary was calculated so that the probability of futility stopping at or before that meeting was $b(t)$ at this alternative hypothesis.

The overall one-sided significance level of the study was 0.025 which is equivalent to a two sided $p=0.05$ significance level. Five analyses were planned after 100, 250, 500, 750, and 1000 patients. Under the assumption that there were five equally spaced interim analyses the power of the study was 90.7%. Changes in the number or spacing of the interim analyses would have a minor effect on the power. With this design, assuming that the pattern of deaths and extubations was similar to the FACTT fluid study, there was an 82% chance that the study would show both a significant effect of VFD and a nominally positive benefit in mortality.

The DSMB was advised to consider mortality differences in deciding whether to stop the trial. They might decline to stop the trial for efficacy if the mortality difference would make the positive benefit in VFDs difficult to interpret and they might decline to stop the trial for futility if there is a positive mortality benefit. For example, if there was no difference in VFDs but a trend towards a survival benefit the DSMB might continue past a futility boundary. The stopping rules were set up so that this would not invalidate the trial if such judgments were made. The efficacy boundary was developed without regard to the futility boundary. Thus if the futility boundary was crossed but the trial was not stopped, the trial can still achieve a 0.025 one-sided significance level.

<table>
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<tr>
<th>No. of Patients</th>
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<th>Difference Efficacy</th>
<th>Difference Futility</th>
<th>Error Spending Type I (1-sided)</th>
<th>Type II Futility</th>
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<th>Probability of Stopping Efficacy</th>
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_Table Legend: Stopping Boundaries:_ The table shows the characteristics of this boundary if we had the interim reports described above. The second column is the nominal p-value to stop for efficacy; the third and fourth columns are the difference in VFD to stop for efficacy and futility. The next columns are the error spending functions. The type I error spending function is the probability that the upper boundary will be exceeded under the null hypothesis. The type II error spending function is the probability that the statistic will be below the lower boundary at an interim analysis or under the upper boundary at the final analysis under the alternative hypothesis. The probability of stopping for futility is given in the seventh column and the probability of stopping for efficacy in the eighth column. The final column shows the confidence interval (CI) for the difference in VFD if the trial stopped for efficacy at that look and the treatment effect just exceeded the stopping boundary.
References

**eTable.** Median Daily Calories Delivered by Enteral Feedings by Study Group

<table>
<thead>
<tr>
<th>Day</th>
<th>N-3</th>
<th>N</th>
<th>Control</th>
<th>N</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>185 (294)</td>
<td>139</td>
<td>180 (425)</td>
<td>125</td>
<td>0.52</td>
</tr>
<tr>
<td>1</td>
<td>480 (1120)</td>
<td>136</td>
<td>480 (1248)</td>
<td>122</td>
<td>0.62</td>
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<tr>
<td>2</td>
<td>432 (1170)</td>
<td>123</td>
<td>812 (1346)</td>
<td>104</td>
<td>0.42</td>
</tr>
<tr>
<td>3</td>
<td>480 (1176)</td>
<td>110</td>
<td>770 (1211)</td>
<td>92</td>
<td>0.35</td>
</tr>
<tr>
<td>4</td>
<td>480 (1167)</td>
<td>100</td>
<td>900 (1322)</td>
<td>79</td>
<td>0.28</td>
</tr>
<tr>
<td>5</td>
<td>630 (1177)</td>
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<td>875 (1308)</td>
<td>70</td>
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</tr>
<tr>
<td>6</td>
<td>1124 (986)</td>
<td>77</td>
<td>1238 (1063)</td>
<td>61</td>
<td>0.31</td>
</tr>
<tr>
<td>7</td>
<td>1479 (835)</td>
<td>68</td>
<td>1410 (967)</td>
<td>53</td>
<td>0.66</td>
</tr>
<tr>
<td>8</td>
<td>1433 (892)</td>
<td>60</td>
<td>1460 (909)</td>
<td>44</td>
<td>0.69</td>
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<tr>
<td>9</td>
<td>1361 (860)</td>
<td>51</td>
<td>1592 (851)</td>
<td>39</td>
<td>0.23</td>
</tr>
<tr>
<td>10</td>
<td>1376 (840)</td>
<td>39</td>
<td>1320 (634)</td>
<td>37</td>
<td>0.44</td>
</tr>
<tr>
<td>11</td>
<td>1470 (822)</td>
<td>35</td>
<td>1419 (945)</td>
<td>34</td>
<td>0.42</td>
</tr>
<tr>
<td>12</td>
<td>1680 (686)</td>
<td>32</td>
<td>1521 (1006)</td>
<td>28</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Median daily calories received from enteral feeds were similar in both groups for days 0 through 12. Values are kcal/day reported as medians (IQR).
eFigure 1. Percent of Total Plasma Fatty Acids for Arachidonic (AA) and Eicosapentanoic Acid (EPA)

On average, AA accounted for about 10% of total plasma fatty acids at baseline and decreased to 8% by day six. EPA only accounted for 0.5% of total plasma fatty acids at baseline. This significantly increased to almost 3.5% by day three in the n-3 group but remained 0.5% in the control group. Levels were measured in the first 60 patients. Due to unavailable samples, actual measurements are from 24 n-3 and 30 control patients at baseline, 24 in each group at day 3, 17 in each group on day 6 and 8 n-3 and 9 control patients on day 12. N-3 = open black circles; Control = open red triangles.
Plasma IL-6 levels decreased over time but did not differ in both groups. Plasma IL-8 levels also did not differ over time between groups.
eFigure 2b. Plasma Leukotriene E4 (LTE4) Levels

The n-3 supplement had no effect on plasma levels of LTE4.
Urinary levels of the oxidative stress marker, F2-isoprostane were similar between groups and did not change over time, while levels of F3-isoprostane, metabolized from n-3 fatty acids, increased in the n-3 group on day six. * P<0.001
**eFigure 3a. Mean Serum Glucose Levels**

Mean 8AM serum glucose levels did not differ between groups and were less than 150 mg/dL for the first seven days. Error bars represent 95% CI.

**eFigure 3b. Mean Morning Insulin Drip Rates**

Average insulin use was similar between groups for the first week. Error bars represent 95% CI.
Although not statistically significant on any specific day, vasopressor use was higher in the n-3 group at baseline and through day 7.