

Meeting Nutritional Targets of Critically Ill Patients by Combined Enteral and Parenteral Nutrition: review and rationale for the EFFORTcombo trial

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37 **Abstract**

38 While medical nutrition therapy is an essential part of the care for critically ill patients, uncertainty
39 exists about the right form, dosage, timing and route in relation to the phases of critical illness. As
40 enteral nutrition (EN) is often withheld or interrupted during the ICU stay, combined EN and
41 parenteral nutrition (PN) may represent an effective and safe option to achieve energy and protein
42 goals as recommended by international guidelines. We hypothesize that critically ill patients at high
43 nutritional risk may benefit from such a combined approach during their stay on the intensive care
44 unit (ICU). Therefore, we aim to test if an early combination of EN and high-protein PN (EN+PN) is
45 effective in reaching calorie and protein goals in patients at high nutritional risk, while avoiding
46 overfeeding. This approach will be tested in the here presented EFFORTcombo trial. Nutritionally
47 high-risk ICU patients will be randomized to either high (≥ 2.2 mg/kg/d) or low protein
48 (≤ 1.2 mg/kg/d). In the high protein group, the patients will receive EN+PN, in the low protein group,
49 patients will be given EN alone. EN will be started in accordance to international guidelines in both
50 groups. Efforts will be made to reach nutrition goals within 48–96 hours. The efficacy of the proposed
51 nutritional strategy will be tested as an innovative approach by functional outcomes at ICU- and
52 hospital-discharge, as well as at a 6-month follow-up.

53 **Registration:**

54 EFFORT Trial: NCT03160547
55 EFFORTcombo Trial: EudraCT-No.: 2018-003703-19

56 **Introduction**

57 During the past decades, the optimal amount of nutrition and route of feeding in critically ill patients
58 has been debated controversially in the literature⁽¹⁾. It is currently unclear what the optimal protein
59 energy targets should be and exactly when they should be reached⁽²⁾. Current international nutrition
60 guidelines recommend the initiation of medical nutrition therapy in the form of **enteral nutrition**
61 **(EN)** within 24–48 hours in the critically ill patient who is unable to maintain sufficient oral intake^{(3;}
62 ^{4; 5; 6)}. However, EN alone is often insufficient to achieve energy and protein targets particularly in
63 the early phase of critical illness due to frequent interruptions for procedures and metabolic or
64 gastrointestinal (GI) intolerance⁽⁷⁾.

65 **Parenteral nutrition (PN)** provides advantages in achieving target nutrition goals earlier, which
66 might be particularly relevant in patients at high nutrition risk. In fact, the **combined use of EN and**
67 **PN (EN+PN)** may reduce large nutrition deficits in critically ill patients and might be attractive in
68 those patients who cannot achieve their energy and protein goals during their ICU stay from EN

69 alone⁽⁸⁾. One strategy to optimize protein intake is to combine EN and PN (EN+PN) early after
70 admission to the ICU to reach nutrition targets in patients at nutritional risk as soon as possible.
71 Another approach would be the early initiation of EN with the addition of supplemental PN if the
72 nutritional targets cannot be reached by EN alone (SPN) after several days.

73 For critically ill patients, achieving the protein goal is perhaps more important than achieving the
74 calorie goal, as several large-scale randomized controlled trials (RCTs) have not been able to
75 demonstrate any benefit from near goal caloric delivery^(9; 10; 11). The few RCTs evaluating protein
76 targets will be discussed in this manuscript, but clear evidence is still lacking. In fact, determining
77 the optimal protein dose and timing for critically ill patients is a high priority research question⁽¹²⁾.
78 Even with a combined enteral and parenteral nutrition approach, it may remain challenging to reach
79 the currently recommended protein goals with available nutrition products.

80 The EFFORT trial investigates the influence of higher prescription of protein (≥ 2.2 g/kg/day) versus
81 usual protein prescription (≤ 1.2 g/kg/day) on the outcome of nutritionally-high-risk critically ill
82 patients⁽¹³⁾. One of the biggest challenges in this trial will be continuously achieving adequate
83 amounts of protein in the higher dose group^(14; 15). Since this might be more consistently achieved
84 through an early combination of EN+PN, we plan to conduct a sub-study in the EFFORT trial wherein
85 patients randomized to the higher dose group automatically receive combined EN+PN versus EN
86 alone in the usual care group, known as the EFFORTcombo trial. The purpose of this paper is
87 therefore to critically review the current evidence, to generate hypotheses and thus, to provide the
88 scientific rationale for the concept of combining EN+PN applied in the early phase of critical illness
89 in nutritionally-high risk critically ill patients and to present the details of trial methods.

90 **Current evidence and discussions about enteral and parenteral** 91 **nutrition**

92 EN is the most common route of feeding in the ICU⁽¹⁶⁾ and is uniformly recommended in current
93 international nutrition guidelines^(3; 4; 5; 6). However, recent data demonstrated that EN is still often
94 withheld or started with significant delay after admission to the ICU in the clinical routine^(7; 17). The
95 progression of EN into a full feed is highly subjective to the clinician^(7; 17) and often takes several
96 days due to feeding intolerance and common interruptions of EN^(18; 19; 20). **Thus, EN may lead to**
97 **protein-calorie deficiency with a possible negative impact on patient outcome— especially in the**
98 **patient's first ICU-week^(21; 22; 23).**

99 For years, PN was thought to be associated with neutral or even harmful effects, as older studies
100 suggested that the risk/benefit ratio for use of PN in the ICU-setting may be much narrower than that

101 for use of EN^(24; 25). Few studies indicated that the use of PN was associated with more infectious
102 complications, most likely related to hyperalimentation and hyperglycaemia, as consistently shown
103 in earlier meta-analyses^(26; 27; 28; 29). The “Early Parenteral Nutrition Completing Enteral Nutrition in
104 Adult Critically Ill Patients (**EPaNIC**) study by Casaer et al. demonstrated some potentially harmful
105 effects of early PN in critically ill patients ^(24; 30; 31; 32; 33). In this study, patients were randomized to
106 early supplementation of insufficient EN with PN versus withholding PN for one week⁽²⁴⁾. Patients
107 in the early PN group received intravenous glucose under conditions of intensive insulin therapy for
108 the first three days, when EN was still insufficient, and then, if the patient was still in the ICU, PN
109 was started on day three. In the late PN group, PN was only initiated at day eight. The major findings
110 demonstrated that early PN led to a prolonged dependency on intensive care treatments and an
111 increased infection-rates. In contrast, withholding PN improved clinical outcomes, which was
112 associated with relevant cost saving effects. Importantly, in the large subgroup with a contraindication
113 for EN upon admission, harm by early PN was even more pronounced, whereas the authors suggested
114 a suppression of the physiological response mechanism autophagy by feeding in the PN group as
115 reason for the observed negative effects. Yet, there are several limitations, that limit the validity and
116 generalizability of the findings. For example, the application of glucose instead of PN under
117 conditions of tight glycaemic control within the first few days is rather rare at other ICUs. As
118 evidenced by the primary publication, the harm signal was evident in the early group even before PN
119 started on day 3, so the harm cannot be attributed to the introduction of PN on day 3. Furthermore,
120 the majority of patients underwent surgery (90%) and within these 60% cardiac surgery, resulting in
121 an overall short ICU-stay (3–4 days) with a rather low mortality. Enrolled patients were thus very
122 low nutritional risk and would not have received any artificial nutrition in many ICUs around the
123 world. Thus, the results of the EPANIC trial cannot be expanded to nutritionally high-risk patients in
124 other settings.

125 Nevertheless, based on the EPaNIC findings and because EN was thought to be cheaper, safer, and
126 more physiologic, international nutrition guidelines recommend that the enteral route should be
127 preferably used in critically ill patients without a contraindication to EN ^(3; 34; 35; 36) and did not support
128 the routine use of PN in the early phase of critical illness ⁽³⁷⁾. However, the more recent evidence
129 from randomized studies about the safety and efficacy of PN might make physicians more
130 comfortable with prescribing PN earlier ^(38; 39).

131 The **CALORIES** trial by Harvey et al. involved 2388 critically ill patients receiving exclusive PN or
132 EN as soon as possible within 36 hours after admission. No significant differences were found in

133 adverse events, mortality or in the infectious complications, demonstrating the equivalence of EN and
134 PN. However, this study included less severely ill patients⁽³⁸⁾. More recently, Reigner et al.
135 investigated the effects of EN vs. PN in the **NUTRIREA-2** trial including 2410 patients receiving
136 invasive mechanical ventilation and vasopressor support for shock⁽³⁹⁾. In this isocaloric trial, early
137 EN did not reduce mortality or the risk of secondary infections, but was associated with an increased
138 risk of digestive complications such as vomiting, diarrhoea and bowel ischemia when compared with
139 early PN⁽³⁹⁾. Both the NUTRIREA-2 and CALORIES studies contrasted previously mentioned safety
140 concerns about PN and overall challenged the paradigm that EN is superior to PN with respect to
141 clinical outcomes in critical illness. The rather low amount of delivered protein in the EN and PN
142 group, as well as the short duration of these studies may represent the main reasons why no clinical
143 advantages could be detected either in the EN or in the PN group.

144 Given the fact that GI-dysfunction is commonly observed in severely ill patients, and that PN was
145 demonstrated to be safe in the more recent trials, early high-protein PN may help to securely and
146 rapidly achieve the recommended nutrition goals during feeding intolerance and GI-symptoms. The
147 described concerns about EN-safety and EN-progression illuminate a promising opportunity for PN
148 as alternative nutrition strategy to bridge the gap between the nutritional goals and delivered
149 calories/proteins, whenever EN is withheld or reduced, at any time point during the ICU stay.

150 **Experience in combining enteral and parenteral nutrition**

151 **Pichard and colleagues** systemically investigate the concept of EN and PN in the ICU to reduce the
152 overall nutrition deficiency⁽⁴⁰⁾. The pragmatic concept was introduced with the idea to start PN in
153 patients with proven intolerance to EN and defined as supplemental PN (SPN). In an RCT, patients
154 who were EN-intolerant, and therefore were unable to reach their nutritional target by day three were
155 randomized to control group (EN alone) or SPN. Nutritional targets were measured by indirect
156 calorimetry. Only patients receiving less than 60% of their target during the first three days were
157 enrolled, therefore leading to a considerable protein-energy debt in all enrolled patients. In this trial,
158 increased nutritional adequacy and a reduced number of nosocomial infections was observed in the
159 SPN group⁽⁴¹⁾.

160 In a different but related concept, the effect of a combined EN+PN strategy was tested in the recent
161 **TOP-UP pilot** trial, where PN was started immediately after randomization without testing for EN
162 intolerance to achieve the prescribed nutrition goals, referred to as combined EN+PN⁽⁴²⁾. The energy
163 targets were calculated in a pragmatic approach based on the actual body weight, with the overall
164 goal to reach the full energy target at day one post randomization. The proposed nutrition strategy

165 was feasible and effective regarding the separation of protein-calorie intake between the two groups.
166 Considering the clinical relevance, no overall benefit could be demonstrated in this small pilot study,
167 however, the results revealed some encouraging trends of improved functional outcomes in the
168 combined EN+PN group, which needs to be evaluated in following confirmatory studies.

169 The most recent **EAT-ICU trial** tested the effects of an early goal-directed nutrition vs. standard
170 nutritional care in adult critically ill patients⁽¹¹⁾. In the early goal-directed nutrition-group, the
171 nutritional requirements were estimated by indirect calorimetry and 24-hour urinary urea. This group
172 received an intense EN+PN therapy to cover 100% of the calculated target. Patients randomized to
173 the control group received standard care, providing 25 kcal/kg/day by EN alone. While the feasibility
174 of this strategy was demonstrated by a significant separation of both treatment groups with respect to
175 energy and protein uptake, no significant effect was detected regarding the clinical relevance.
176 However, frequent hyperglycaemia despite extraordinarily high dosages of administered insulin
177 demonstrated rather poor metabolic control, which overall might have influenced the evaluated
178 physical outcome assessment as primary endpoint.

179 **Table 1** gives a short summary of the characteristics of the above-mentioned trials.

180 **What can we learn from recent trials?**

181 **Focus on the right patients**

182 One of the reasons why recent trials aiming at high amounts of calories or protein in the ICU-setting
183 have failed to demonstrate a positive outcome might be inappropriate patient populations. For
184 example, well-nourished patients following elective surgery, with a short ICU-LOS, such as those
185 studied in the EPaNIC trial are unlikely to benefit from augmented feeding approaches (or requiring
186 artificial feeding at all). Critically ill patients are a heterogenous group of patients with respect to the
187 extent to which they will benefit from artificial nutrition therapy.

188 The patients` previous **nutritional state** is of paramount importance as it determines the availability
189 of self-defence mechanisms such as endogenous antioxidant mechanisms^(43; 44). On the other hand,
190 patients who are either previously malnourished or at risk of malnutrition – either under- or
191 overweight –, or with expected prolonged ICU-stay will most likely benefit from an intense nutrition
192 therapy^(45; 46; 47; 48; 49).

193 In extension to the assessment of nutritional risk, increasing attention is paid to the presence of
194 sarcopenia, frailty and the associated impaired physical functioning, as they have been demonstrated
195 to be important predictors of a longer ICU- and hospital-length of stay, post-discharge mortality,

196 quality of life and lower likelihood to return to home, as summarized in greater detail in recent
197 reviews^(50; 51; 52). Notably, sarcopenic patients might benefit from an intense nutritional therapy, as
198 recently demonstrated by Koga et al. in a retrospective analysis, where sarcopenic patients supplied
199 with early EN showed a reduced hospital-mortality compared to those who did not receive early EN,
200 while that effect was not visible in non-sarcopenic patients⁽⁵³⁾.

201 Focus on Protein

202 The influence of protein on the outcome of critically ill patients has been discussed in controversially
203 ^(13; 54), but the above-displayed evidence leads to the conclusion that nutrition interventions targeting
204 only the energy adequacy did not show statistically significant improvements in many studies.
205 Increased protein intake however, was associated with improved long-term physical recovery and
206 lower mortality in observational trials^(47; 55; 56; 57) and did not influence duration of renal dysfunction
207 ⁽⁵⁸⁾.

208 One systematic review performed by Davies et al. showed no relationship between protein delivery
209 and mortality whereas both the low and high protein groups in this review were protein-malnourished
210 (0.67 g/kg/d and 1.02 g/kg/d)⁽⁵⁹⁾. However, even in nutrition trials targeting the adequate provision
211 of protein, enteral nutrition failed to provide more than 1.5 g/kg day⁽¹⁵⁾, highlighting the need for
212 high-protein nutrition products or effective strategies to reach the protein goals. Heyland et al recently
213 performed a meta-analysis assessing the effect of higher vs. lower protein intake but the effect could
214 not be analysed in detail due to high heterogeneity of the existing trials and incomplete datasets. The
215 authors were only able to aggregate the effect of higher protein dosing on mortality (risk ratio: 0.89;
216 95% confidence interval: 0.66–1.19, p= 0.42)⁽¹³⁾. Despite the current lack of evidence and
217 controversial discussion, current guidelines recommend the daily provision of 1.2–2.5 g/kg protein^{(3;}
218 ^{5; 60)}.

219 Focus on functional outcomes

220 Outcome measures should be patient-centered, reliable, accurate, and simple to measure in ways that
221 minimize bias. The majority of large RCTs trials are measuring “hard” outcomes, because they are
222 objective, comparatively easy to obtain and clearly observable by researchers. Major outcome
223 parameters, such as mortality have been used in nutrition-trials despite observed decreasing overall
224 mortality rates and therefore many nutrition trials have remained nonsignificant. Although these
225 parameters are undoubtedly important, they do not adequately capture the patients’ perspective after
226 discharge from hospital and might not be sensitive enough for nutrition interventions⁽⁶¹⁾. With the
227 paradigm “**add life to years, not years to life**” more and more interventions aim to increase the
228 quality of life after critically illness ^(62; 63; 64; 65). In this connection, the evaluation of mid- and long-

229 term survival by functional outcomes are increasingly considered, because they evaluate muscle
230 mass, muscle function and physical function closely connected to the patient's quality of life in the
231 longer-term⁽⁶⁶⁾. Furthermore, functional outcomes reflect the overall state of the patient and are
232 affected by a variety of treatments, not only nutrition and mobilization.

233 More recent nutrition studies have used physical outcome assessment, or surrogate parameters and
234 some have revealed trends of improved functional outcomes intense nutrition therapy groups^{(11; 16; 42;}
235 ⁶⁷⁾. In addition, Wu et al. observed unchanged "classic" parameters such as hospital-LOS,
236 postoperative morbidity rates, and standard blood biochemistry profiles, in a patient cohort after
237 esophagectomy. However, these patients had better physical functioning and less fatigue⁽⁶⁸⁾.

238 On the other hand, physical outcome assessment is complex, and its performance requires adequate
239 teaching of study sites to receive reliable data for a rigorous knowledge transfer. Poor metabolic
240 control for example reflected by hyperglycaemia and a low number of patients, might have
241 confounded the physical outcome assessment as primary endpoint in the EAT-ICU trial⁽¹¹⁾.
242 Additionally, the primary endpoint in this study showed some weakness as a) little evidence exists
243 about its use, as it has rarely been used before, b) the assessment at 6 months after ICU-discharge
244 bares the risk, that the effects may be influenced by other relevant aspects than the ICU-treatment
245 itself and c) the physical outcome showed a large variance in the assessment, emphasizing the need
246 for strict adherence to standardized operation protocols. Based on these findings received from rather
247 smaller clinical studies, a well-timed physical outcome assessment matching the study intervention
248 is encouraged to be evaluated in following confirmatory studies⁽⁶⁹⁾.

249 **Conclusion**

250 Based on the evidence gathered from recent trials the authors conclude as follows:

- 251 1. Targeting energy adequacy only might not be enough to improve the outcome of critically ill
252 patients. Increasing attention should be paid on effective supplementation strategies to achieve
253 recommended protein goals.
- 254 2. In iso-energetic trials, the route of administration might not influence "standard" outcome
255 parameters as mortality and hospital-LOS
- 256 3. PN, as well as EN+PN seem to be safe, feasible and effective to achieve the prescribed
257 nutritional targets in critically ill patients.
- 258 4. Without consideration of metabolic tolerance, early aggressive EN+PN may not be effective
259 in improving patient outcomes in unselected patients.

260 5. In nutritionally high-risk patients, combined EN+PN may improve functional and other
261 patient-reported outcomes.

262 **From the EFFORT trial to the EFFORTcombo trial**

263 Based on our review of the current evidence, we hypothesize that a combination of EN+high-protein-
264 PN vs. EN alone in nutritionally high-risk patients can improve the functional outcomes. **To test this**
265 **hypothesis, we plan the nested sub-study “EFFORTcombo” in the context of the EFFORT trial.**

266 The **EFFORT Trial** (clinicaltrials.gov/NCT03160547) was developed as multi-centre pragmatic
267 volunteer driven, registry based RCT in which 4000 patients will be randomly assigned to either a
268 higher prescribed dose of protein (≥ 2.2 g/kg/d) or usual protein prescription (≤ 1.2 g/kg/d)⁽¹³⁾.
269 However, the EFFORT trial does not specify how these determined protein dosages can be achieved.
270 As protein delivery has been challenging in the past and only 55% of prescribed protein (equal to
271 0.7 g/kg/d) are actually delivered as reported in the International Nutrition Survey (INS)⁽¹⁴⁾, we
272 propose that the addition of high-protein-PN to EN compared to EN alone, represents a promising
273 nutrition strategy to increase nutritional adequacy to achieve the goals set in the original EFFORT
274 trial. In comparison to the EFFORT trial, in the proposed multicenter EFFORTcombo substudy a)
275 patients randomized to the high protein dosage will receive a combination of high-protein PN and EN
276 and b) the main outcome for this substudy is short-term physical function as assessed by the six-
277 minute walk test.

278 In addition, we will use a high-protein PN product and thus expect to reach the nutrition goals faster
279 and more securely through this combination as shown in Figure 1. We hypothesize that the augmented
280 protein delivery to these nutritionally high-risk-patients will translate into improved functional and
281 patient-reported outcomes. Written informed consent will be obtained from all patients or their legal
282 representatives before enrolment. The ethic committee of the RWTH Aachen University approved
283 the study (EK339/19) and local jurisdictional approval will be obtained for each centre.

284 **Inclusion and exclusion criteria**

285 As a nested sub-study within the EFFORT trial, the EFFORTcombo study includes mechanically
286 ventilated critically ill adult patients (≥ 18 years), who are at high nutritional risk as defined in detail
287 in our published EFFORT protocol⁽¹³⁾. **Table 2** illustrates in detail all in- and exclusion criteria.

288 **Investigational high-protein product**

289 To provide high-protein-PN in patients randomized to the EN+PN group, we will use Olimel® N12
290 with electrolytes provided by Baxter® International Inc. Olimel is a 3-in-1 parenteral admixture
291 solution containing the following drug substances: dextrose solution, amino acid solution with

292 electrolytes (sodium, potassium, magnesium, phosphate) and lipid emulsion with an olive oil/soybean
293 oil ratio of 80:20 and 12 g nitrogen per litre. This product will be similar in energy density to the
294 standard EN solutions (1–1.4 kcal/ml). Olimel® N12 will be administered via central venous line
295 until the daily target of ≥ 2.2 g/kg/d is reached.

296 Peri-Olimel is a PN-product that can be used either peripherally or centrally and will be used
297 whenever a central venous line for PN is not available. Both products are indicated for parenteral
298 nutrition for adults.

299 Nutrition protocol

300 As soon as the patient is hemodynamically stable and there is a nasogastric tube or feeding tube in
301 place, EN will be started within 24–48 hours after admission to ICU, as per local standards. If the
302 patient has not been started on EN but there is an indication and intention to start on EN in the first
303 7 days, the patient will still be considered eligible for this study. The type of enteral formula should
304 be of similar caloric density (1–1.5 kcal/ml), but otherwise used in accordance to local standards. In
305 both groups, targets will be set using pre-ICU known weight (e.g. dry actual weight). For patients
306 with BMI >30 kg/m², ideal body weight based on a BMI of 25 kg/m² will be used. As per current
307 guidelines, we recommend monitoring for metabolic and GI-tolerance as well as the provision of
308 usual nutritional therapy by credentialed clinicians with expertise in directing the feeding of critically
309 ill patients. **If equipoise regarding the nutritional regimen or protein dosage is not given in the**
310 **clinician's prescription for an individual patient, the patient will not be included in the trial.**
311 Metabolic and feeding tolerance will be assessed by blood glucose, insulin dose, glucose infusion
312 rates, phosphate, urea, triglycerides and electrolytes, which will be monitored frequently, as clinically
313 indicated and consideration of recent guidelines for monitoring of nutrition therapy will be endorsed
314 ⁽⁷⁰⁾.

315 Those patients randomized into the high-protein group will receive EN+PN, with **PN added as soon**
316 **as possible** following randomization. While the identification and randomization of appropriate
317 patients will take 24-48 hours, the PN should be started within 48-96 hours. The study PN solution
318 will be started at 25 ml/hr and increased if tolerated (e.g. the infusion rate can be increased by 25 ml
319 every 4–6 hours) so that $>80\%$ of protein nutrition goals will be reached within 48–96 hours of
320 starting PN. We aim to avoid overfeeding calories and if the protein target cannot be met by combined
321 EN+PN, protein supplements (enteral protein supplements or intravenous amino acids) should be
322 added as per local standards to reach the goal of ≥ 2.2 g/kg/d. The **PN-rate will be adjusted** in a
323 compensatory fashion to ensure that patients receive $>80\%$ of their target goal rate on a continuous

324 basis, for example if EN infusion rates change due to GI-intolerance or interruption. Therefore, PN
325 should be continued for a minimum of 7 days even at a minimal rate (10 ml/h).

326 Both EN and PN will be **continued for a minimum of 7 days post randomization** and be continued
327 on the ward. PN should be continued at a minimum of 10 ml/h until the 7th day to enable easy
328 compensations of the fluctuation in oral nutrition and/or EN-rates as well on the normal ward. The
329 EN-rate will be always adjusted to the individual patients, while considering the minimum PN-rate
330 of 10 ml/h. At 7 days post randomization, if the patient is still in the ICU, and PN is clinically
331 indicated to achieve high-protein goals, Olimel® N12E will be used in the high dose group. In the
332 low dose group, if a patient develops a contraindication to EN, after day 7, PN can be used with
333 product selection and duration determined by local standards but protein goals should not be above
334 1.2 g/kg/day. In either group, after the end of the 7 days post randomization study period, if the patient
335 has been discharged from the ICU and PN is clinically indicated, standard PN solutions can be used.
336 Olimel® N12E will be discontinued at ICU-discharge (unless it occurs before day 7 as explained
337 below), day 28 (maximum of PN treatment if the patients are still on ICU), or until death, whichever
338 comes first.

339 **The primary endpoint - functional outcome assessment**

340 The primary objective of this sub-study is to demonstrate improved short-term physical function by
341 a 6-minute walk test at hospital discharge. We also will assess in-hospital secondary outcomes and
342 patient-reported 6-month outcomes similar to the NEXIS trial (Clinicaltrials.gov, NCT03021902).
343 These secondary outcomes include the overall strength of upper and lower extremity (Medical
344 Research Council sum score), quadriceps- and handgrip-strength (dynamometry), body composition
345 (ultrasound and available CT-scans), overall physical function (Short Physical Performance Battery
346 and Functional Status Score for the ICU), which will be assessed longitudinally while the patient is
347 still in the hospital. The physical functioning (Katz activities of daily living and Lawtons instrumental
348 activities of daily living) as well as health related quality of life (Short Form-36 and EQ-5D5L) will
349 be assessed while the patient is in the hospital and 6 months after discharge. All outcome assessment
350 will be performed by trained outcome assessors strictly following detailed standard operating
351 protocols. All assessors will be blinded to the treatment group.

352 **Summary**

353 Taken together, international observational studies revealed considerable practice variations, and the
354 existing clinical trial data, albeit weak and outdate, did not always support the routine use of PN in
355 the early phase of critical illness. Importantly, the more recent evidence about the safety and efficacy

356 of PN might make physicians more comfortable with prescribing PN earlier to bridge the gap between
357 nutrition goals and actual delivery of calories and protein. This might be especially for patients at
358 high nutritional risk, or patients with an increased risk for prolonged ICU-stay. In this context, we are
359 proposing the EFFORTcombo trial that evaluates the effects of an early combined EN + high-protein
360 PN nutrition strategy to decrease the nutritional deficiencies in the critically ill patients at nutritional
361 risk. We hypothesize that this nutritional strategy will improve the functional outcomes of these
362 nutritionally high-risk patients.

363 **List of Abbreviations**

EN	Enteral Nutrition
EN+PN	Combined Enteral and Parenteral Nutrition
GI	Gastrointestinal
ICU	Intensive Care Unit
LOS	Length of Stay
PN	Parenteral Nutrition
RCT	Randomized Controlled Trial
SPN	Supplementary Parenteral Nutrition

364 **Declarations**

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375 and to help to draft a research agenda for future studies about combined EN+PN in critically ill
376 patients. Baxter Healthcare Corporation had no influence in the design, analysis or writing of this
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Conflicts of Interest

378
379 Gunnar Elke has received lecture fees and travel expenses by Baxter Healthcare Corporation,
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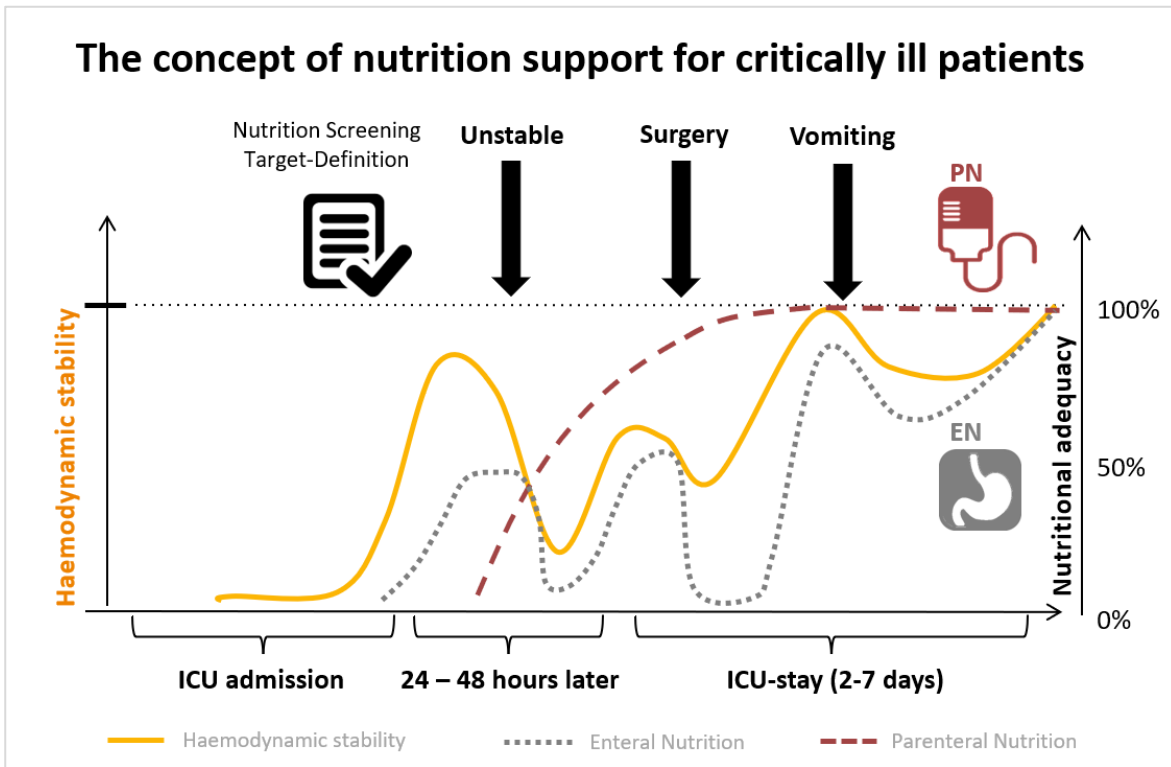
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Author contributions

396
397 A.H., C.S. and D.K.H. equally contributed to the conception and design of the research together with,
398 S.J.S., R.S., C.H., C.L., G.E. and P.M. A.H. and C.S. drafted the manuscript together with D.K.H.
399 Figures were provided by A.H. and C.S.. A.H., C.S., K.C.C., J.N., L.S., J.B., S.L. and T.L. contributed
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401 interpretation of the reviewed data, critically revised the manuscript, agree to be fully accountable for
402 ensuring the integrity and accuracy of the work, and read and approved the final manuscript.



404
405 *Figure 1: The concept of nutrition support for critically ill patients*

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407 **Tables**

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Table 1: Comparison of recent trials combining enteral nutrition and parenteral nutrition, abbreviations: EN= enteral nutrition, PN= parenteral nutrition, SPN= supplemental parenteral nutrition, EGDN=early goal directed nutrition, BMI= body mass index, BW= body weight IBW= ideal body weight, APACHE II= Acute Physiology and Chronic Health Evaluation II Score, SAPS II= Simplified Acute Physiology II Score, SOFA= Sequential Organ Failure Assessment Score

Trial	Heidegger 2013 ⁽⁴¹⁾	Wischmeyer ⁽⁴²⁾	Allingstrup 2017 ⁽¹¹⁾
Trial focus	EN vs. SPN	EN vs. EN+PN in over- or underweight patients	EGDN vs. standard of care PN to reach target: <ul style="list-style-type: none"> • EGDN group: <24 hours • Standard group: > 7 days
Enrolled patients	305	125	203
Mean Age in years	60.5	55.4	65.5
Mean BMI in kg/m²	25.9	33.3 (52% BMI < 25 48% BMI > 35)	22
Mean baseline disease severity scores	<ul style="list-style-type: none"> • APACHE II Score= 22.5 • SAPS II = 48 	<ul style="list-style-type: none"> • APACHE II Score= 20.7 • SOFA= 6 	<ul style="list-style-type: none"> • SAPS II Score =47.5 • SOFA Score =8
Calculation of Energy	<ul style="list-style-type: none"> • 25 kcal/kg/d (for women) and 30 kcal/kg/d (for men), using IBW or anamnestic BW for patients with a BMI ≤ 20 • Indirect calorimetry in 65% of patients 	<ul style="list-style-type: none"> • BMI <25: ≥25 kcal/kg/d actual BW • BMI > 35: ≥20 kcal/kg/d adjusted BW (= IBW + [actual weight – IBW] x 0.25, where IBW is based on a BMI of 25) 	<ul style="list-style-type: none"> • EGDN group: indirect calorimetry • Standard group: 25 kcal/kg/d
Energy delivered	Days 4–8: <ul style="list-style-type: none"> • SPN group: 28 kcal/kg/d (103%) • EN group: 20 kcal/kg/d (77%) 	First 7 days: <ul style="list-style-type: none"> • EN+PN group: 95% • EN group: 68% First 27 days: <ul style="list-style-type: none"> • EN+PN: 90% of target • EN group: 67% of target 	<ul style="list-style-type: none"> • EGDN group: 97% • Standard group: 64%
Calculation of protein	1–2 g/kg/d using IBW	≥1.2/kg/d Using actual body weight for patients with BMI <25 and adjusted body weight for patients with BMI >35	<ul style="list-style-type: none"> • EGDN group: ≥1.5 g/kg/day, calculated by urea excretion using Bistrian’s equation • Standard group: 1.2 g/kg/d
Protein delivered	Not reported	First 7 days: <ul style="list-style-type: none"> • EN+PN: 86% of target • EN group: 61% of target First 27 days: <ul style="list-style-type: none"> • EN+PN: 82% of target • EN group: 60% of target 	<ul style="list-style-type: none"> • EGDN group: 97% • Standard group: 45%

412

Inclusion Criteria for the EFFORT and EFFORTcombo trials	
<ul style="list-style-type: none"> • ≥18 years old • Nutritionally high-risk: <ul style="list-style-type: none"> ○ Low (≤25) or high BMI (≥35) ○ Moderate to severe malnutrition (as defined by local assessments) ○ Frailty (Clinical Frailty Scale, ≥5 or more) ○ Sarcopenia (SARC-F score, ≥4 or more) ○ From point of screening, projected duration of mechanical ventilation >4 days. • Requiring mechanical ventilation with actual or expected total duration of mechanical ventilation >48 hours 	
Exclusion Criterion	Rationale for Exclusion
Criteria from the original EFFORT trial	
>96 continuous hours of mechanical ventilation before screening	Intervention is likely most effective when delivered early
Expected death or withdrawal of life-sustaining treatments within 7 days from screening	Patients unlikely to receive benefit
Pregnancy	Unknown effect on the fetus
The responsible clinician feels that the patient either needs low or high protein	Uncertainty about protein dosage does not exist, patient safety issues
Patient requires PN only, and sites do not have the products to reach the high-dose protein group	Site will be unable to reach high-protein-dose prescription
Additional criteria in EFFORTcombo	
Patients in hospital >5 days prior to ICU admission or severe pre-existing weakness	Confounding of results
Pre-existing severe neuromuscular, cognitive or language impairment	Patient will be unable to perform physical outcome assessment
Lower extremity impairments that prevents the patient from walking (previously or newly acquired)	Patient will be unable to perform physical outcome assessment
Absolute contraindication to EN	Randomization impossible
Severe metabolic disorders including electrolyte disorders, uncontrolled hyperglycaemia, hyperlipidaemia, hypophosphatemia, or impaired nitrogen utilization	Intervention potentially hazardous
Severe chronic liver disease (MELD-score >20) or acute fulminant hepatitis.	Protein supplementation may be harmful in patients with severe liver disease

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