Effect of high versus standard protein provision on functional recovery in people with critical illness (PRECISe): an investigator-initiated, double-blinded, multicentre, parallel-group, randomised controlled trial in Belgium and the Netherlands

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Summary

Background Increased protein provision might ameliorate muscle wasting and improve long-term outcomes in critically ill patients. The aim of the PRECISe trial was to assess whether higher enteral protein provision (ie, 2·0 g/kg per day) would improve health-related quality of life and functional outcomes in critically ill patients who were mechanically ventilated compared with standard enteral protein provision (ie, 1·3 g/kg per day).

Methods The PRECISe trial was an investigator-initiated, double-blinded, multicentre, parallel-group, randomised controlled trial in five Dutch hospitals and five Belgian hospitals. Inclusion criteria were initiation of invasive mechanical ventilation within 24 h of intensive care unit (ICU) admission and an expected duration of invasive ventilation of 3 days or longer. Exclusion criteria were contraindications for enteral nutrition, moribund condition, BMI less than 18 kg/m², kidney failure with a no dialysis code, or hepatic encephalopathy. Patients were randomly assigned to one of four randomisation labels, corresponding with two study groups (ie, standard or high protein; two labels per group) in a 1:1:1:1 ratio through an interactive web-response system. Randomisation was done via random permuted-block randomisation in varying block sizes of eight and 12, stratified by centre. Participants, care providers, investigators, outcome assessors, data analysts, and the independent data safety monitoring board were all blinded to group allocation. Patients received isocaloric enteral feeds that contained 1·3 kcal/mL and 0·06 g of protein/mL (ie, standard protein) or 1·3 kcal/mL and 0·10 g of protein/mL (ie, high protein). The study-nutrition intervention was limited to the time period during the patient's ICU stay in which they required enteral feeding, with a maximum of 90 days. The primary outcome was EuroQoL 5-Dimension 5-level (EQ-5D-5L) health utility score at 30 days, 90 days, and 180 days after randomisation, adjusted for baseline EQ-5D-5L health utility score. This trial was registered with ClinicalTrials.gov (NCT04633421) and is closed to new participants.

Findings Between Nov 19, 2020, and April 14, 2023, 935 patients were randomly assigned. 335 (35·8%) of 935 patients were female and 600 (64·2%) were male. 465 (49·7%) of 935 were assigned to the standard protein group and 470 (50·3%) were assigned to the high protein group. 430 (92·5%) of 465 patients in the standard protein group and 419 (89·1%) of 470 patients in the high protein group were assessed for the primary outcome. The primary outcome, EQ-5D-5L health utility score during 180 days after randomisation (assessed at 30 days, 90 days, and 180 days), was lower in patients allocated to the high protein group than in those allocated to the standard protein group, with a mean difference of –0·05 (95% CI –0·10 to –0·01; p=0·031). Regarding safety outcomes, the probability of mortality during the entire follow-up was 0·38 (SE 0·02) in the standard protein group and 0·42 (0·02) in the high protein group (hazard ratio 1·14, 95% CI 0·92 to 1·40; p=0·22). There was a higher incidence of symptoms of gastrointestinal intolerance in patients in the high protein group (odds ratio 1·76, 95% CI 1·06 to 2·92; p=0·030). Incidence of other adverse events did not differ between groups.

Interpretation High enteral protein provision compared with standard enteral protein provision resulted in worse health-related quality of life in critically ill patients and did not improve functional outcomes during 180 days after ICU admission.

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Introduction

Patients who survive critical illness often have low quality of life. This reduced quality of life has been attributed to persistent muscle wasting and weakness, among other factors,[1] which develop during the first week of intensive care unit (ICU) admission.[2] Quality of life can remain impaired for years after ICU discharge,[3] but increased protein provision could improve functional outcomes after critical illness by alleviating muscle catabolism and weakness.[4,5] However, evidence is controversial as observational data show both benefit and harm.[2,6,7] Due to scarce prospective data, uncertainty remains about whether high dose protein is beneficial,[4] with contemporary guidelines recommending wide targets of between 1·2 g/kg per day and 2·0 g/kg per day.[8,9]

The EFFORT Protein trial[10] reported no effect of high protein nutrition on time-to-discharge-alive from hospital or on 60-day mortality in critically ill patients. In addition to mortality, long-term physical function and patient-reported quality of life are important outcomes after critical illness.[11–13] Although health-related quality of life

Research in context

Evidence before this study

We co-authored an update to a systematic review and meta-analysis by the authors of the EFFORT Protein trial. We searched MEDLINE, Embase, and Central through OVID from database inception to May 29, 2023, using the search terms "critical illness", "critical care", "intensive care units", "proteins", "amino acids", and "peptides" for randomised controlled trials of critically ill adult patients, comparing higher versus lower protein with similar energy intake between groups and reporting clinical or patient-centred outcomes, or both, with no language restrictions. This search yielded 24 randomised controlled trials. A further update to this search with the same search terms on PubMed, from May 29, 2023, to April 30, 2024, yielded no additional relevant trials. There was considerable variation in inclusion criteria, nature of the interventions, and protein doses in both the intervention and control groups. The meta-analysis showed heterogeneity in mortality between the different studies. No statistically significant differences were found between higher and lower protein provision regarding clinical outcomes such as mortality, intensive care unit (ICU) length of stay, hospital length of stay, and duration of mechanical ventilation. However, trial sequential analyses indicated that these conclusions remain uncertain, and that more data are needed to substantiate these findings. Higher protein provision appeared to be associated with higher mortality than lower protein provision in critically ill patients with acute kidney injury.

The largest randomised trial to date addressing high protein provision in critically ill people is the pragmatic, registry-based, open-label EFFORT Protein trial. This trial reported no statistically significant difference in its primary endpoint, time-to-discharge-alive from hospital. The meta-analysis further retrieved five randomised trials that reported health-related quality of life via various instruments. Health-related quality of life was reported in surviving people only and these trials did not account for death as a potential competing risk. There was no difference between higher and lower protein groups. However, the small sample sizes and heterogeneity precluded firm conclusions on the effect of high protein nutrition in critically ill patients on health-related quality of life based on this meta-analysis. Overall, accumulating evidence suggests that higher protein provision in critically ill people does not lead to clinical benefit, but uncertainty remains due to scarce high-quality trials, particularly addressing patient-reported outcome measures. Advice on protein dose in critically ill patients in current guidelines from the American Society for Parenteral and Enteral Nutrition still ranges from 1·2 g/kg per day to 2·0 g/kg per day. Accordingly, there is a high demand for additional high-quality evidence concerning the effect of protein provision in people who are critically ill.

Added value of this study

To our knowledge, the PRECISe trial is the largest randomised controlled trial assessing the effect of high protein nutrition in critically ill patients in an ICU with health-related quality of life as a primary endpoint, specifically targeting a group of patients with an extended ICU stay. Furthermore, PRECISe is the largest fully blinded randomised controlled trial, the largest on enteral protein only, and the largest with individual prospective follow-up in this area of research. Finally, PRECISe is the first large multicentre trial comparing high versus standard protein provision in critically ill people to yield a statistically and clinically significant result on the primary outcome.

Implications of all the available evidence

The PRECISe trial showed lower health-related quality of life in critically ill patients receiving high enteral protein nutrition than in critically ill patients receiving standard enteral protein nutrition. This finding strengthens emerging evidence that the high end of current recommendations from the American Society for Parenteral and Enteral Nutrition guidelines on protein provision in critically ill patients do not yield clinical benefits. Accumulating evidence suggests that caution is warranted when dosing nutritional protein in critically ill patients. Future research should investigate whether high protein provision can be beneficial in specific groups of patients, during later stages of critical illness, and in patients who undergo active physical rehabilitation.

has been included as a secondary outcome in some previous trials of nutritional therapy,[14,15] no large clinical trial of a nutritional intervention in critical care has used quality of life as the primary outcome.

On the basis of strong evidence and consensus, guidelines from the European Society for Clinical Nutrition and Metabolism recommend enteral feeding over parenteral feeding to administer nutrition. These guidelines recommend a daily protein intake of 1·3 g/kg, whereas guidelines from the American Society for Parenteral and Enteral Nutrition recommend a daily protein intake ranging from 1·2 g/kg to 2·0 g/kg. The aim of the PRECISe trial was to assess whether higher enteral protein provision (ie, 2·0 g/kg per day) would improve health-related quality of life and functional outcomes in critically ill patients who were mechanically ventilated compared with standard enteral protein provision (ie, 1·3 g/kg per day).[16]

Methods

Study design

The PRECISe trial was an investigator-initiated, double-blinded, multicentre, parallel-group, randomised controlled trial in five Dutch hospitals and five Belgian hospitals (appendix p 17). The protocol was approved by independent medical ethics committees of Maastricht University (METC 20–039) and University Hospital Brussels (2020/223). The study protocols and statistical analysis plan are available online (https://intensivecare.mumc.nl/precise-clinical-trial). The major amendments from the first version of the study protocol were a sample-size adaptation and the addition of a fifth Dutch site. An outline of the protocol has been published elsewhere.[16]

A trial steering committee and a data safety monitoring board provided trial oversight. Data were collected and managed via web-based electronic case-report forms (Castor Electronic Data Capture, Amsterdam, Netherlands) and manually reviewed by the Clinical Trial Unit (Future Health) of Ziekenhuis Oost-Limburg (Genk, Belgium). In addition, checks and automatic queries were built in. On-site monitoring visits, including source data verification, were done by the Clinical Trial Center Maastricht (Maastricht, Netherlands)

Participants

Adult patients with an unplanned ICU admission were screened for inclusion; patients who had undergone uncomplicated elective surgery with a short ICU stay were not screened. Inclusion criteria were aimed at a population at risk of reduced health-related quality of life after an ICU stay, with anticipated long exposure to the intervention. Inclusion criteria were initiation of invasive mechanical ventilation within 24 h of ICU admission and an expected duration of invasive ventilation of 3 days or longer. Exclusion criteria were contraindications for enteral nutrition, moribund condition, BMI less than 18 kg/m², kidney failure with a no dialysis code, or hepatic encephalopathy (appendix p 18). Sex was recorded as assigned at birth.

At Dutch sites, patients were enrolled by treating physicians via deferred consent. Proxies of the patients were informed about study participation in person by a member of the study team who asked for written informed consent at the earliest convenience. At Belgian sites, proxies of the patients were informed in person about the study by a member of the study team who asked for written informed consent (appendix pp 4, 52). All patients who regained capacity were asked to confirm the proxy consent (appendix p 4).

Randomisation and masking

Patients were randomly assigned to one of four randomisation labels, corresponding with two study groups (ie, standard or high protein; two labels per group) in a 1:1:1:1 ratio through an interactive web-response system (ALEA randomisation system, ALEA Clinical Services, Abcoude, Netherlands). Randomisation was done via random permuted-block randomisation in varying block sizes of eight and 12, stratified by centre. The system was accessed through a website by local clinical or research staff, who also performed randomisation (JLMB, RJJvG, AB, ADBD, VF, SL, DL, CS, EDW, ARHvZ, BCTvB, JJ, IM, MCGvdP, and DM). The allocation sequence was generated by the Clinical Trial Center Maastricht in collaboration with Nutricia Research (Utrecht, Netherlands).

Some local investigators were clinicians who could be involved in the direct care of enrolled patients (ST, AB, ADBD, VF, SL, DL, CS, EDW, ARHvZ, BCTvB, TF, ICCvdH, JJ, HM, PBM, MCP, SvS, MCGvdP, and DM).

Blinded study feeds were supplied by Nutricia in identical 500 mL containers with a study label. Previous studies have shown the feasibility of this approach to maintain double blinding.[17] The two labels per study group were to minimise the risk of full unblinding. Participants, care providers, investigators, outcome assessors (JLMB, RJJvG, ADBD LB-R, IH, IM, MCP, MR, and SvS), data analysts (JLMB and SMJvK), and the independent data safety monitoring board were all blinded to group allocation. The success of masking was not assessed specifically.

Unblinding was done in a stepwise manner. After database lock on Jan 15, 2024, which feeding labels belonged together to form the two treatment groups were revealed. Final group assignment was revealed only after completion of statistical analyses on Feb 26, 2024.

Procedures

Patients received isocaloric enteral feeds that contained 1·3 kcal/mL and 0·06 g of protein/mL (ie, standard protein) or 1·3 kcal/mL and 0·10 g of protein/mL (ie, high protein). These tube feeds were commercially available, nutritionally complete, whole-protein tube

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See **Online** for appendix

feeds that are both clinically applied in the treatment of critically ill patients who are mechanically ventilated (ie, Nutrison Protein Plus [Nutricia, Utrecht, Netherlands] for standard protein and Nutrison Protein Intense [Nutricia, Utrecht, Netherlands] for high protein; appendix p 18). Enteral nutrition was started within 48 h of ICU admission at 25% of the calculated final energy target. To avoid early overfeeding, the dose of study feeds was gradually increased by a further 25% per day, in accordance with guidelines from the European Society for Clinical Nutrition and Metabolism,[8] until 100% of the energy target (ie, 25 kcal/kg per day) was reached on day 4. This energy target corresponded with a protein target of 1·3 g/kg per day in the standard protein group and 2·0 g/kg per day in the high protein group. The study-nutrition intervention was limited to the time period during the patient's ICU stay in which they required enteral feeding, with a maximum of 90 days. Energy targets were calculated on the basis of a patient's actual bodyweight upon admission. To avoid overfeeding, targets were adjusted for those with a BMI of more than 27 kg/m² to a bodyweight that would result in a BMI of 27 kg/m². Pump rates for study nutrition administration were provided by the randomisation system upon randomisation, based on height and bodyweight. Pump rates were adjusted daily at fixed times to ensure exact 24-h intervals.

Protein targets were prioritised over energy targets. Adjustment of nutritional targets based on the intake of non-nutritional energy, such as propofol or based on indirect calorimetry, was not allowed as it might have led to a reduction in protein administration. Protein supplements, either enteral or parenteral, were not permitted. At all times, study nutrition was the preferred type of enteral nutrition, meaning that study nutrition could only be ceased on specific demand of the treating physician. In patients who were readmitted to the ICU within 48 h and still required enteral nutrition, the assigned study nutrition was resumed. To improve nutritional adequacy, a volume-based protocol was used.[18] The daily volume goal was adjusted to compensate for missed volume due to feeding interruptions in the previous 24 h from day 5 onwards, referred to as catch-up feeding.

Sites were encouraged to increase nutritional adequacy by avoiding routine assessment of gastric residual volumes, but no mandatory directions were in place. Use of prokinetic drugs was at the discretion of the treating physicians. To avoid potentially associated risks, supplemental parenteral nutrition was prohibited during the first 7 days of ICU admission. Parenteral nutrition was permitted from day 8 onwards, and its prescription was at the discretion of the treating physicians.

Follow-up assessments were done by the respective sites at 30 days, 90 days, and 180 days after randomisation and included questionnaires and physical tests (appendix p 18). When an in-person follow-up visit was not possible, questionnaires were sent by post or email or administered by telephone.

Outcomes

Outcomes were adapted from a core outcome set for clinical research in critically ill patients who are mechanically ventilated.[12] The primary outcome was EuroQoL 5-Dimension 5-level (EQ-5D-5L) health utility score at 30 days, 90 days, and 180 days after randomisation, adjusted for baseline EQ-5D-5L health utility score. The EQ-5D-5L health utility score is computed by converting the responses to the five items of the EQ-5D-5L questionnaire (ie, mobility, self-care, usual activities, pain and discomfort, and anxiety and depression) to one summary value. This calculation is done with country-specific value sets, which are also available for the Netherlands and Belgium.[19,20] Deceased patients receive an EQ-5D-5L health utility score of 0, whereas patients with a health-related quality of life that is valued worse than death receive a negative score. EQ-5D-5L thus incorporates deceased patients and, accordingly, we assigned patients who died during follow-up an EQ-5D-5L health utility score of 0. Minimum scores are –0·532 in Belgium and –0·446 in the Netherlands. Higher EQ-5D-5L health utility scores indicate better health-related quality of life (appendix pp 4–5, 41–42, 107). Baseline EQ-5D-5L, reflecting health-related quality of life before the onset of critical illness, was obtained from a proxy upon provision of informed consent. Baseline proxy-completed EQ-5D-5L is an accurate estimate of self-completed EQ-5D-5L.[21]

Secondary outcomes included mortality as time to event, up to 180 days after randomisation, and longitudinally measured functional outcomes. There was no allowance of multiplicity for the secondary outcomes. In addition, we recorded key outcomes of other trials investigating high protein nutrition in critically ill people, such as time-to-discharge-alive from the hospital[10] and days alive and at home at day 90 after index ICU admission (appendix p 19).[22]

Adverse events of special interest were recorded in the daily electronic case-report form and reported to the ethical review boards. Study-emergent special adverse events were immediately reported to the study team, discussed by the prinicipal investigators, and reported to the medical ethical committees.

Statistical analysis

The initial sample was calculated to detect a clinically important difference of 0·06 in mean EQ-5D-5L health utility score on the natural scale. The estimated common SD was 0·3 at 180 days,[23] which equates to a standardised effect size of 0·2. With a two-sided significance level of 0·05, a statistical power of 80%, and an estimated loss to follow-up of 5%,[16] the initial sample size was established as 824 participants via the standard formula to test for differences in independent means in cross-sectional analysis.[24] During the preplanned interim safety

analysis done by the data safety monitoring board after 50% of the planned inclusions, actual overall mortality was higher than anticipated, increasing the SD of the primary outcome. After excluding safety issues, the data safety monitoring board advised us to adjust the sample size to account for the increased SD. A Monte Carlo simulation of raw longitudinal EQ-5D-5L data from the actual study population, done after 709 inclusions, showed that 935 patients were required to obtain sufficient power. After approval from the data safety monitoring board, the trial steering committee, and the independent ethics committees, the final sample size was increased to 935. Because the primary outcome was not evaluated during the single, planned, safety analysis, there was no need to adjust the α for the primary outcome.

All statistical analyses were conducted on an intention-to-treat basis in strict adherence to the statistical analysis plan. Analyses were done only after database lock and completed before unblinding with R version 4.3.2. The R codes used for the adjusted sample size calculation are available online (https://github.com/sandervkuijk/sample_size_simulation_PRECISe). Codes for data preparation and analysis of the PRECISe dataset were uploaded to the same data repository before unblinding and are available online (https://github.com/sandervkuijk/PRECISe).

Categorical data are presented as numbers and percentages, and continuous variables are presented as mean (SD) for normally distributed data and median (IQR) for other data.

The primary outcome, EQ-5D-5L health utility score during 180 days after ICU admission, was analysed with a restricted maximum likelihood linear mixed-effects regression model in combination with the Nelder–Mead algorithm. The data had a three-level structure (ie, repeated measurements were clustered within participants and participants were clustered within centres). We used an unstructured variance–covariance matrix, and the degrees of freedom were estimated via the method by Pinheiro and Bates.[25] The fixed factors were treatment group, time, a treatment group by time interaction term, and baseline EQ-5D-5L. No missing outcome data were imputed because the mixed-effects model accounts for missing data and is valid under the missing-at-random assumption. The modelling steps were included in section 5 of the statistical analysis plan.

For time-to-event analyses (ie, overall mortality and time-to-discharge-alive from the hospital up to 180 days), Kaplan–Meier survival curves were constructed. Cox proportional hazards frailty models were used to investigate treatment effects and crude, unadjusted hazard ratios were reported with a 95% CI. The proportional hazards assumption was assessed with scaled Schoenfeld residuals. For the analysis of time-to-discharge-alive from the hospital, patients who died during index hospital stay were censored to a timepoint of the last surviving person to account for death as a competing risk. We conducted an additional post-hoc analysis of time-to-discharge-alive with the generalised Wilcoxon test, which gives more weight to events early during follow-up.

In line with the statistical analysis plan, sensitivity analyses were done for the primary outcome and overall

	Standard protein (n=465)	High protein (n=470)
Age, years	63 (14)	62 (14)
Sex		
Female	156 (34%)	179 (38%)
Male	309 (67%)	291 (62%)
BMI	27 (5)	28 (6)
Type of admission		
Medical	341 (73%)	308 (66%)
Surgical	124 (27%)	162 (35%)
Emergency surgery	107/124 (86%)	138/162 (85%)
Complications of elective surgery	17/124 (14%)	24/162 (15%)
Admission diagnosis system		
Respiratory	173 (37%)	149 (32%)
Cardiovascular	128 (28%)	129 (27%)
Neurological	67 (14%)	82 (17%)
Trauma	42 (9%)	48 (10%)
Sepsis*	21 (5%)	26 (6%)
Gastrointestinal	19 (4%)	22 (5%)
Miscellaneous	8 (2%)	4 (1%)
Metabolic or endocrine	4 (1%)	5 (1%)
Genitourinary	2 (<1%)	4 (1%)
Haematological	1 (<1%)	1 (<1%)
Diabetes	84 (18%)	90 (19%)
COVID-19 infection	73 (16%)	71 (15%)
Acute kidney injury†	97 (21%)	105 (22%)
Sepsis	229 (49%)	230 (49%)
Glasgow Coma Scale	15 (6–15)	15 (8–15)
APACHE II score‡	22 (7)	21 (7)
APACHE IV score‡	83 (26)	81 (26)
SOFA score§	10 (3)	9 (3)
SAPS II¶	48 (14)	47 (14)
EQ-5D-5L health utility score‖	0·78 (0·25)	0·77 (0·26)
Charlson Comorbidity Index**	3 (2–4)	3 (1–4)
NRS-2002 score††	4 (1)	4 (1)
Rockwood Clinical Frailty Scale‡‡	3 (2)	3 (2)

Data are mean (SD), n (%), n/N (%), or median (IQR). APACHE=Acute Physiology and Chronic Health Evaluation. EQ-5D-5L=EuroQoL 5-Dimension 5-level. KDIGO=Kidney Disease Improving Global Outcomes. NRS-2002=Nutritional Risk Screening 2002. SAPS=Simplified Acute Physiology Score. SOFA=Sequential Organ Failure Assessment. *Only patients with a not-otherwise-specified cause of sepsis as admission diagnosis. Patients with a specified cause of sepsis were categorised under the corresponding system. †Acute kidney injury was defined on the basis of KDIGO classification, which ranges from 1 to 3. KDIGO scores were calculated at randomisation and a score of 1 or more was considered to indicate acute kidney injury. ‡APACHE II scores range from 0 to 71. APACHE IV scores range from 0 to 286. Higher scores indicate greater severity of disease. §SOFA scores range from 0 to 20. Higher scores indicate greater severity of organ failure. ¶SAPS II ranges from 0 to 163. Higher scores indicate greater severity of disease. ‖EQ-5D-5L health utility score ranges from –0·5 to 1·0. Deceased patients are assigned a score of 0. A score less than 0 is valued as a health-related quality of life worse than death, a higher score indicates better health-related quality of life, and a score of 1·0 indicates perfect health-related quality of life. **The Charlson Comorbidity Index provides a weighted score by considering comorbid conditions. Higher scores indicate more severe comorbid conditions. ††NRS-2002 ranges from 0 to 7. Higher scores indicate greater risk of malnutrition. ‡‡The Rockwood Clinical Frailty Scale is a global clinical measure of fitness and frailty in older people and ranges from 1 to 9. Higher scores indicate greater severity of frailty.

Table 1: **Baseline characteristics of the intention-to-treat population**

mortality up to 180 days, adjusted for sex, Acute Physiology and Chronic Health Evaluation (APACHE) II score, APACHE IV admission diagnosis, and Nutritional Risk Screening (NRS)-2002 score.

Treatment effects of other longitudinally measured outcomes were also assessed via linear mixed-effects models, similar to the analysis of the primary outcome. Cross-sectionally assessed continuous or categorical outcomes were analysed with linear or generalised linear mixed-effects models, as appropriate, with centre as a random intercept.

Prespecified subgroups that were deemed relevant or used in similar trials were analysed for the primary outcome and for overall mortality to assess potential heterogeneity in treatment effects. Subgroups, were defined on pre-randomisation characteristics (appendix p 20). The results of subgroup analyses were reported as point estimates and 95% CIs. As correction for multiplicity was not predefined in the statistical analysis plan, these CIs cannot be used in place of hypothesis testing. For the primary outcome, a two-sided p value of less than 0·05 was considered to indicate statistical significance.

The period between randomisation and first assessment of the primary outcome was 30 days. To enter the analysis for the primary outcome, patients had to have at least one measurement of the EQ-5D-5L health utility score at 30 days, 90 days, or 180 days, otherwise patients were considered lost to follow-up for the primary outcome. Patients who died at any timepoint after randomisation remained in the analysis. Data collected before loss to follow-up were used for analysis of secondary and tertiary outcomes. All patients or proxies who withdrew consent allowed the use of already collected data.

This trial was registered with ClinicalTrials.gov (NCT04633421) and is closed to new participants.

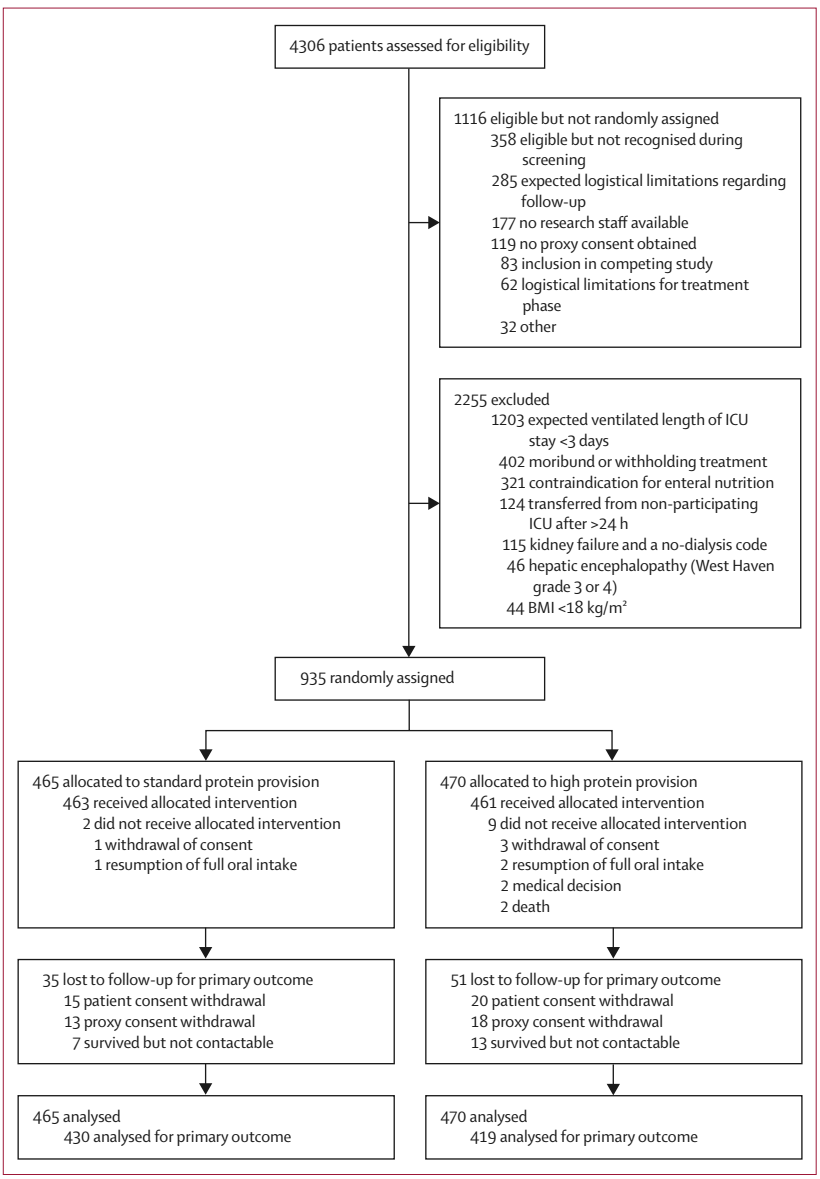

Figure 1: **Trial profile**
ICU=intensive care unit.

Role of the funding source

Use of the EQ-5D-5L health utility score as a primary endpoint was advocated by the funders during grant application. The funders of the study had no further role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Of the 4306 patients who were assessed for eligibility, 3371 (78·3%) were not eligible and 935 (21·7%) were randomly assigned between Nov 19, 2020, and April 14, 2023. Of these 935 patients, 465 (49·7%) were assigned to the standard protein group and 470 (50·3%) were assigned to the high protein group (appendix p 17). 335 (35·8%) of 935 patients were female and 600 (64·2%) were male (table 1). Two (0·4%) of 465 patients in the standard protein group and nine (1·9%) of 470 patients in the high protein group did not receive study nutrition. 35 (7·5%) of 465 patients in the standard protein group and 51 (10·9%) of 470 patients in the high protein group were lost to follow-up before assessment of the primary outcome (figure 1). 430 (92·5%) of 465 patients in the standard protein group and 419 (89·1%) of 470 patients in the high protein group were assessed for the primary outcome. Baseline EQ-5D-5L was collected for 394 (84·7%) of 465 patients in the standard protein group and 391 (83·2%) of 470 patients in the high protein group.

Median duration of study nutrition was 9 days (IQR 4–19) in patients allocated to standard enteral protein and 10 days (5–21) in patients allocated to high enteral protein (appendix p 20). Median cumulative protein intake, both enteral and parenteral, during the

entire intervention period was 1·19 g/kg per day (0·63–1·26) in the standard protein group and 1·87 g/kg per day (0·96–2·00) in the high protein group (figure 2; appendix pp 6, 21, 23). Daily energy intake did not differ between groups (figure 3; appendix pp 7, 22–23). Nutritional energy intakes more than 25 kcal/kg per day occurred incidentally in individual patients, mostly due to catch-up feeding that was given to compensate for missed targets the day before (appendix p 23). There were 36 protocol deviations recorded in the standard protein group and 48 recorded in the high protein group (appendix p 24).

The primary outcome, EQ-5D-5L health utility score during 180 days after randomisation (assessed at 30 days, 90 days, and 180 days), was lower in patients allocated to the high protein group than in those allocated to the standard protein group, with a mean difference of –0·05 (95% CI –0·10 to –0·01; p=0·031; table 2; appendix p 8).

There was no uniform treatment effect on muscle-related outcomes between both groups during the 180 days follow-up period, measured in surviving people only and without data imputation for deceased patients (table 2; appendix pp 9–12).

Regarding safety outcomes, the probability of mortality (appendix pp 12, 24, 107–108, 111) during the entire follow-up was 0·38 (SE 0·02) in the standard protein group and 0·42 (0·02) in the high protein group (hazard ratio 1·14, 95% CI 0·92 to 1·40; p=0·22; appendix p 12). There was a higher incidence of symptoms of gastrointestinal intolerance in patients in the high protein group. Incidence of other adverse events did not differ between groups (table 3).

There was significantly greater use of prokinetic drugs and longer duration of stay at a rehabilitation facility in patients allocated to high enteral-protein provision than in patients allocated to standard enteral-protein provision (appendix pp 14–26). The hazard ratio for being discharged alive during 180 days after randomisation was 0·91 (95% CI 0·80–1·04) for patients allocated to the high protein group (appendix p 13). The post-hoc generalised Wilcoxon test showed p=0·043, indicating a statistically significant longer time-to-discharge-alive for the high protein group than for the standard protein group (appendix p 14).

The preplanned sensitivity analysis for the primary outcome, correcting for APACHE II score, sex, APACHE IV admission diagnosis, and NRS-2002 score, yielded similar results as the primary analysis (mean difference –0·05; 95% CI –0·10 to –0·00; p=0·038). In the preplanned sensitivity analysis for overall mortality, correcting for the same parameters, the hazard ratio for overall mortality in patients allocated to high enteral protein increased to 1·24 (95% CI 0·99 to 1·55; p=0·063). Preplanned exploratory analyses favoured standard enteral protein across most subgroups regarding EQ-5D-5L health utility score and overall mortality (appendix pp 15–16). These analyses suggest that the unfavourable effects of high enteral protein were most prominent in female patients and patients with a medical admission. We observed no unfavourable effects of high

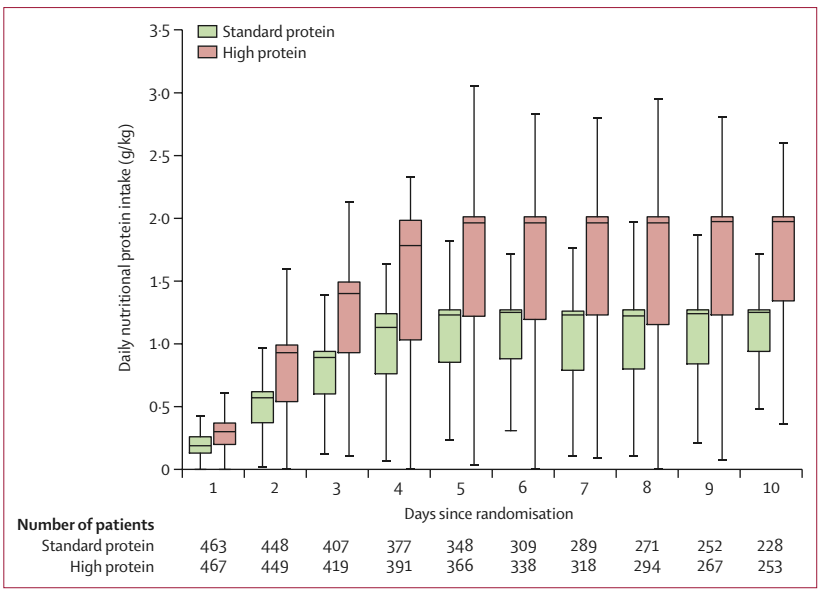

Figure 2: **Protein intake on days 1–10 after randomisation**
Daily amount of delivered protein (g/kg) during the first 10 days after randomisation. Intake of protein was calculated for all days during ICU admission where nutritional intake could be fully quantified. Days with oral intake and partly observed days due to ICU discharge or consent withdrawal were not included. Horizontal lines in boxes represent medians; bottoms of boxes show 25th percentile and tops of boxes show 75th percentile. Ends of whiskers represent the upper adjacent value (ie, 75th percentile plus 1·5 times the IQR) and the lower adjacent value (ie, 25th percentile minus 1·5 times the IQR). ICU=intensive care unit.

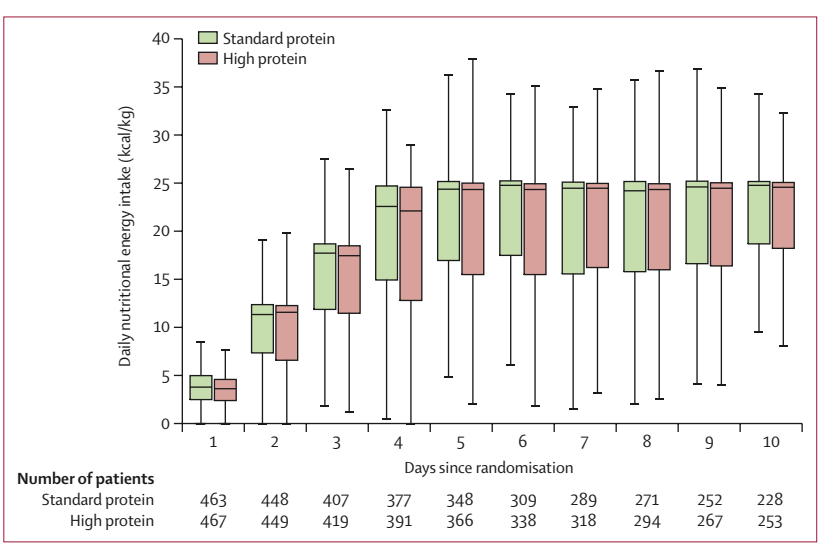

Figure 3: **Nutritional energy intake on days 1–10 after randomisation**
Daily amount of delivered nutritional energy (kcal/kg) during the first 10 days after randomisation. Intake of nutritional energy was calculated for all days during ICU admission where nutritional intake could be fully quantified. Days with oral intake and partly observed days due to ICU discharge or consent withdrawal were not included. Horizontal lines in boxes represent medians; bottoms of boxes show 25th percentile and tops of boxes show 75th percentile. Ends of whiskers represent the upper adjacent value (ie, 75th percentile plus 1·5 times the IQR) and the lower adjacent value (ie, 25th percentile minus 1·5 times the IQR). Nutritional energy intakes more than 25 kcal/kg per day occurred incidentally, mostly due to catch-up feeding that was given to compensate for missed targets on the previous day (appendix p 23). ICU=intensive care unit.

	Standard protein (n=465)	High protein (n=470)	Treatment effect	p value
Primary outcome				
EQ-5D-5L health utility score	430	419	−0·05 (−0·10 to −0·01)	0·031
After 30 days	0·33 (0·33)	0·29 (0·32)	..	..
After 90 days	0·38 (0·38)	0·34 (0·38)	..	..
After 180 days	0·39 (0·39)	0·36 (0·40)	..	..
Secondary outcomes				
SF-36	219	192	0·70 (−0·98 to 2·38)	0·41
After 30 days	41·7 (17·3)	45·0 (19·2)	..	..
After 90 days	50·7 (21·8)	53·3 (21·7)	..	..
After 180 days	58·4 (22·6)	60·3 (22·7)	..	..
Physical component summary of SF-36	219	192	0·46 (−1·22 to 2·14)	0·59
After 30 days	31·9 (8·1)	32·7 (9·2)	..	..
After 90 days	36·4 (10·1)	37·3 (10·3)	..	..
After 180 days	40·2 (10·8)	41·0 (10·9)	..	..
Mental component summary of SF-36	219	192	1·02 (−0·80 to 2·84)	0·27
After 30 days	37·0 (9·9)	38·5 (10·3)	..	..
After 90 days	41·0 (11·5)	42·5 (10·4)	..	..
After 180 days	43·7 (11·2)	44·6 (10·7)	..	..
Hospital Anxiety and Depression Scale	225	198	−0·43 (−1·02 to 0·15)	0·15
After 30 days	17·3 (3·9)	16·9 (3·7)	..	..
After 90 days	17·5 (3·8)	17·0 (3·4)	..	..
After 180 days	17·4 (3·5)	17·3 (3·5)	..	..
Impact of Event Scale–Revised	219	195	−1·54 (−4·26 to 1·18)	0·27
After 30 days	20·2 (16·1)	17·6 (14·3)	..	..
After 90 days	17·6 (16·0)	16·2 (15·7)	..	..
After 180 days	16·5 (15·5)	16·7 (16·8)	..	..
Percentage of predicted 6-min walking distance	154	133	5·55 (0·04 to 11·07)	0·048
After 30 days	60·6 (23·9)	61·6 (24·2)	..	..
After 90 days	68·0 (28·3)	73·9 (25·8)	..	..
After 180 days	72·6 (24·9)	81·8 (23·4)	..	..
MRC-SUM score	221	201	−0·23 (−1·60 to 1·12)	0·73
After 30 days	48·8 (11·5)	49·6 (11·7)	..	..
After 90 days	54·3 (6·7)	54·0 (8·5)	..	..
After 180 days	56·6 (5·6)	56·9 (5·9)	..	..
Percentage of predicted handgrip strength	212	188	−3·87 (−9·53 to 1·80)	0·18
After 30 days	66·8 (32·2)	68·5 (31·1)	..	..
After 90 days	83·0 (30·1)	75·0 (31·4)	..	..
After 180 days	92·8 (31·4)	89·5 (30·7)	..	..
EQ-5D-5L visual analogue score	289	254	−1·53 (−4·47 to 1·42)	0·31
After 30 days	52·0 (23·0)	47·7 (22·9)	..	..
After 90 days	61·4 (21·0)	63·0 (19·6)	..	..
After 180 days	66·7 (17·9)	66·0 (20·4)	..	..

(Table 2 continues on next page)

enteral protein in patients with acute kidney injury or multiorgan failure on ICU admission.

Discussion

In this investigator-initiated, double-blinded, multicentre, parallel-group, randomised controlled trial, high enteral protein provision in critically ill patients who were mechanically ventilated resulted in a lower health-related quality of life than provision of standard enteral protein, measured by the EQ-5D-5L health utility score during 180 days after ICU admission. Moreover, our post-hoc analysis showed a statistically significant increase in time-to-discharge-alive from the hospital in patients allocated to high protein provision compared with patients allocated to standard protein provision. Furthermore, incidence of gastrointestinal intolerance and use of prokinetics were greater in patients assigned to the high protein group. These findings contrast with the original notion that high protein provision during critical illness might improve functional outcome. Subgroup analyses indicated that high enteral protein provision might be particularly harmful in female patients and patients with a medical admission, although these results should be interpreted with care as subgroup analyses were not corrected for multiplicity.

The PRECISe trial, as is being increasingly advocated for, focused on patient-reported and functional outcomes as long-lasting functional disabilities can result in low health-related quality of life in patients in an ICU.[3] The EQ-5D-5L health utility score is an appropriate outcome measure for studies with a high mortality rate because it addresses death as a potential competing risk by retaining deceased patients and assigning them a score of 0.[26] When patient-reported and functional outcomes are exclusively assessed in surviving patients, death as a potential competing risk is ignored.[27] This exclusion of deceased patients could explain why the results of our secondary and tertiary outcomes, which were measured in surviving patients only, were inconsistent with the EQ-5D-5L health utility score.

The effect of high versus low protein provision on a wide array of outcome measures in critically ill patients has been addressed in several randomised controlled trials,[28] of which the EFFORT Protein trial is the largest.[10] Some smaller randomised trials have dealt with the effect of protein intake on health-related quality of life and functional outcomes after critical illness;[17,28,29] however, the PRECISe trial is the first with adequate power to detect a statistically and clinically significant difference in a functional outcome. In addition to providing new evidence concerning the harmful effects of high protein provision on health-related quality of life in critically ill patients, the PRECISe trial strengthens the results of the EFFORT Protein trial, which could not support the hypothesis that high protein nutrition improves clinical outcome in critically ill patients. This open-label, registry-based trial found a hazard ratio for

the primary outcome, time-to-discharge-alive from the hospital, of 0·91 (95% CI 0·77–1·07).[10] To enable comparison of our results with those of the EFFORT Protein trial, we added this outcome to our statistical analysis plan and found an almost identical hazard ratio and CI.

However, dissimilar to the EFFORT Protein trial, we found no signal of harm for high enteral protein provision in patients with acute kidney injury and multiorgan failure. However, in the EFFORT Protein trial, the onset of acute kidney failure was monitored for 7 days after randomisation, whereas we assigned only patients with acute kidney failure at the time of randomisation to this particular subgroup.

The mechanism underlying the deleterious effects of higher enteral protein doses is unknown. The increased amino acid supply might have surpassed the capacity for protein synthesis, leading to increased amino-acid oxidation and production of potentially toxic deamination products.[30] Additionally, exogenous protein in the acute phase of critical illness might delay recovery by suppressing autophagy, the process of intracellular breakdown and recycling of old, damaged, or atypical proteins and other harmful substances from the cytoplasm.[6,31] The observed sex difference in the subgroup analyses is intriguing but hypothesis-generating, and requires substantiation in future research. An explanation for the possible interaction between high enteral protein provision and sex could be the relatively lower lean body mass in women, leading to a higher protein delivery relative to muscle mass when protein is dosed per total body mass. Exploratory analyses further showed that the negative effects of high protein were more prominent in medical than in surgical patients. These findings need substantiation in future research, but protein demands might be higher in post-operative patients (eg, to facilitate wound healing).

A limitation of this trial is that the difference in EQ-5D-5L health utility scores between study groups was less than the chosen minimum clinically important difference of 0·06. However, there is no consensus on this value, and differences ranging from 0·04 to 0·07 are considered clinically relevant.[32] Second, the dose of the study feed was not adjusted for non-nutritional calories, as it would have affected protein dose. Although the contribution of non-nutritional calories was low, it might have caused overfeeding in specific patients. However, energy delivery was similar between both groups, suggesting that it was not a systemic issue within the trial. A similar strategy has been used in other trials, such as the TARGET trial,[33] that reported no detrimental effects of energy provision exceeding 30 kcal (including non-nutritional calories) per kg of ideal bodyweight regarding clinical outcomes and EQ-5D-5L health utility score at 6-month follow-up.[15] Finally, although the longitudinal assessment during 6 months of patient-reported and functional outcomes is considered a strength of our trial, there was a relatively high amount of missing data. The percentage of incomplete records was higher for physical tests, requiring in-person follow-up, than for questionnaires. The highest amount of missing data was observed for the 6-min walking test, which is the most demanding physical test, making it likely prone to bias.

	Standard protein (n=465)	High protein (n=470)	Treatment effect	p value
(Continued from previous page)				
Rockwood Clinical Frailty Scale	300	269	0·03 (–0·25 to 0·31)	0·83
After 30 days	5·5 (1·9)	5·7 (1·9)	..	..
After 90 days	4·3 (1·8)	4·3 (2·0)	..	..
After 180 days	3·7 (1·8)	3·7 (1·9)	..	..

Data are mean (SD); coefficients from linear mixed-regression analysis, with study site as a random effect; or p values. For EQ-5D-5L and SF-36, higher scores indicate better health-related quality of life. For the Hospital Anxiety and Depression Scale and Impact of Event Scale–Revised, higher scores indicate worse symptoms and more disability. The number of patients for each outcome is the number of patients contributing to the mixed linear model (ie, each patient with at least one observed value). Number of observations per timepoint differed from the total number of patients contributing to the mixed linear model. The exact number of observations per timepoint are reported in the appendix (p 13). EQ-5D-5L=EuroQoL 5-Dimension 5-level. MRC-SUM=Medical Research Council Scale for Muscle Strength. SF-36=36-Item Short Form Health Survey.

Table 2: **Primary and secondary efficacy outcomes in the intention to-treat population**

	Standard protein	High protein
Deaths		
Overall mortality*	0·38 (0·02)	0·42 (0·02)
Study-emergent serious adverse events†		
Pneumatosis intestinalis	0/465 (<1%)	1/470 (<1%)
Adverse events of special interest		
ICU-acquired infections	112/465 (24%)	112/469 (24%)
Ventilator-acquired pneumonia	115/465 (25%)	111/469 (24%)
Extracorporeal membrane oxygenation	27/465 (6%)	28/469 (6%)
Acute kidney injury‡	98/465 (21%)	95/469 (20%)
Refeeding hypophosphataemia§	40/465 (9%)	53/469 (11%)
Hepatic dysfunction¶	39/465 (8%)	35/469 (8%)
Gastrointestinal intolerance or symptoms‖	26/465 (6%)	43/469 (9%)
All-cause mortality after ICU discharge**	36/286 (13%)	35/268 (13%)

Data are mortality probability (SE) or n/N (%), unless otherwise stated. ICU=intensive care unit. *Mortality probabilities 180 days after randomisation, calculated with the Kaplan–Meier method. †No study emergent adverse events were collected. Due to the nature of the patient population (ie, critically ill), patients could have many events that might be classified as adverse events. As this is part of the expected disease course, only serious adverse events that resulted in death or life-threatening situations, likely related to possible complications of nutritional support, are reported. ‡Defined as creatinine concentration more than two times baseline concentration (including the use of renal replacement therapy). §Defined as phosphate <0·65 mmol/L, a decrease of >0·16 mmol/L from previous phosphate in ICU and no other explanation for hypophosphataemia. ¶Defined as a bilirubin >3 mg/dL. ‖Vomiting, ischaemia, diarrhoea, abdominal distension, gastric paresis, bleeding, or ulcer. **Occurring between ICU discharge and end of trial.

Table 3: **Adverse events in the safety population**

Physical performance or in-person follow-up was no hindrance to assessing the primary outcome, for which missingness was considered to be missing at random (ie, conditional on observed covariates). Inclusion of only complete data would likely have resulted in bias in effect measures, as the sample available for analysis would not be a random sample of the population anymore. Moreover, it would have greatly decreased power to detect differences between groups. The generalised linear mixed-effects model assumes data are missing at random and, therefore, will produce unbiased estimates. For that reason, we conducted sensitivity analyses in which covariates likely contributing to the missing-at-random mechanism were added as fixed effects.

Considering death as a competing risk appeared to be particularly important in the PRECISe trial, considering the numerical difference in mortality between the two groups. Strengths of this trial included the double blinding; high achievement of enteral protein targets, which enhanced internal validity; and the use of a patient-reported primary outcome that incorporated mortality as a competing risk.

Further research is needed to clarify protein needs during different stages of critical illness[34] and to investigate the influence of physical therapy and exercise on muscle anabolism and protein use.[28] Our results warrant further research on sex differences in the response to protein provision in critically ill people. To conclude, caution is warranted when dosing nutritional protein in critically ill patients. Further research should aim to clarify protein requirements in different subgroups and in different phases of critical illness.

Contributors

The PRECISe trial was designed by DM, RJJvG, and MCGvdP in consultation with BCTvB, SMJvK, ZP, AMD, and JLMB. Overall trial management was done by JLMB and KT under the supervision of MCGvdP and DM. The PRECISe Trial Steering Committee consisted of JLMB, AB, VF, EDW, ARHvZ, AMD, FD, ZP, LCMV, PJMW, SMJvK, MCGvdP, and DM. AB, ADBD, VF, SL, DL, CS, EDW, ARHvZ, MCGvdP, and DM were principal investigators at the study sites. ST, LB-R, TF, IH, ICCvdH, JJ, HM, PBM, IM, MCP, MR, and SvS contributed to patient enrolment and data collection. KT, MMJD, and JLMB were responsible for data management. SMJvK and JLMB conducted the statistical analyses. JLMB, ST, RJJvG, MCGvdP, and DM wrote the manuscript and directly accessed and verified the underlying data reported in the study. All other authors reviewed and edited drafts of the manuscript and approved the final version. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

EDW receives honoraria for scientific lectures from Baxter Healthcare, Nutricia–Danone, and Nestlé. ARHvZ receives grants from AOP Pharma, Nutricia–Danone, Fresenius Kabi, PAION, and Rousselot; receives consulting fees from AOP Pharma, Medcaptain, and PAION; receives honoraria for lectures from Abbott, AOP Pharma, Baxter, Nestlé, Nutricia–Danone, Fresenius Kabi, GE Healthcare, and Dutch Medical Food; receives support for travel from Nutricia–Danone and Dutch Medical Food; is a member of the adult intensive care unit patient nutrition guideline committee of the European Society for Clinical Nutrition and Metabolism, the executive team of SepsisNet Netherlands, and the executive team of the Netherlands Society for Parenteral and Enteral Nutrition; and is the European Society of Intensive Care Medicine Section Feeding, Rehabilitation Endocrinology and Metabolism chair. ZP receives grants from Fresenius Kabi, Nestlé, and Baxter; receives consulting fees from Fresenius Kabi, Nestlé, Baxter, Faraday Pharmaceuticals, and Bioage Pharmaceuticals; and receives honoraria for lectures from Baxter, Nestlé, Fresenius Kabi, and Nutricia. MCGvdP receives grants from the Netherlands Organisation of Health Research and Development and the Belgian Health Care Knowledge Centre; receives in-kind support from Nutricia; receives consulting fees from Nutricia and Nestlé; and receives honoraria for lectures and support for travel from Nutricia. All other authors declare no competing interests.

Data sharing

Data collected for this study will not be publicly available due to privacy regulations. The study protocol and statistical analysis plan are available in the appendix (pp 28–133). The data dictionary is provided in the statistical analysis plan (appendix pp 122–130). De-identified individual participant data will be made available to researchers or other organisations upon reasonable request through a written proposal to marcel.vande.poll@mumc.nl and dieter.mesotten@zol.be from 6 months after publication. Each proposal will be judged on relevance and methodological appropriateness by the senior authors. Before transferring the data, requestors must sign a data transfer agreement with a fully approved protocol and publication policy.

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