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Impact of Early Low-Calorie Low-Protein versus Standard-Calorie Standard-Protein Feeding on Outcomes of Ventilated Adults with Shock: Design and Conduct of a Randomised, Controlled, Multicentre, Open-Label, Parallel-Group Trial (NUTRIREA-3)

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ABSTRACT

Introduction: International guidelines include early nutritional support (≤48 h after admission), 20-25 kcal/kg/d, and 1.2-2 g/kg/d protein at the acute phase of critical illness. Recent data challenge the wisdom of providing standard amounts of calories and protein during acute critical illness. Restricting calorie and protein intakes seemed beneficial, suggesting a role for metabolic pathways such as autophagy, a potential key mechanism in muscle protection during critical illness. However, the optimal calorie and protein supply at the acute phase of severe critical illness remains unknown. NUTRIREA-3 will be the first trial to compare standard calorie and protein feeding complying with guidelines to low-calorie low-protein feeding. We hypothesised that nutritional support with calorie and protein restriction during acute critical illness decreased day-90 mortality and/or dependency on ICU management in mechanically ventilated patients receiving vasoactive amine therapy for shock, compared to standard calorie and protein targets.

Methods and analysis: NUTRIREA-3 is a randomised, controlled, multicentre, open-label trial comparing two parallel groups of patients receiving invasive mechanical ventilation and vasoactive amine therapy for shock and given early nutritional support according to one of two strategies: early calorie-protein restriction (6 kcal/kg/d-0.2-0.4 g/kg/d) or standard calorie-protein targets (25 kcal/kg/d-1.0-1.3g/kg/d) at the acute phase defined as the first 7 days in the ICU. We will include 3044 patients in 61 French ICUs. Two primary end-points will be evaluated: day-90 mortality and time to ICU discharge readiness. The trial will be considered positive if significant between-group differences are found for one or both alternative primary endpoints. Secondary outcomes include hospital-acquired infections and nutritional, clinical, and functional outcomes.

Ethics and dissemination: The NUTRIREA-3 study has been approved by the appropriate

ethics committee. Patients are included after informed consent. Results will be submitted for publication in peer-reviewed journals.

Trial Registration: ClinicalTrials: NCT01802099. Date of registration: February 27, 2013.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- NUTRIREA-3 is a pragmatic randomised controlled trial whose large number of patients recruited in numerous intensive care units (ICUs) enhance the reliability and general applicability of the results.
- We included a well-defined population of very severely critically ill patients requiring at least vasoactive drugs and mechanical ventilation, at high risk for death or protracted recovery, and therefore most likely to benefit from improved early nutritional support.
- We used two strong patient-centred primary outcomes, i.e., 90-day mortality and ICU dependency, and we evaluated important secondary outcomes, including long-term function, in keeping with recommendations about studies on of nutritional support in critically ill patients.
- NUTRIREA-3 is the first study to evaluate the potential benefits of calorie and protein restriction versus standard calorie and protein targets during early nutritional support, using very different amounts of calories and proteins.
- A limitation is that blinding of nutritional strategies is not feasible.

INTRODUCTION

Severe critical illness is associated during the acute phase with anorexia, metabolic disorders, endocrine dysfunction, and a major catabolic response responsible for severe skeletal and diaphragmatic muscle wasting(1). Among critically ill patients requiring mechanical ventilation (MV) and catecholamines for shock, nearly 40% to 50% die, and functional recovery is often delayed in survivors (2). Nutritional support is crucial, as malnutrition is associated with poor outcomes. Prescribing nutritional support in the critically ill is the result of a complex decision-making process designed to optimise three key parameters: the timing, the dose, and the route of artificial feeding. International guidelines encourage early nutritional support (≤48 h after admission), via the enteral route if not contraindicated, with 20-25 kcal/kg/d, and 1.2-2 g/kg/d protein at the acute phase(3, 4). These targets are rarely achieved in patients with severe critical illnesses, who frequently experience gastroparesis responsible for intolerance to enteral nutrition(5). Observational studies have indicated that calorie and protein deficiencies were associated with nosocomial infections, ICU-acquired weakness, delayed weaning off MV, longer stays, and higher mortality(6-12).

However, recent data challenge the wisdom of providing standard amounts of calories and protein during the acute phase of critical illness(13, 14). Studies showed no outcome benefits with higher intakes(15, 16). Instead, adding parenteral nutrition to increase intakes was associated with longer ICU stays and more infectious complications(17, 18). Higher protein intakes during the acute phase may be associated with greater muscle wasting and ICU-acquired weakness(1, 19). Restricting calorie and protein intakes seemed beneficial, suggesting a role for metabolic pathways such as autophagy, a potential key mechanism in muscle protection during critical illness(20, 21). The recent EDEN and PERMIT trials showed no differences in patient outcomes between hypocaloric and standard feeding(22-24).

However, in both studies, calorie intakes were below-target in the standard groups. Moreover, patients in both PERMIT trial groups received similar protein intakes, as protein solutions were added in the hypocaloric group. Thus, the optimal calorie and protein supply at the acute phase of severe critical illness remains unknown(14, 25-28).

We designed the NUTRIREA-3 trial to compare standard calorie and protein feeding complying with guidelines to low-calorie low-protein feeding in a well-defined group of severely ill ICU patients requiring at least MV and vasoactive drugs. These patients typically have poor outcomes with long ICU stays, high frequencies of ICU-acquired weakness and infections, and high mortality(1, 29). Reported impacts of nutritional support were greatest in the most severely ill ICU patients (3, 4, 30, 31). Our hypothesis is that, in those severe critically ill patients, low-calorie low-protein feeding at the early phase of critical illness improves muscle preservation, thereby improving outcomes, and most notably diminishing mortality and dependency on ICU care.

METHODS AND ANALYSIS

Trial design

NUTRIREA-3 is a randomised, controlled, multicentre, open-label trial comparing two parallel groups of patients.

Participants, interventions, outcomes

Participating units

Of the 61 French ICUs participating in the study, 34 are in university hospitals. All participating ICU staff members have attended training in the study procedures and protocols for providing nutritional support.

Study population and recruitment modalities

Inclusion criteria are age older than 18 years; invasive MV for an expected duration of at least 48 hours after inclusion, started in the ICU within the past 24 h, or started before ICU admission with ICU admission within the 24 h after intubation; treatment with a vasoactive agent for shock (adrenaline, dobutamine, or noradrenaline); nutritional support expected to be started within 24 h after intubation or within 24 h after ICU admission when MV was started before ICU admission; and patient and/or next-of-kin informed about the study and having consented to participation in the study. If the patient is unable to receive information and no next-of-kin can be contacted during screening for the study, trial inclusion will be completed as an emergency procedure by the ICU physician, in compliance with French law.

Exclusion criteria are specific nutritional needs, such as pre-existing long-term home enteral or parenteral nutrition, for chronic bowel disease; dying patient, not-to-be-resuscitated

order, or other treatment limitation decision at ICU admission; pregnancy, recent delivery, or lactation; adult under guardianship; and department of corrections inmate.

Interventions

After study inclusion, patients will be allocated at random to one of two nutritional support strategies (Figure 1). The designated feeding strategy will be initiated as soon as possible after randomisation (in all patients, within 24 hours after intubation or ICU admission in patients with MV started before admission) and continued until extubation and withdrawal of vasoactive support, or death, or day 7, whichever occurs first.

In the low-calorie low-protein (Low) group, the calorie target will be 6 kcal/kg/day and the protein target 0.2-0.4 g/kg/d during the acute phase, i.e. from D0 to D7. On D8, the calorie target will be 30 kcal/kg/d and the protein target 1.2-2.0 g/kg/d.

In the standard-calorie/standard-protein (Standard) group, the first-line calorie target calculated based on body weight is 25 kcal/kg/day and the protein target 1.0-1.3 g/kg/d during the acute phase, i.e. from D0 to D7. On D8, the calorie target will be 30 kcal/kg/d and the protein target 1.2-2.0 g/kg/d.

Nutritional support protocol

The nutritional support protocol, including measures designed to evaluate tolerance, is standardised as indicated below.

General principles of nutritional support in both study arms

Nutritional support is started as soon as possible after randomisation and no later than 24 hours after intubation or after ICU admission if intubation preceded ICU admission. Daily nutritional intakes needed to meet the allocated calorie target will be calculated based on body weight (BW). In obese patients (BMI>30 Kg/m²), the body weight yielding a BMI of

30 will be used. In patients with BMI<18.5, the following corrected body weight will be used: (ideal body weight + actual body weight)/2. The calorie/protein ratios of nutritional solutions currently available in French hospitals will ensure that the protein intake complies with the allocated nutritional regimen.

Randomised controlled trials showed that feeding route during the acute phase had no impact on major clinical outcomes of critically ill patients (32, 33). Thus, during the acute phase, bedside physicians will be free, each day, to choose the best feeding route, according to clinical considerations, to ensure that the calorie target is achieved. After the acute phase, enteral feeding remains the preferred route in patients without contraindications (4). Thus, on day 8, in the absence of contraindications to enteral nutrition, parenteral nutrition will be stopped in those patients fed via the parenteral route and enteral nutrition started. From day 8 onwards, supplemental parenteral nutrition may be added in the event of intolerance to enteral nutrition precluding the achievement of the predefined calorie targets.

Nutritional support is prescribed as a flow rate (mL/hour) and started at the prescribed flow rate (as opposed to increased gradually). The feed is delivered continuously over the 24-hour cycle, with no interruptions. Actual feed delivery is monitored regularly based on the volumes delivered relative to the predefined daily calorie targets. In addition, special attention is directed to avoiding delays. Any interruption in feed delivery is reported to the ICU physician in charge. Except in special situations, nutritional support is not interrupted while transporting the patient. However, when EN or PN must be interrupted (e.g., for a specific gastrointestinal or radiological investigation), the flow rate is not increased to compensate for the interruption. Finally, all patients are in the semi-recumbent supine position (torso inclined 30° to 45° relative to the horizontal plane).

After extubation, regardless of time since randomisation, decisions about the continued need for, and optimal route of, nutritional support are made by the physician in

charge of the patient. Patients who are reintubated within 7 days after trial inclusion are managed until the end of the acute phase according to the arm they were randomised to during the first intubation period.

Enteral nutrition (EN)

Iso-osmotic iso-caloric normal-protein polymeric preparations are used during the first week, after which the choice of feed is at the discretion of the physician. The feed is delivered via a 14-French silicone gastric tube. Tube position in the middle of the stomach is checked on a radiograph obtained at ICU admission or immediately after tube placement, as well as when the tube is changed or repositioned.

A predefined protocol is used to manage upper gastrointestinal intolerance to enteral nutrition. This protocol was used in the NUTRIREA-2 trial(33). To minimise the risk of gastric intolerance and consequently of vomiting, the volume of supplemental water given enterally will be as small as possible during the first study week. Residual gastric volume is not monitored(34). The tolerance of enteral nutrition is defined based only on episodes of significant vomiting or regurgitation (passage of enteral nutrition formula into the mouth, outside the mouth, or into the endotracheal tube in the absence of care procedures or mobilisation). Minimal regurgitation or vomiting triggered by tracheal aspiration or oral cavity care is not taken to indicate intolerance. EN intolerance leads to the following two measures. First, treatment with a prokinetic agent is initiated after confirmation that there are no contraindications. The study ICUs use the prokinetic agent of their choice, according to their standard practice. The prokinetic agent is discontinued when EN at the highest prescribed flow rate has been well tolerated for 48 hours. Second, if gastric intolerance persists despite prokinetic therapy, the flow rate is decreased by 25 mL/h every 6 hours until the signs of intolerance resolve. Therefore, EN is stopped (and the gastric tube placed under suction) only in patients with intolerance despite a flow rate ≤25 mL/h. All interruptions in

EN delivery must be reported to the physician in charge of the patient. This precaution is particularly important in patients receiving insulin. EN is resumed at the prescribed flow rate (appropriate to the patient's needs) after 6 hours have elapsed with no further signs of intolerance. Patients at high risk for gastric intolerance, such as those turned in the prone position for acute respiratory distress syndrome (ARDS), receive prophylactic prokinetic treatment starting at the first turn in the prone position (35, 36).

Parenteral nutrition (PN)

Ternary admixtures packaged in bags and containing the three groups of macronutrients are used according to standard practice in each participating centre. Supplemental electrolytes are supplied in a solution separate from the parenteral feed, according to the needs of each patient. PN is delivered continuously via a central venous catheter (CVC). Special attention is directed to preventing infections by complying with the standard protocols for CVC insertion and maintenance used in each of the participating centres. Proper CVC position is checked on a radiograph.

Additional intakes

Additional water, electrolytes, vitamins, and trace elements are given intravenously according to the needs of each individual patient as assessed by the physician in charge and using the standard preparations and protocols available in each study ICU.

Monitoring of intestinal transit

The volume and appearance of the stools are monitored daily. The occurrence of constipation (no stool for more than 6 days) or diarrhoea (more than 300 mL of liquid stool or 4 loose stools per day) will be reported and will lead to the appropriate diagnostic and therapeutic management (15, 37, 38).

Study outcomes

Primary endpoints

Two primary end-points will be analysed: all-cause mortality by day 90, and time to readiness for ICU discharge. Information on vital status will be collected on the 90th day after patient inclusion. For discharged patients, information on this primary endpoint will be collected by a telephone call to the patient's home. The time of ICU discharge to a regular ward may be affected by the availability of beds on regular wards, which may induce bias. The study will therefore consider the time to readiness for ICU discharge. A patient will be considered ready for ICU discharge as soon as all predefined clinical conditions for ICU discharge are fulfilled (Table 1), regardless of ward-bed availability. Readiness for ICU discharge will be checked daily in all patients weaned from invasive MV and vasoactive drugs. A similar strategy regarding this endpoint has been used previously in studies on nutrition in the ICU(17, 18).

The trial will be considered positive if significant between-group differences are found for one or both alternative primary endpoints.

Secondary outcomes

- Daily mean values during the first week, throughout the time on IMV and from weaning off MV to readiness for ICU discharge of the following:
    - number of calories (in Kcal) delivered enterally and/or parenterally
    - ratio (as a %) of prescribed over delivered calories
- Proportion of patients who achieved their calorie target from day 0 to day 7
- Daily mean values from day 0 to day 7 and during MV of the following:
    - protein supply (g) given enterally and/or parenterally
    - volume of fluids (in mL) received (daily mean from day 0 to day 7 and during MV)

- From day 0 to day 7:
    - SOFA score changes
    - Changes in daily maximum blood glucose levels
    - Proportion of patients with hypoglycaemia
    - Total insulin dose received daily
- Days on insulin treatment from day 0 to readiness for ICU discharge
- Proportion of patients with at least one ICU-acquired infection; an independent blinded committee will adjudicate all ICU-acquired infections
- Ventilator-associated pneumonia (VAP): the diagnosis of VAP is suspected based on the development or persistence of lung infiltrates on the chest radiograph with at least two of the following criteria: body temperature ≥38.5 or ≤35.5ºC, leucocytosis (>10 000/mm^3) or leucopenia (<4000/mm^3), and purulent tracheobronchial aspirate, from H48 after intubation to H48 after extubation. The diagnosis will have to be confirmed by a positive *semi-quantitative* bacteriological test: bronchoalveolar lavage (>10^{-4} cfu/mL), brush (>10^{-3} cfu/mL), tracheal aspirate (>10^{-6} cfu/mL), or protected distal specimen (>10^{-3} cfu/mL)(39, 40). VAP episodes are recorded from 48 hours after intubation until day 2 after extubation.
    - Proportion of patients with at least one VAP episode.
    - Total number of VAP episodes in each group.
- Other ICU-acquired infections:
    - Proportion of patients with at least one episode of bacteraemia
    - Proportion of patients with at least one central venous catheter (CVC)-related infection
    - Proportion of patients with at least one episode of urinary tract infection
    - Proportion of patients with at least one soft tissue infection

- Proportion of patients with other nosocomial infections

– Descriptive bacteriological data: organisms recovered in the overall population with nosocomial infections, and antimicrobial resistance profiles

– Proportion of patients with at least one episode of liver dysfunction, defined as serum bilirubin >50 µmoL/L and/or elevation >3N of one or more liver enzymes (γ-glutamyltransferase, alkaline phosphatase, and ASAT-ALAT) at the end of MV, on day 7 (in patients on MV for more than 7 days), and at ICU discharge

– Proportion of patients with at least one episode of vomiting or regurgitation while on MV

– Proportion of patients with at least one episode of diarrhoea defined as liquid stools in a volume greater than 300 mL/24 hours in patients with a faecal collector or as more than four loose stools/24 hours (15)

– Proportion of patients with at least one episode of constipation (no stool for more than 6 days)

– Proportion of patients with at least one documented episode of bowel ischaemia defined as absent blood flow in one of the main arteries supplying the bowel (superior mesenteric artery, inferior mesenteric artery, or celiac artery) with evidence of bowel wall compromise on an imaging study (computed tomography angiography, angiography, or magnetic resonance angiography) or presence of criteria for colonic ischaemia according to the Favier classification system (stage I, petechiae; stage II, petechiae and superficial ulcers; and stage III, necrotic ulcers and polypoid lesions) by endoscopy (rectosigmoidoscopy or colonoscopy) (41)

– Mean changes in serum albumin, pre-albumin, and C-reactive protein (CRP) measured at baseline, at the end of MV, on day 7 (in patients on MV for more than 7 days), and at ICU discharge

- Changes in mean body weight determined at baseline, on day 7, and at ICU discharge
- Days on MV
- Hospital stay length (days in hospital)
- ICU mortality, 28-day mortality, and hospital mortality
- Proportions of patients mobilised from day 0 to day 7 and total number of active mobilisations, using predetermined criteria (42) (Table 2).
- Total Medical Research Council (MRC) score and proportion of patients with ICU-acquired paresis at the time of readiness for ICU discharge (43, 44); the MRC score can range from 0 (quadriplegia) to 60 (normal muscle strength); scores <48 will define ICU-acquired paresis.
- Proportion of patients with at least one criterion for persistent altered health status at the time of readiness for ICU discharge, among the following: tracheostomy, non-invasive ventilation, ongoing renal-replacement therapy, parenteral nutrition, enteral nutrition via a nasogastric tube; Glasgow Coma Scale score <15, and treatment-limitation decision(45)
- SF-36 score completed during a phone call to the patient by an independent blinded research nurse or psychologist 3 months and 1 year after study inclusion(46, 47)

Organisation of the trial

Figure 2 is the study diagram.

Recruitment modalities

All patients treated with invasive MV and vasopressor support for shock within 24 h after intubation, or within 24 h after ICU admission if already intubated will be screened for eligibility by the ICU physicians and clinical research nurses, around the clock and 7 days a week. Patients will be included after checking inclusion and non-inclusion criteria. A log of patients considered for study participation will be kept and will include any reasons for non-

inclusion and refusals of consent.

Randomisation

Randomisation is centralised and performed using a secure, computer-generated, interactive, web-response system available at each study centre. Randomisation is stratified on study centre with a 1:1 ratio.

Blinding

The trial will be open, since the nature of the intervention precludes blinding of healthcare staff to group assignment. However, the absence of blinding cannot have an impact on either of the primary endpoints. Day-90 mortality is an objective endpoint with no evidence that absence of blinding may affect the data (48). Given more subjective nature, the primary endpoint of readiness to discharge alive from the ICU will be checked daily by the bedside physician according to predefined criteria, in order to strongly limit the risk of detection bias. Moreover, the secondary endpoints relevant to nosocomial infections will be validated by an adjudication committee.

Sample size

Assuming a 43% day-90 mortality rate in the Standard group and a 5% absolute decrease in day-90 mortality (to 38%) in the Low group, with the alpha risk set at 4.9% (as two interim analyses are planned) and the beta risk at 20%, 1522 patients are needed in each group, i.e., a theoretical total of 3044 patients.

This sample size will provide 94% power to detect a 1.5 day difference in time to ICU discharge alive between the two groups (mean, 14.5 days in the control group versus 13.0 days in the experimental group).

No corrections will be made for multiple comparisons. Indeed, adjusting for multiplicity is controversial and there is no consensus about the appropriate analysis (49). Moreover, adjusting for multiplicity may lead to increased sample size, and subsequent decreased feasibility of the study. Last, most recent studies with a similar design did not use corrections for multiple comparisons (17, 18).

The ICU stay lengths in survivors and mortality rates used for the sample size estimation are those obtained in the NUTRIREA-1 and -2 trials, which used similar inclusion criteria.

Interim analysis

Given the need for a large sample size, two interim analyses will be scheduled, one after enrolment of 1000 patients and the other after enrolment of 2000 patients. Members of the independent Data Safety Monitoring Board (DSMB) will not be otherwise involved in the trial. This DSMB consists of one methodologist and two intensivists. For both interim analyses, the DSMB will have access to unblinded results on day-90 mortality, time to discharge alive from the ICU, variations in SOFA scores from day 0 to day 7, amounts of calories and proteins received daily from day 0 to day 7, and nosocomial infections. The results of the interim analyses will not be disclosed unless they lead the DSMB to request premature trial discontinuation.

Statistical analysis

Each patient will remain in the group assigned by randomisation, regardless of subsequent events. A statistical analysis report will be written to describe all the findings, according to CONSORT Statement recommendations, while taking into account the specific features of the trial, most notably the nonpharmacological nature of the intervention. The

baseline features of the groups established by randomisation will be compared using descriptive statistics; no statistical tests will be performed.

Primary endpoint

Day-90 mortality will be reported as the point estimate with the 95% confidence interval in each group. The difference in proportions with the 95% confidence interval will also be estimated. Day-90 mortality will be compared between the two groups using the chi-square test.

Time to readiness for ICU discharge will be analysed using the competing risk approach, with death in the ICU as a competing risk.

Secondary endpoints

The incidence of patients with at least one nosocomial infection will be estimated and compared between the groups using a competing-risk model, with death and ICU discharge alive as competing events. The incidence of patients with at least one VAP episode will be estimated using a competing-risk model, with death and survival for 48 hours without pneumonia as competing events. For CVC-related infections, the competing risks will be death and CVC removal and for urinary tract infections they will be death and urinary catheter removal. Bacteraemia, soft tissue infections, and other infections will be analysed using the same method as for the pooled nosocomial infections. For descriptive bacteriological data (organisms recovered with their resistance profiles for each nosocomial infection), only descriptive analyses will be performed. For the proportions of patients with at least one episode of vomiting or regurgitation, diarrhoea, constipation, documented acute colonic pseudo-obstruction, documented bowel ischaemia, mechanical complication of CVC insertion, hypoglycaemia from day 0 to day 7, and liver dysfunction, the method will be the same as for nosocomial infections. Changes over time in delivered calories and proteins will be represented graphically by boxplots created each day on the same graph; changes over

time will be compared between the two groups using a mixed linear model, after data transformation if necessary. The same analysis will be performed for volume of feeds delivered each day. The proportion of patients who achieved 100% of their daily calorie target will be determined at each follow-up time point (in days) and compared between the two groups using a logistic random-effects model. Day-28 mortality will be analysed in the same way as day-90 mortality. For ICU and hospital mortality rates, competing-risk models will be used, with ICU discharge and hospital discharge as events competing with death during the stay. Changes over time in SOFA, total insulin, blood glucose, nutritional markers and body weight will be analysed using the method described above for the number of calories delivered. For the proportion of mobilised patients, patients with at least one criterion of persistent altered health status at the time of readiness for ICU discharge, and patients with ICU-acquired paresis, the method will be the same as for nosocomial infections. The Medical Research Council (MRC) sum score at the time of readiness for ICU discharge will be compared between the two groups using the non-parametric Wilcoxon test. The total quality-of-life SF-36 score will be compared between the two groups using a mixed linear model.

Data collection and follow-up

The following data will be recorded until the patient is extubated: demographic and clinical data, nutrition monitoring data, treatments given, laboratory tests, invasive devices, functional evaluation, and data relevant to nosocomial infections. The patient will be followed up for 1 year after study inclusion; at hospital discharge, on D28 and D90, and at 1 year, the vital status will be recorded. The SF-36 score will be recorded on D90 and 1 year after study inclusion. Below is a flow-chart of patient follow-up. Table 3 is the study flow-chart.

Data entry and monitoring

An Internet-based data collection tool will be used for this study to store the data of all the participants. This electronic case-report form (eCRF) is a secure, interactive, web-response system available at each study centre. It is provided and managed by the biometrical unit of the Tours University Hospital (CIC INSERM 1415, Tours, France). Access to the eCRF will require only an Internet connection and a browser.

Monitoring of the data collected and of the screening forms in each participating centre will be carried out by the Research Division Promotion Department of the Nantes University hospital. Research assistants will regularly perform on-site checks of adherence to the protocol and accuracy of recorded data.

Trial Status

Inclusions started in July 2018. The scheduled interim analysis were performed on the first 1000 (by October 2009) and 2000 (by March 2020) included patients, respectively. Both analyses led the DSMB to recommend continuation of the study. Recruitment in the trial was interrupted from March to June 2020 because of the COVID-19 crisis, when all ICUs were full with COVID-19 patients and all research teams were working only on COVID-19 trials. By August 19, 2020, 2764 patients had been included. Recruitment is expected to be complete by December 2020.

Ethics and dissemination

Ethical review board

The NUTRIREA-3 trial was approved by the competent French authorities on 20 April 2016 (*Comité de Protection des Personnes Sud-Méditerranée 2*, registration 2018-

A00424-51) and registered on ClinicalTrials (NCT01802099) on June 2018.

Consent

The patients are included after providing their signed informed consent to trial participation. For patients unable to consent because of impaired consciousness or severe critical illness, information about the study is provided to their next of kin. Patients who are unable to consent and for whom no relative is available to consent to study participation within a timeframe compatible with the study design are included after completion of an emergency consent form by the bedside physician. The relatives are informed of the inclusion as soon as possible. Patients are asked to confirm their willingness to participate in the trial once they regain decision-making capacity. Data of patients without relatives who die without previously recovering consciousness will be included in the statistical analysis.

Confidentiality and source data archiving

The medical data about each patient will be communicated only to the institution (i.e., the sponsor) with which the chief investigator is affiliated or to a person appointed by the chief investigator and the sponsor under conditions that ensure the confidentiality of the patient data. During or at completion of the study, the data collected from the study participants and communicated by the individuals involved in the study will be rendered anonymous. Study investigators will archive all study data for at least 15 years after the end of the study.

Dissemination policy

The publication policy will comply with international recommendations (N Engl J Med, 1997; 336:309-315) and the CONSORT statement (http://www.consort-statement.org). Findings will be published in peer-reviewed journals and presented during national and international scientific meetings. Communications and scientific reports relevant to this study

will be under the responsibility of the coordinator of the study (JR), who will obtain the approval of the other investigators.

Patient and public involvement

Neither patients nor the public are involved in the study.

AUTHORS' CONTRIBUTIONS:

ALG and JR prepared the first draft of the manuscript.

JR, JBL, DM, ALG, and BG wrote the manuscript.

JR, JBL, ALG, DM, and BG participated in designing the NUTRIREA-3 study.

ALG and BG wrote the statistical analysis plan and performed the sample size estimation.

JR and DM obtaining funding for the study.

JR, JBL, DA, LA, YH, PA, JB, MAM, NVB, LB, HNB, DC, LC, AC, CC, MD, VD, MD, AD, JD, SV, NAB, LMD, JO, OG, SG, BG, SJ, FL, CL, PL, BM, JM, OM, FM, EM, JPM, SN, WP, GPi, GPl, JPQ, AR, LG, JR, JPR, FS, DS, MS, BS, FR, FT, NT, DT, GT, NTR, JFT, FT, PT, TV, IV, and CV contribute to acquire the study data.

All authors revised the manuscript for important intellectual content and read and approved the final version of the manuscript.

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COMPETING INTEREST STATEMENT

JR had travel and accommodation expenses to attend scientific meetings covered by Baxter, and Fresenius.

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References

1. Puthucheary ZA, Rawal J, McPhail M, et al. Acute skeletal muscle wasting in critical illness. JAMA 2013;310(15):1591-1600.

2. Hermans G, Van den Berghe G. Clinical review: intensive care unit acquired weakness. Crit Care 2015;19:274.

3. Singer P, Blaser AR, Berger MM, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr 2018.

4. Taylor BE, McClave SA, Martindale RG, et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). Crit Care Med 2016;44(2):390-438.

5. Blaser AR, Starkopf J, Kirsimagi U, et al. Definition, prevalence, and outcome of feeding intolerance in intensive care: a systematic review and meta-analysis. Acta Anaesthesiol Scand 2014;58(8):914-922.

6. Alberda C, Gramlich L, Jones N, et al. The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study. Intensive care medicine 2009;35(10):1728-1737.

7. Elke G, Wang M, Weiler N, et al. Close to recommended caloric and protein intake by enteral nutrition is associated with better clinical outcome of critically ill septic patients: secondary analysis of a large international nutrition database. Crit Care 2014;18(1):R29.

8. Compher C, Chittams J, Sammarco T, et al. Greater Protein and Energy Intake May Be Associated With Improved Mortality in Higher Risk Critically Ill Patients: A Multicenter, Multinational Observational Study. Crit Care Med 2017;45(2):156-163.

9. Allingstrup MJ, Esmailzadeh N, Wilkens Knudsen A, et al. Provision of protein and energy in relation to measured requirements in intensive care patients. Clin Nutr 2012;31(4):462-468.

10. Faisy C, Candela Llerena M, Savalle M, et al. Early ICU energy deficit is a risk factor for Staphylococcus aureus ventilator-associated pneumonia. Chest 2011;140(5):1254-1260.

11. Villet S, Chiolero RL, Bollmann MD, et al. Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients. Clin Nutr 2005;24(4):502-509.

12. Wei X, Day AG, Ouellette-Kuntz H, et al. The Association Between Nutritional Adequacy and Long-Term Outcomes in Critically Ill Patients Requiring Prolonged Mechanical Ventilation: A Multicenter Cohort Study. Crit Care Med 2015;43(8):1569-1579.

13. Casaer MP, Van den Berghe G. Nutrition in the acute phase of critical illness. N Engl J Med 2014;370(25):2450-2451.

14. Preiser JC, van Zanten AR, Berger MM, et al. Metabolic and nutritional support of critically ill patients: consensus and controversies. Crit Care 2015;19(1):35.

15. Doig GS, Simpson F, Finfer S, et al. Effect of evidence-based feeding guidelines on mortality of critically ill adults: a cluster randomized controlled trial. JAMA 2008;300(23):2731-2741.

16. Heyland DK, Murch L, Cahill N, et al. Enhanced Protein-Energy Provision via the Enteral Route Feeding Protocol in Critically Ill Patients: Results of a Cluster Randomized Trial. Crit Care Med 2013.

17. Fivez T, Kerklaan D, Mesotten D, et al. Early versus Late Parenteral Nutrition in Critically Ill Children. N Engl J Med 2016;374(12):1111-1122.

18. Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med 2011;365(6):506-517.

19. Casaer MP, Wilmer A, Hermans G, et al. Role of disease and macronutrient dose in the randomized controlled EPaNIC trial: a post hoc analysis. Am J Respir Crit Care Med 2013;187(3):247-255.

20. Vanhorebeek I, Gunst J, Derde S, et al. Insufficient activation of autophagy allows cellular damage to accumulate in critically ill patients. J Clin Endocrinol Metab 2011;96(4):E633-645.

21. Choi AM, Ryter SW, Levine B. Autophagy in human health and disease. N Engl J Med 2013;368(7):651-662.

22. Arabi YM, Aldawood AS, Haddad SH, et al. Permissive Underfeeding or Standard Enteral Feeding in Critically Ill Adults. N Engl J Med 2015;372(25):2398-2408.

23. Needham DM, Dinglas VD, Bienvenu OJ, et al. One year outcomes in patients with acute lung injury randomised to initial trophic or full enteral feeding: prospective follow-up of EDEN randomised trial. BMJ 2013;346:f1532.

24. Rice TW, Wheeler AP, Thompson BT, et al. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. JAMA 2012;307(8):795-803.

25. Marik PE, Hooper MH. Normocaloric versus hypocaloric feeding on the outcomes of ICU patients: a systematic review and meta-analysis. Intensive Care Med 2016;42(3):316-323.

26. Marik PE, Rice TW. Feeding the Critically Ill: More Questions Than Answers! Am J Respir Crit Care Med 2017;195(5):555-556.

27. Preiser JC. High protein intake during the early phase of critical illness: yes or no? Crit Care 2018;22(1):261.

28. Singer P, Cohen J. Nutrition in the ICU: proof of the pudding is in the tasting. Intensive Care Med 2015;41(1):154-156.

29. Iwashyna TJ, Ely EW, Smith DM, et al. Long-term cognitive impairment and functional disability among survivors of severe sepsis. JAMA 2010;304(16):1787-1794.

30. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med 2017;43(3):304-377.

31. Artinian V, Krayem H, DiGiovine B. Effects of early enteral feeding on the outcome of critically ill mechanically ventilated medical patients. Chest 2006;129(4):960-967.

32. Harvey SE, Parrott F, Harrison DA, et al. Trial of the route of early nutritional support in critically ill adults. N Engl J Med 2014;371(18):1673-1684.

33. Reignier J, Boisrame-Helms J, Brisard L, et al. Enteral versus parenteral early nutrition in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2). Lancet 2018;391(10116):133-143.

34. Reignier J, Mercier E, Le Gouge A, et al. Effect of not monitoring residual gastric volume on risk of ventilator-associated pneumonia in adults receiving mechanical ventilation and early enteral feeding: a randomized controlled trial. JAMA 2013;309(3):249-256.

35. Poulard F, Dimet J, Martin-Lefevre L, et al. Impact of Not Measuring Residual Gastric Volume in Mechanically Ventilated Patients Receiving Early Enteral Feeding: A Prospective Before-After Study. JPEN J Parenter Enteral Nutr 2009.

36. Reignier J, Dimet J, Martin-Lefevre L, et al. Before-after study of a standardized ICU protocol for early enteral feeding in patients turned in the prone position. Clin Nutr 2010;29(2):210-216.

37. Gacouin A, Camus C, Gros A, et al. Constipation in long-term ventilated patients: associated factors and impact on intensive care unit outcomes. Critical care medicine 2010;38(10):1933-1938.

38. van der Spoel JI, Schultz MJ, van der Voort PH, et al. Influence of severity of illness, medication and selective decontamination on defecation. Intensive Care Med 2006;32(6):875-880.

39. Chastre J, Fagon JY. Ventilator-associated pneumonia. Am J Respir Crit Care Med 2002;165(7):867-903.

40. Hubmayr RD, Burchardi H, Elliot M, et al. Statement of the 4th International Consensus Conference in Critical Care on ICU-Acquired Pneumonia--Chicago, Illinois, May 2002. Intensive Care Med 2002;28(11):1521-1536.

41. Favier C, Bonneau HP, Tran Minh V, et al. Endoscopic diagnosis of regressive ischemic colitis. Endoscopic, histologic and arteriographic correlations. Nouv Presse Med 1976;5(2):77-79.

42. Wright SE, Thomas K, Watson G, et al. Intensive versus standard physical rehabilitation therapy in the critically ill (EPICC): a multicentre, parallel-group, randomised controlled trial. Thorax 2017.

43. Bittner EA, Martyn JA, George E, et al. Measurement of muscle strength in the intensive care unit. Crit Care Med 2009;37(10 Suppl):S321-330.

44. Sharshar T, Bastuji-Garin S, Stevens RD, et al. Presence and severity of intensive care unit-acquired paresis at time of awakening are associated with increased intensive care unit and hospital mortality. Crit Care Med 2009;37(12):3047-3053.

45. Santamaria JD, Duke GJ, Pilcher DV, et al. The timing of discharge from the intensive care unit and subsequent mortality. A prospective, multicenter study. Am J Respir Crit Care Med 2015;191(9):1033-1039.

46. Ware J, Jr., Kosinski M, Gande B. SF-36® Health Survey Manual & Interpretation Guide. : Lincoln, RI: Quality Metric Incorporated; 2005.

47. Oeyen SG, Vandijck DM, Benoit DD, et al. Quality of life after intensive care: a systematic review of the literature. Crit Care Med 2010;38(12):2386-2400.

48. Anthon CT, Granholm A, Perner A, et al. No firm evidence that lack of blinding affects estimates of mortality in randomized clinical trials of intensive care interventions: a systematic review and meta-analysis. Journal of clinical epidemiology 2018;100:71-81.

49. Li G, Taljaard M, Van den Heuvel ER, et al. An introduction to multiplicity issues in clinical trials: the what, why, when and how. Int J Epidemiol 2017;46(2):746-755.

FIGURE LEGENDS

Figure 1: Study interventions

Figure 2: Study diagram

Table 1: Criteria for readiness for ICU discharge

A patient will be considered ready for ICU discharge when he/she meets all of the following criteria:
▪ No longer in need of, or at risk for needing, invasive mechanical ventilation
▪ No longer in need of, or at risk for needing, vasoactive support
▪ No agitation or altered consciousness requiring close monitoring and management
▪ No severe acute metabolic or haematologic disorder requiring close monitoring and management

Table 2: Mobilisation scale

Remains in bed	▪ no mobilisation, ▪ turned in bed, ▪ sitting position in bed with the head of the bed elevated
Mobilised in the bed	▪ passive mobilisation of the legs in bed ▪ active mobilisation of the legs in bed ▪ cycling motions in bed
Mobilised out of bed	▪ sits on the edge of the bed with the feet on the floor ▪ sits in a chair ▪ stands ▪ marches in place ▪ walks

Table 3: Study flow chart of patient follow-up

	Inclu-sion	D0*	D1 to Dn	End of study proto-col	Ready for ICU discharge	D28	D90	One year End of follow-up **
Eligibility: check inclusion and exclusion criteria	X							
Patient information and consent	X							
Randomisation		X						
Demographic characteristics		X						
Vital signs		X						
Weight		X	X					
Ventilation		X	X					
Laboratory tests		X	X*					
SOFA		X	X					
Nutritional evaluation		X	X					
Treatments used		X	X					
Daily nutritional intake		X	X					
Fluid intake		X	X					
Nosocomial infections			X					
Final extubation				X				
Final discontinuation of nutritional support				X				
Health status					X			
MRC score					X			
Survived / died					X	X	X	X
SF-36							X	X

* from time of inclusion to 11:59 pm

** Information will be collected by phone contact with patients or relatives.

Figure 1: Study interventions

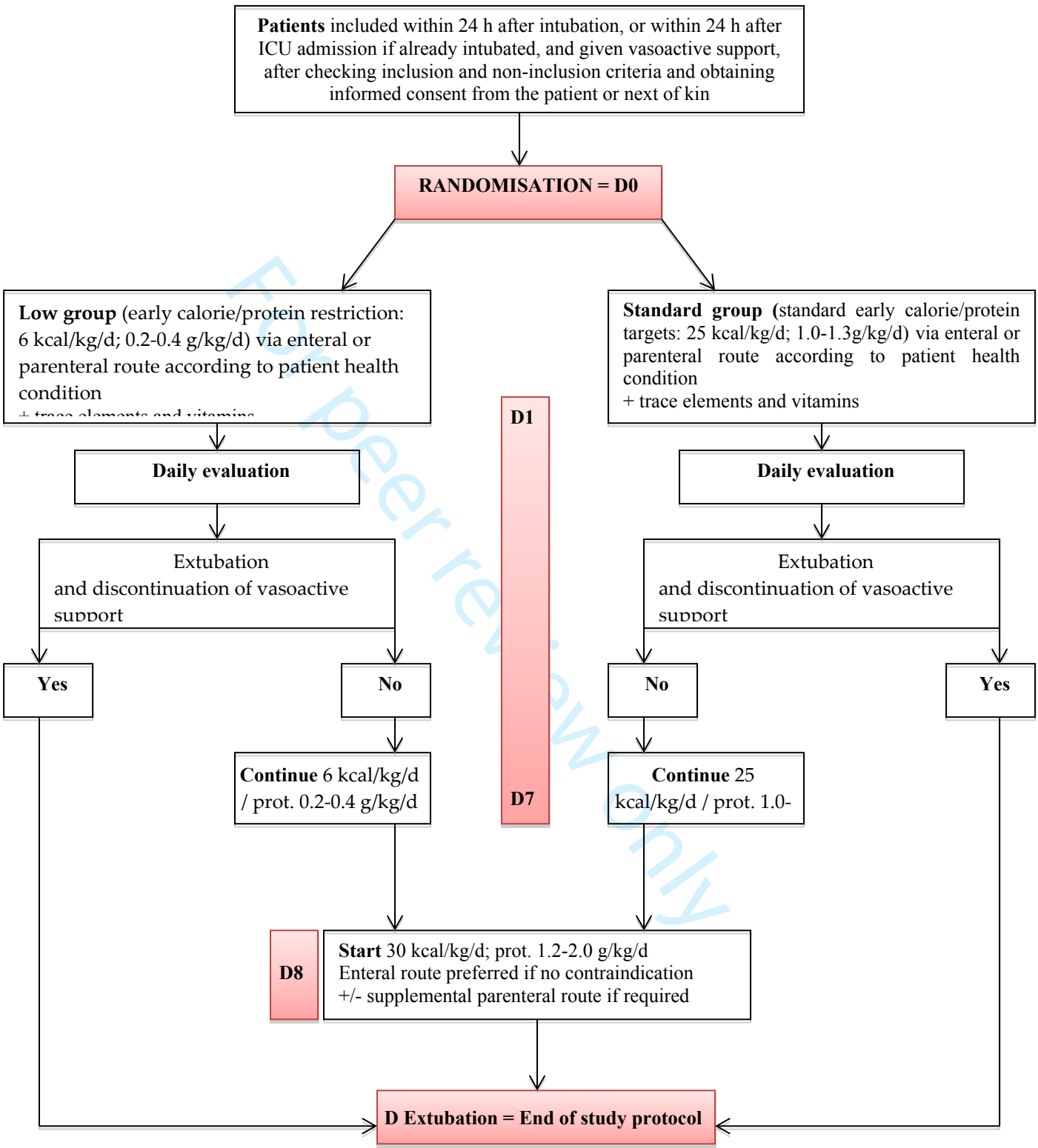
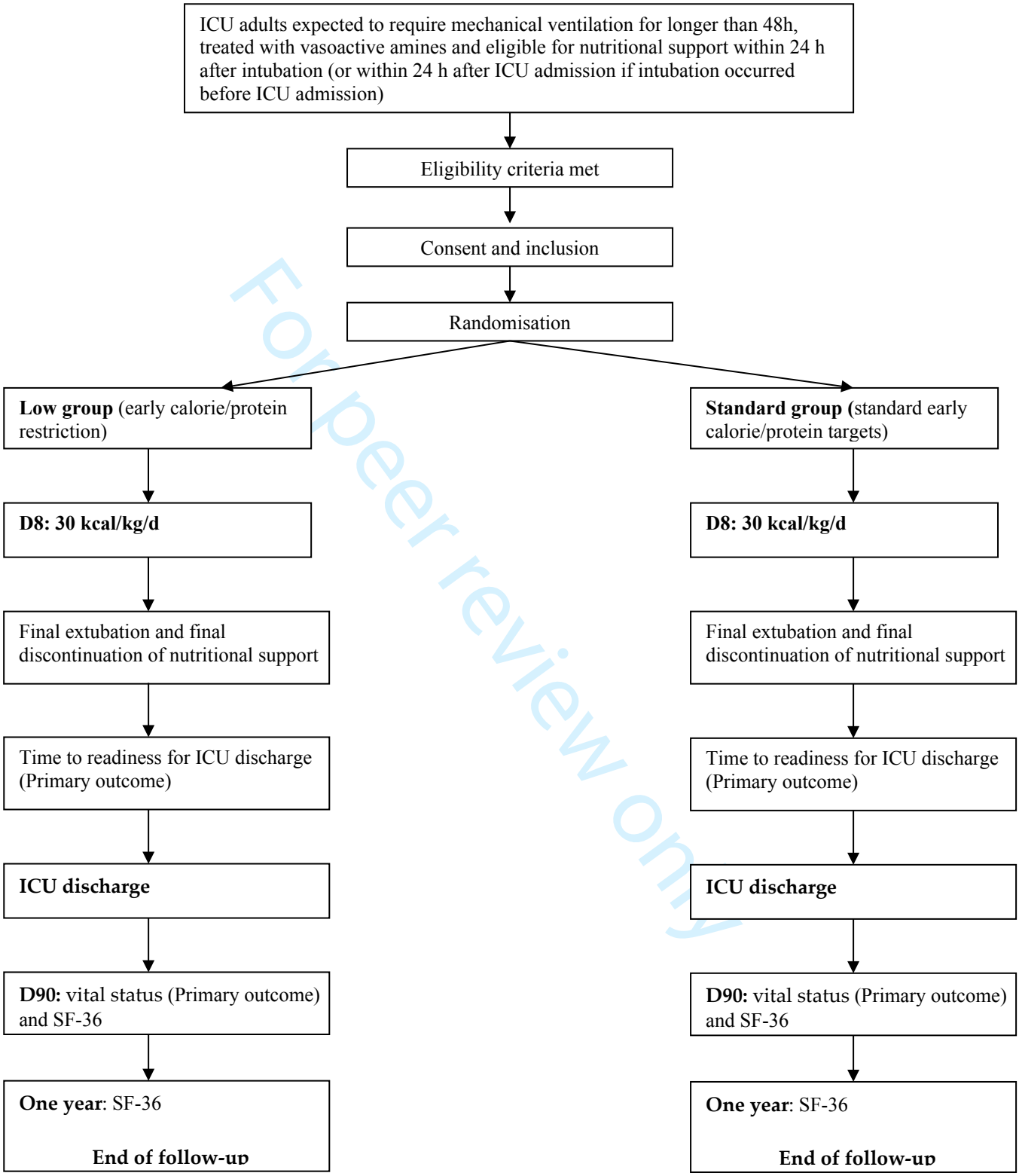
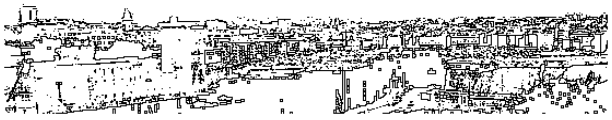


Figure 2: Study diagram





Comité de Protection des Personnes Sud-Méditerranée II

AVIS

Le Comité de Protection des Personnes Sud-Méditerranée II, agréé par arrêté ministériel en date du 31 mai 2012, constitué selon l'arrêté du Directeur Général de l'Agence Régionale de Santé de la région Provence Alpes Côte d'Azur en date du 20 avril 2016,

- en application des dispositions du Code de la Santé Publique et de la réglementation en vigueur applicables sur un projet de recherche mentionnée au 1° ou au 2° de l'article L. 1121-1 du code de la santé publique ne portant pas sur un produit mentionné à l'article L. 5311-1 du même code

- ayant été saisi par **le CHU de Nantes,** promoteur d'un dossier de recherche impliquant la personne humaine intitulée:

Impact of early low-calorie low-protein versus standard calorie standars protein feeding on outcomes of ventilated adults with shock : a randomised, controlled, multicentre, open-label, parallel-group, study (NUTRIREA-3)

Référencée chez le promoteur **: RC18 0006**
Identifiée sous le numéro ID RCB : **2018-A00424-51**
et dont l'investigateur coordonnateur est le **Pr Jean Reignier.**

- ayant, après vérification de la conformité réglementaire, enregistré ce dossier le **22/02/2018** sous la référence interne **218 B14**,

- ayant examiné ce dossier de recherche lors de sa séance plénière du **06/04/2018** au cours de laquelle

D. DUSSOL, PH. ROLLAND, V. PRADEL, H. BAGHDADI, C. SICHEL, D. BRAGUER, D. TAILLEFER, J. RICOEUR, G. NAURAYE, P. D'ANGIO . P. BLIEK

le quorum général étant constaté,

après avoir entendu le rapporteur du collège technique, le rapporteur du collège social et l'avis du méthodologiste ont délibéré,

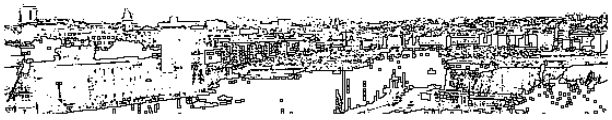
a décidé de demander au promoteur des compléments d'information et de révisions.

Le Comité,

- ayant reçu le **17/04/2018** l'ensemble des informations et des documents demandés,

- sur la base du dossier de recherche ainsi constitué :

  - Courrier de demande d'autorisation du 14/02/2018
  - Lettre de réponse du 17/04/2018
  - Lettre de réponse du 16/04/2018
  - Formulaire de demande d'autorisation du 17/04/2018



- Document additionnel du 14/02/2018
- Protocole de recherche v2 du 16/04/2018
- Résumé du protocole en français V2 du 16/04/2018
- Note d'information patient v2 du 16/04/2018
- Note d'information patient A postériori v2 du 16/04/2018
- Note d'information proche hors procédure d'urgence et formulaire de consentement v2 du 16/04/2018
- Attestation de consentement proche ou personne de confiance
- Attestation de consentement patient
- Attestation de consentement de procédure d'urgence
- CV des investigateurs des principaux de site
- Attestation d'assurance
- Justification d'adéquation des moyens du lieu de recherche

lors de sa séance plénière du **04/05/2018** au cours de laquelle

C. BAGNIS, PH. ROLLAND, H. BAGHDADI, C. SICHEL, D. BRAGUER, M. RAFFRAY, D. TAILLEFER, J. RICOEUR, M. GABORIAU TABARY, P. D'ANGIO .

le quorum général étant constaté,

après avoir entendu le rapporteur du collège technique, le rapporteur du collège social et l'avis du méthodologiste ont délibéré,

a émis un

AVIS FAVORABLE

à la mise en oeuvre de cette recherche impliquant la personne humaine, considérant que les conditions de validité de la recherche, notamment celles définies dans l'article L. 1123-7 du code de la santé publique, étaient réunies.

Le Président
M. Pierre Henri ROLLAND

Il appartient au promoteur ou à son mandataire d'informer le Comité de "*la date effective de commencement de la recherche correspondant à la date de la signature du consentement par la première personne qui se prête à la recherche en France* » (Art. R. Art R1123-40du Code de la Santé Publique) et « *si, dans le délai de deux ans suivant l'avis du comité de protection des personnes, la recherche biomédicale n'a pas débuté, cet avis devient caduc. Toutefois, sur justification produite avant l'expiration dudit délai, celui-ci peut être prorogé par le comité concerné*". (Art R1123-26).

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CENTRE HOSPITALIER
UNIVERSITAIRE DE NANTES

Nantes, october 19th, 2020

The University Hospital of Nantes, represented for this paper by the acting Director of Medical Affairs and Research M.Lazarevic by delegation of the chief executive M. El Saïr, certify that the NUTRIREA-3 study

"Impact of Early Low-Calorie Low-Protein versus Standard-Calorie Standard-Protein Feeding on Outcomes of ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-3)"

was supported by the French Ministry of Health under National PHRC call 2017.
The principal investigator coordinator of this study is Professor Jean Reignier, attached to our hospital.

The total amount of this grant is 1 443 324 €.

This information can be checked on the site of DGOS:
https://solidarites-sante.gouv.fr/systeme-de-sante-et-medico-social/recherche-et-innovation/l-innovation-et-la-recherche-clinique/appels-a-projets/article/les-projets-retenus

To assert that right.

Milan LAZAREVIC
Directeur de la recherche et de l'innovation

Anne OMNES
CHU
Délégation à la recherche clinique
44093 NANTES CEDEX 1

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Impact of Early Low-Calorie Low-Protein versus Standard-Calorie Standard-Protein Feeding on Outcomes of Ventilated Adults with Shock: Design and Conduct of a Randomised, Controlled, Multicentre, Open-Label, Parallel-Group Trial (NUTRIREA-3)

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Manuscript ID	bmjopen-2020-045041.R1
Article Type:	Protocol
Date Submitted by the Author:	16-Mar-2021
Complete List of Authors:	Reignier, Jean; Centre Hospitalier Universitaire de Nantes, Médecine intensive réanimation Le Gouge, Amélie; Centre Hospitalier Regional Universitaire de Tours, INSERM CIC 1415 Lascarrou, Jean-Baptiste; Centre Hospitalier Universitaire de Nantes, Service de Médecine Intensive Réanimation annane, djillali; Hôpital Raymond Poincaré, Service de Médecine Intensive Réanimation Argaud, Laurent Argaud; Centre Hospitalier Universitaire de Lyon, Service de Médecine Intensive Réanimation Hourmant, Yannick; CHU Nantes, Pôle Anesthésie Réanimations, Service d'Anesthésie Réanimation Chirurgicale Asfar, Pierre; Centre Hospitalier Universitaire d'Angers, Service de Médecine Intensive Réanimation Badie, Julio; Hôpital Nord Franche-Comté, Service de Médecine Intensive Réanimation Nay, Mai-Anh; Centre Hospitalier Régional d'Orleans Hôpital de La Source, Service de Médecine Intensive Réanimation Botoc, Nicolae-Vlad; Centre Hospitalier de Saint-Malo, Service de Médecine Intensive Réanimation Brisard, Laurent; CHU Nantes, Service d'Anesthésie Réanimation Chirurgicale Bui, Hoang-Nam; CHU de Bordeaux, Service de Médecine Intensive Réanimation Chatellier, Delphine; CHU Poitiers, Service de Médecine Intensive Réanimation Chauvelot, Louis; CHU Lyon, Service de Médecine Intensive Réanimation Combes, Alain; Hôpital Universitaire Pitié Salpêtrière, Service de Médecine Intensive Réanimation Cracco, Christophe; Centre Hospitalier d'Angouleme, Service de Médecine Intensive Réanimation Darmon, Michael; Hôpital Saint-Louis, Service de Médecine Intensive Réanimation Das, Vincent; CHI André Grégoire, Médecine Intensive Réanimation Debarre, Matthieu; Centre Hospitalier de Saint Brieuc, Médecine Intensive Réanimation Delbove, Agathe; Centre Hospitalier Bretagne Atlantique, Réanimation

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Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Nutrition and metabolism
Keywords:	Adult intensive & critical care < INTENSIVE & CRITICAL CARE, NUTRITION & DIETETICS, Clinical trials < THERAPEUTICS

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Impact of Early Low-Calorie Low-Protein versus Standard-Calorie Standard-Protein Feeding on Outcomes of Ventilated Adults with Shock: Design and Conduct of a Randomised, Controlled, Multicentre, Open-Label, Parallel-Group Trial (NUTRIREA-3)

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ABSTRACT

Introduction: International guidelines include early nutritional support (≤48 h after admission), 20-25 kcal/kg/d, and 1.2-2 g/kg/d protein at the acute phase of critical illness. Recent data challenge the appropriateness of providing standard amounts of calories and protein during acute critical illness. Restricting calorie and protein intakes seemed beneficial, suggesting a role for metabolic pathways such as autophagy, a potential key mechanism in safeguarding cellular integrity, notably in the muscle, during critical illness. However, the optimal calorie and protein supply at the acute phase of severe critical illness remains unknown. NUTRIREA-3 will be the first trial to compare standard calorie and protein feeding complying with guidelines to low-calorie low-protein feeding. We hypothesised that nutritional support with calorie and protein restriction during acute critical illness decreased day-90 mortality and/or dependency on ICU management in mechanically ventilated patients receiving vasoactive amine therapy for shock, compared to standard calorie and protein targets.

Methods and analysis: NUTRIREA-3 is a randomised, controlled, multicentre, open-label trial comparing two parallel groups of patients receiving invasive mechanical ventilation and vasoactive amine therapy for shock and given early nutritional support according to one of two strategies: early calorie-protein restriction (6 kcal/kg/d-0.2-0.4 g/kg/d) or standard calorie-protein targets (25 kcal/kg/d-1.0-1.3g/kg/d) at the acute phase defined as the first 7 days in the ICU. We will include 3044 patients in 61 French ICUs. Two primary end-points will be evaluated: day-90 mortality and time to ICU discharge readiness. The trial will be considered positive if significant between-group differences are found for one or both alternative primary endpoints. Secondary outcomes include hospital-acquired infections and nutritional, clinical, and functional outcomes.

Ethics and dissemination: The NUTRIREA-3 study has been approved by the appropriate ethics committee. Patients are included after informed consent. Results will be submitted for publication in peer-reviewed journals.

Trial Registration: ClinicalTrials.gov: NCT03573739. Date of registration: June 29, 2018.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- NUTRIREA-3 is a pragmatic randomised controlled trial whose large number of patients recruited in numerous intensive care units (ICUs) enhance the reliability and general applicability of the results.
- We included a well-defined population of very severely critically ill patients requiring at least vasoactive drugs and mechanical ventilation, at high risk for death or protracted recovery, and therefore most likely to benefit from improved early nutritional support.
- We used two strong patient-centred primary outcomes, i.e., 90-day mortality and ICU dependency, and we evaluated important secondary outcomes, including long-term function, in keeping with recommendations about studies of nutritional support in critically ill patients.
- NUTRIREA-3 is the first study to evaluate the potential benefits of calorie and protein restriction versus standard calorie and protein targets during early nutritional support, using very different amounts of calories and proteins.
- A limitation is that blinding of nutritional strategies is not feasible.

INTRODUCTION

Severe critical illness is associated during the acute phase with anorexia, metabolic disorders, endocrine dysfunction, and a major catabolic response responsible for severe skeletal and diaphragmatic muscle wasting(1). Among critically ill patients requiring mechanical ventilation (MV) and catecholamines for shock, nearly 40% to 50% die, and functional recovery is often delayed in survivors (2). Nutritional support is crucial, as malnutrition is associated with poor outcomes. Prescribing nutritional support in the critically ill is the result of a complex decision-making process designed to optimise three key parameters: the timing, the dose, and the route of artificial feeding. International guidelines encourage early nutritional support (≤48 h after admission), via the enteral route if not contraindicated, with 20-25 kcal/kg/d, and 1.2-2 g/kg/d protein at the acute phase(3, 4). These targets are rarely achieved in patients with severe critical illnesses, who frequently experience gastroparesis responsible for intolerance to enteral nutrition(5). Observational studies have indicated that calorie and protein deficiencies were associated with nosocomial infections, ICU-acquired weakness, delayed weaning off MV, longer stays, and higher mortality(6-12).

However, recent data challenge the appropriateness of providing standard amounts of calories and protein during the acute phase of critical illness(13, 14). Studies showed no outcome benefits with higher intakes(15, 16). Instead, adding parenteral nutrition to increase intakes was associated with longer ICU stays and more infectious complications(17, 18). Higher protein intakes during the acute phase may be associated with greater muscle wasting and ICU-acquired weakness(1, 19). Restricting calorie and protein intakes seemed beneficial, suggesting a role for metabolic pathways such as autophagy, a potential key mechanism in safeguarding cellular integrity, notably in the muscle, during critical illness(20, 21). The recent EDEN and PERMIT trials showed no differences in patient outcomes between

hypocaloric and standard feeding(22-24). However, in both studies, calorie intakes were below-target in the standard groups. Moreover, patients in both PERMIT trial groups received similar protein intakes, as protein solutions were added in the hypocaloric group. Last, the TARGET trial demonstrated no benefit of delivering 100% vs. 70% of the recommended calorie intake on outcomes of critically ill patients(25). Thus, the optimal calorie and protein supply at the acute phase of severe critical illness remains unknown(14, 26-29).

We designed the NUTRIREA-3 trial to compare standard calorie and protein feeding complying with guidelines to low-calorie low-protein feeding in a well-defined group of severely ill ICU patients requiring at least MV and vasoactive drugs. These patients typically have poor outcomes with long ICU stays, high frequencies of ICU-acquired weakness and infections, and high mortality(1, 30). Reported impacts of nutritional support were greatest in the most severely ill ICU patients (3, 4, 31, 32). Our hypothesis is that, in those severe critically ill patients, low-calorie low-protein feeding at the early phase of critical illness improves muscle preservation, thereby improving outcomes, and most notably diminishing mortality and dependency on ICU care.

METHODS AND ANALYSIS

Trial design

NUTRIREA-3 is a randomised, controlled, multicentre, open-label trial comparing two parallel groups of patients.

Participants, interventions, outcomes

Participating units

Of the 61 French ICUs participating in the study, 34 are in university hospitals. All participating ICU staff members have attended training in the study procedures and protocols for providing nutritional support.

Study population and recruitment modalities

Inclusion criteria are age older than 18 years; invasive MV for an expected duration of at least 48 hours after inclusion, started in the ICU within the past 24 h, or started before ICU admission with ICU admission within the 24 h after intubation; treatment with a vasoactive agent for shock (adrenaline, dobutamine, or noradrenaline); nutritional support expected to be started within 24 h after intubation or within 24 h after ICU admission when MV was started before ICU admission; and patient and/or next-of-kin informed about the study and having consented to participation in the study. If the patient is unable to receive information and no next-of-kin can be contacted during screening for the study, trial inclusion will be completed as an emergency procedure by the ICU physician, in compliance with French law.

Exclusion criteria are specific nutritional needs, such as pre-existing long-term home enteral or parenteral nutrition, for chronic bowel disease; dying patient, not-to-be-resuscitated

order, or other treatment limitation decision at ICU admission; pregnancy, recent delivery, or lactation; adult under guardianship; and department of corrections inmate.

Interventions

After study inclusion, patients will be allocated at random to one of two nutritional support strategies (Figure 1). The designated feeding strategy will be initiated as soon as possible after randomisation (in all patients, within 24 hours after intubation or ICU admission in patients with MV started before admission) and continued until extubation and withdrawal of vasoactive support, or death, or day 7, whichever occurs first.

In the low-calorie low-protein (Low) group, the calorie target will be 6 kcal/kg/day and the protein target 0.2-0.4 g/kg/d during the acute phase, i.e. from D0 to D7. On D8, the calorie target will be 30 kcal/kg/d and the protein target 1.2-2.0 g/kg/d.

In the standard-calorie/standard-protein (Standard) group, the first-line calorie target calculated based on body weight is 25 kcal/kg/day and the protein target 1.0-1.3 g/kg/d during the acute phase, i.e. from D0 to D7. On D8, the calorie target will be 30 kcal/kg/d and the protein target 1.2-2.0 g/kg/d.

Daily nutritional intakes needed to meet the allocated calorie target will be calculated based on body weight (BW). In obese patients (BMI>30 Kg/m²), the body weight yielding a BMI of 30 will be used. In patients with BMI<18.5, the following corrected body weight will be used: (ideal body weight + actual body weight)/2. The calorie/protein ratios of nutritional solutions currently available in French hospitals will ensure that the protein intake complies with the allocated nutritional regimen.

Nutritional support protocol

The nutritional support protocol, including measures designed to evaluate tolerance, is standardised as indicated below.

General principles of nutritional support in both study arms

Nutritional support is started as soon as possible after randomisation and no later than 24 hours after intubation or after ICU admission if intubation preceded ICU admission.

Randomised controlled trials showed that feeding route during the acute phase had no impact on major clinical outcomes of critically ill patients when iso-caloric nutrition was provided in both arms(33, 34). Thus, during the acute phase, bedside physicians will be free, each day, to choose the best feeding route, according to clinical considerations, to ensure that the calorie target is achieved. After the acute phase, enteral feeding remains the preferred route in patients without contraindications (4). Thus, on day 8, in the absence of contraindications to enteral nutrition, parenteral nutrition will be stopped in those patients fed via the parenteral route, and enteral nutrition started. From day 8 onwards, supplemental parenteral nutrition may be added in the event of intolerance to enteral nutrition precluding the achievement of the predefined calorie targets.

Nutritional support is prescribed as a flow rate (mL/hour) and started at the prescribed flow rate (as opposed to increased gradually). The feed is delivered continuously over the 24-hour cycle, with no interruptions. Actual feed delivery is monitored regularly based on the volumes delivered relative to the predefined daily calorie targets. In addition, special attention is directed to avoiding delays. Any interruption in feed delivery is reported to the ICU physician in charge. Except in special situations, nutritional support is not interrupted while transporting the patient. However, when EN or PN must be interrupted (e.g., for a specific gastrointestinal or radiological investigation), the flow rate is not increased to compensate for the interruption. Finally, all patients are in the semi-recumbent supine position (torso inclined 30° to 45° relative to the horizontal plane).

After extubation, regardless of time since randomisation, decisions about the continued need for, and optimal route of, nutritional support are made by the physician in charge of the patient. Patients who are reintubated within 7 days after trial inclusion are managed until the end of the acute phase according to the arm they were randomised to during the first intubation period.

Enteral nutrition (EN)

Iso-osmotic iso-caloric normal-protein polymeric preparations are used during the first week in both groups, after which the choice of feed is at the discretion of the physician. The feed is delivered via a 14-French silicone gastric tube. Tube position in the middle of the stomach is checked on a radiograph obtained at ICU admission or immediately after tube placement, as well as when the tube is changed or repositioned.

A predefined protocol is used to manage upper gastrointestinal intolerance to enteral nutrition. This protocol was used in the NUTRIREA-2 trial(34). To minimise the risk of gastric intolerance and consequently of vomiting, the volume of supplemental water given enterally will be as small as possible during the first study week. Residual gastric volume is not monitored(35). The tolerance of enteral nutrition is defined based only on episodes of significant vomiting or regurgitation (passage of enteral nutrition formula into the mouth, outside the mouth, or into the endotracheal tube in the absence of care procedures or mobilisation). Minimal regurgitation or vomiting triggered by tracheal aspiration or oral cavity care is not taken to indicate intolerance. EN intolerance leads to the following two measures. First, treatment with a prokinetic agent is initiated after confirmation that there are no contraindications. The study ICUs use the prokinetic agent of their choice, according to their standard practice. The prokinetic agent is discontinued when EN at the highest prescribed flow rate has been well tolerated for 48 hours. Second, if gastric intolerance persists despite prokinetic therapy, the flow rate is decreased by 25 mL/h every 6 hours until

the signs of intolerance resolve. Therefore, EN is stopped (and the gastric tube placed under suction) only in patients with intolerance despite a flow rate ≤25 mL/h. All interruptions in EN delivery must be reported to the physician in charge of the patient. This precaution is particularly important in patients receiving insulin. EN is resumed at the prescribed flow rate (appropriate to the patient's needs) after 6 hours have elapsed with no further signs of intolerance. Patients at high risk for gastric intolerance, such as those turned in the prone position for acute respiratory distress syndrome (ARDS), receive prophylactic prokinetic treatment starting at the first turn in the prone position (36, 37).

Parenteral nutrition (PN)

Ternary admixtures packaged in bags and containing the three groups of macronutrients are used according to standard practice in each participating centre. Supplemental electrolytes are supplied in a solution separate from the parenteral feed, according to the needs of each patient. PN is delivered continuously via a central venous catheter (CVC). Special attention is directed to preventing infections by complying with the standard protocols for CVC insertion and maintenance used in each of the participating centres. Proper CVC position is checked on a radiograph.

Additional intakes

Additional water, electrolytes, vitamins, and trace elements are given intravenously according to the needs of each individual patient as assessed by the physician in charge and using the standard preparations and protocols available in each study ICU.

Monitoring of intestinal transit

The volume and appearance of the stools are monitored daily. The occurrence of constipation (no stool for more than 6 days) or diarrhoea (more than 300 mL of liquid stool or 4 loose stools per day) will be reported and will lead to the appropriate diagnostic and therapeutic management (15, 38, 39). Enteral nutrition is not stopped for diarrhoea, which

leads to the following measures. First, treatments that accelerate bowel transit, including prokinetic agents, are stopped. Second, a stool test for *Clostridium difficile* toxin is performed in patients receiving antibiotics. Third, the enteral solution is changed if the first measure is ineffective and the *C. difficile* toxin test is negative. Finally, if the diarrhoea persists despite the measures listed above, the rate of enteral feeding is reduced until the diarrhoea resolves then increased again gradually until the desired flow rate (40).

Blood glucose control

Close monitoring and strict application of the blood glucose-control and insulin-therapy protocols used at each study centre will be ensured. Blood glucose targets will be at the discretion of each physician in charge, according to the usual practice and protocols in their ICU. In patients receiving insulin therapy, blood glucose levels will be determined at least hourly if nutritional support is discontinued or decreased (because of poor tolerance of enteral nutrition) for as long as the patient remains intolerant to, or off, nutrition.

Study outcomes

Primary endpoints

Two primary end-points will be analysed: all-cause mortality by day 90, and time to readiness for ICU discharge. Information on vital status will be collected on the 90th day after patient inclusion. For discharged patients, information on this primary endpoint will be collected by a telephone call to the patient's home. The time of ICU discharge to a regular ward may be affected by the availability of beds on regular wards, which may induce bias. The study will therefore consider the time to readiness for ICU discharge. A patient will be considered ready for ICU discharge as soon as all predefined clinical conditions for ICU discharge are fulfilled (Table 1), regardless of ward-bed availability. Readiness for ICU discharge will be checked daily in all patients weaned from invasive MV and vasoactive

drugs. A similar strategy regarding this endpoint has been used previously in studies on nutrition in the ICU(17, 18).

The trial will be considered positive if significant between-group differences are found for one or both alternative primary endpoints.

Secondary outcomes

- Daily mean values during the first week, throughout the time on endotracheal mechanical ventilation (MV) and from weaning off MV to readiness for ICU discharge of the following:
    - number of calories (in Kcal) delivered enterally and/or parenterally
    - ratio (as a %) of prescribed over delivered calories
- Proportion of patients who achieved their calorie target from day 0 to day 7
- Daily mean values from day 0 to day 7 and during MV of the following:
    - protein supply (g) given enterally and/or parenterally
    - volume of fluids (in mL) received (daily mean from day 0 to day 7 and during MV)
- From day 0 to day 7:
    - SOFA score changes
    - Changes in daily maximum blood glucose levels
    - Proportion of patients with hypoglycaemia
    - Total insulin dose received daily
- Days on insulin treatment from day 0 to readiness for ICU discharge
- Proportion of patients with at least one ICU-acquired infection; an independent blinded committee will adjudicate all ICU-acquired infections.

– Ventilator-associated pneumonia (VAP): the diagnosis of VAP is suspected based on the development or persistence of lung infiltrates on the chest radiograph with at least two of the following criteria: body temperature ≥38.5 or ≤35.5ºC, leucocytosis (>10 000/mm^3) or leucopenia (<4000/mm^3), and purulent tracheobronchial aspirate, from H48 after intubation to H48 after extubation. The diagnosis will have to be confirmed by a positive *semi-quantitative* bacteriological test: bronchoalveolar lavage (>10^{-4} cfu/mL), brush (>10^{-3} cfu/mL), tracheal aspirate (>10^{-6} cfu/mL), or protected distal specimen (>10^{-3} cfu/mL)(41, 42). VAP episodes are recorded from 48 hours after intubation until day 2 after extubation.

  - Proportion of patients with at least one VAP episode
  - Total number of VAP episodes in each group

– Other ICU-acquired infections:

  - Proportion of patients with at least one episode of bacteraemia
  - Proportion of patients with at least one central venous catheter (CVC)-related infection
  - Proportion of patients with at least one episode of urinary tract infection
  - Proportion of patients with at least one soft tissue infection
  - Proportion of patients with other nosocomial infections

– Descriptive bacteriological data: organisms recovered in the overall population with nosocomial infections, and antimicrobial resistance profiles

– Proportion of patients with at least one episode of liver dysfunction, defined as serum bilirubin >50 µmoL/L and/or elevation >3N of one or more liver enzymes (γ-glutamyltransferase, alkaline phosphatase, and ASAT-ALAT) at the end of MV, on day 7 (in patients on MV for more than 7 days), and at ICU discharge

- Proportion of patients with at least one episode of vomiting or regurgitation while on MV
- Proportion of patients with at least one episode of diarrhoea defined as liquid stools in a volume greater than 300 mL/24 hours in patients with a faecal collector or as more than four loose stools/24 hours (15)
- Proportion of patients with at least one episode of constipation (no stool for more than 6 days)
- Proportion of patients with at least one documented episode of bowel ischaemia defined as absent blood flow in one of the main arteries supplying the bowel (superior mesenteric artery, inferior mesenteric artery, or celiac artery) with evidence of bowel wall compromise on an imaging study (computed tomography angiography, angiography, or magnetic resonance angiography) or presence of criteria for colonic ischaemia according to the Favier classification system (stage I, petechiae; stage II, petechiae and superficial ulcers; and stage III, necrotic ulcers and polypoid lesions) by endoscopy (rectosigmoidoscopy or colonoscopy) (43)
- Mean changes in serum albumin, pre-albumin, and C-reactive protein (CRP) measured at baseline, at the end of MV, on day 7 (in patients on MV for more than 7 days), and at ICU discharge
- Changes in mean body weight determined at baseline, on day 7, and at ICU discharge
- Days on MV
- Hospital stay length (days in hospital)
- ICU mortality, 28-day mortality, and hospital mortality
- Proportions of patients mobilised from day 0 to day 7 and total number of active mobilisations, using predetermined criteria (44) (Table 2)

- Total Medical Research Council (MRC) score and proportion of patients with ICU-acquired paresis at the time of readiness for ICU discharge (45, 46); the MRC score can range from 0 (quadriplegia) to 60 (normal muscle strength); scores <48 will define ICU-acquired paresis.
- Proportion of patients with at least one criterion for persistent altered health status at the time of readiness for ICU discharge, among the following: tracheostomy, non-invasive ventilation, ongoing renal-replacement therapy, parenteral nutrition, enteral nutrition via a nasogastric tube; Glasgow Coma Scale score <15, and treatment-limitation decision(47)
- SF-36 score completed during a phone call to the patient by an independent blinded research nurse or psychologist 3 months and 1 year after study inclusion(48, 49)

Organisation of the trial

Figure 2 is the study diagram.

Recruitment modalities

All patients treated with invasive MV and vasopressor support for shock within 24 h after intubation, or within 24 h after ICU admission if already intubated, will be screened for eligibility by the ICU physicians and clinical research nurses, around the clock and 7 days a week. Patients will be included after checking inclusion and non-inclusion criteria. A log of patients considered for study participation will be kept and will include any reasons for non-inclusion and refusals of consent.

Randomisation

Randomisation is centralised and performed using a secure, computer-generated, interactive, web-response system available at each study centre. Randomisation is stratified on study centre with a 1:1 ratio.

Blinding

The trial will be open, since the nature of the intervention precludes blinding of healthcare staff to group assignment. However, the absence of blinding cannot have an impact on either of the primary endpoints. Day-90 mortality is an objective endpoint with no evidence that absence of blinding may affect the data(50). Given its more subjective nature, the primary endpoint of readiness to discharge alive from the ICU will be checked daily by the bedside physician according to predefined criteria, in order to strongly limit the risk of detection bias. Moreover, the secondary endpoints relevant to nosocomial infections will be validated by an adjudication committee.

Sample size

Assuming a 43% day-90 mortality rate in the Standard group and a 5% absolute decrease in day-90 mortality (to 38%) in the Low group, with the alpha risk set at 4.9% (as two interim analyses are planned) and the beta risk at 20%, 1522 patients are needed in each group, i.e., a theoretical total of 3044 patients.

This sample size will provide 94% power to detect a 1.5-day difference in time to ICU discharge alive between the two groups (mean, 14.5 days in the control group versus 13.0 days in the experimental group).

No corrections will be made for multiple comparisons. Indeed, adjusting for multiplicity is controversial and there is no consensus about the appropriate analysis (51). Moreover, adjusting for multiplicity may lead to increased sample size and subsequent decreased feasibility of the study. Last, most recent studies with a similar design did not use corrections for multiple comparisons (17, 18).

The ICU stay lengths in survivors and mortality rates used for the sample size estimation

are those obtained in the NUTRIREA-1 and -2 trials, which used similar inclusion criteria.

Interim analysis

Given the need for a large sample size, two interim analyses will be scheduled, one after enrolment of 1000 patients and the other after enrolment of 2000 patients. Members of the independent Data Safety Monitoring Board (DSMB) will not be otherwise involved in the trial. This DSMB consists of one methodologist and two intensivists. For both interim analyses, the DSMB will have access to unblinded results on day-90 mortality, time to discharge alive from the ICU, variations in SOFA scores from day 0 to day 7, amounts of calories and proteins received daily from day 0 to day 7, and nosocomial infections. The results of the interim analyses will not be disclosed unless they lead the DSMB to request premature trial discontinuation.

Statistical analysis

Each patient will remain in the group assigned by randomisation, regardless of subsequent events. A statistical analysis report will be written to describe all the findings, according to CONSORT Statement recommendations, while taking into account the specific features of the trial, most notably the nonpharmacological nature of the intervention. The baseline features of the groups established by randomisation will be compared using descriptive statistics; no statistical tests will be performed.

Primary endpoint

Day-90 mortality will be reported as the point estimate with the 95% confidence interval in each group. The difference in proportions with the 95% confidence interval will also be estimated. Day-90 mortality will be compared between the two groups using the chi-square test.

Time to readiness for ICU discharge will be analysed using the competing risk approach (Fine and Gray model), with death in the ICU as a competing risk.

Secondary endpoints

The incidence of patients with at least one nosocomial infection will be estimated and compared between the groups using a Fine and Gray model, with death and ICU discharge alive as competing events. The incidence of patients with at least one VAP episode will be estimated using a Fine and Gray model, with not only death as a competing risk, but also time to extubation +2 days, since after this point any episode of pneumonia would not be classified as VAP. For CVC-related infections, the competing risks will be death and CVC removal; for urinary tract infections they will be death and urinary catheter removal. Bacteraemia, soft tissue infections, and other infections will be analysed using the same method as for the pooled nosocomial infections. For descriptive bacteriological data (organisms recovered with their resistance profiles for each nosocomial infection), only descriptive analyses will be performed. For the proportions of patients with at least one episode of vomiting or regurgitation, diarrhoea, constipation, documented acute colonic pseudo-obstruction, documented bowel ischaemia, mechanical complication of CVC insertion, hypoglycaemia from day 0 to day 7, and liver dysfunction, the method will be the same as for nosocomial infections. Changes over time in delivered calories and proteins will be represented graphically by boxplots created each day on the same graph; changes over time will be compared between the two groups using a mixed linear model, after data transformation if necessary. The same analysis will be performed for volume of feeds delivered each day. The proportion of patients who achieved 100% of their daily calorie target will be determined at each follow-up time point (in days) and compared between the two groups using a logistic random-effects model. Day-28 mortality will be analysed in the same way as day-90 mortality. For ICU and hospital mortality rates, a Fine and Gray model

will be used, with ICU discharge and hospital discharge as events competing with death during the stay. Time to extubation will be analysed using a Fine and Gray model with death and ICU discharge as competing events. Changes over time in SOFA, total insulin, blood glucose, nutritional markers and body weight will be analysed using the method described above for the number of calories delivered. For the proportion of mobilised patients, patients with at least one criterion of persistent altered health status at the time of readiness for ICU discharge, and patients with ICU-acquired paresis, the method will be the same as for nosocomial infections. The Medical Research Council (MRC) sum score at the time of readiness for ICU discharge and days on insulin will be compared between the two groups using the non-parametric Wilcoxon test. The total quality-of-life SF-36 score will be compared between the two groups using a mixed linear model.

Data collection and follow-up

The following data will be recorded until the patient is extubated: demographic and clinical data, nutrition monitoring data, treatments given, laboratory tests, invasive devices, functional evaluation, and data relevant to nosocomial infections. The patient will be followed up for 1 year after study inclusion; at hospital discharge, on D28 and D90, and at 1 year, the vital status will be recorded. The SF-36 score will be recorded on D90 and 1 year after study inclusion. Table 3 is the study flow-chart.

Data entry and monitoring

An Internet-based data collection tool will be used for this study to store the data of all the participants. This electronic case-report form (eCRF) is a secure, interactive, web-response system available at each study centre. It is provided and managed by the biometrical

unit of the Tours University Hospital (CIC INSERM 1415, Tours, France). Access to the eCRF will require only an Internet connection and a browser.

Monitoring of the data collected and of the screening forms in each participating centre will be carried out by the Research Division, Promotion Department, of the Nantes University hospital. Research assistants will regularly perform on-site checks of adherence to the protocol and accuracy of recorded data.

Trial Status

Inclusions started in July 2018. The scheduled interim analysis were performed on the first 1000 (by October 2009) and 2000 (by March 2020) included patients, respectively. Both analyses led the DSMB to recommend continuation of the study. Recruitment in the trial was interrupted from March to June 2020 because of the COVID-19 crisis, when all ICUs were full with COVID-19 patients and all research teams were working only on COVID-19 trials. By August 19, 2020, 2764 patients had been included. Recruitment is expected to be complete by December 2020.

Ethics and dissemination

Ethical review board

The NUTRIREA-3 trial was approved by the competent French authorities on 20 April 2016 (*Comité de Protection des Personnes Sud-Méditerranée 2*, registration 2018-A00424-51) and registered on ClinicalTrials (NCT03573739) in June 2018.

Consent

The patients are included after providing their signed informed consent to trial participation. For patients unable to consent because of impaired consciousness or severe critical illness, information about the study is provided to their next of kin. Patients who are

unable to consent and for whom no relative is available to consent to study participation within a timeframe compatible with the study design are included after completion of an emergency consent form by the bedside physician. The relatives are informed of the inclusion as soon as possible. Patients are asked to confirm their willingness to participate in the trial once they regain decision-making capacity. Data of patients without relatives who die without previously recovering consciousness will be included in the statistical analysis.

Confidentiality and source data archiving

The medical data about each patient will be communicated only to the institution (i.e., the sponsor) with which the chief investigator is affiliated or to a person appointed by the chief investigator and the sponsor under conditions that ensure the confidentiality of the patient data. During or at completion of the study, the data collected from the study participants and communicated by the individuals involved in the study will be rendered anonymous. Study investigators will archive all study data for at least 15 years after the end of the study.

Dissemination policy

The publication policy will comply with international recommendations (N Engl J Med, 1997; 336:309-315) and the CONSORT statement (http://www.consort-statement.org). Findings will be published in peer-reviewed journals and presented during national and international scientific meetings. Communications and scientific reports relevant to this study will be under the responsibility of the study coordinator (JR), who will obtain the approval of the other investigators.

Patient and public involvement

Neither patients nor the public are involved in the study.

References

1. Puthucheary ZA, Rawal J, McPhail M, et al. Acute skeletal muscle wasting in critical illness. JAMA 2013;310(15):1591-1600.

2. Hermans G, Van den Berghe G. Clinical review: intensive care unit acquired weakness. Crit Care 2015;19:274.

3. Singer P, Blaser AR, Berger MM, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr 2018.

4. Taylor BE, McClave SA, Martindale RG, et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). Crit Care Med 2016;44(2):390-438.

5. Blaser AR, Starkopf J, Kirsimagi U, et al. Definition, prevalence, and outcome of feeding intolerance in intensive care: a systematic review and meta-analysis. Acta Anaesthesiol Scand 2014;58(8):914-922.

6. Alberda C, Gramlich L, Jones N, et al. The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study. Intensive care medicine 2009;35(10):1728-1737.

7. Elke G, Wang M, Weiler N, et al. Close to recommended caloric and protein intake by enteral nutrition is associated with better clinical outcome of critically ill septic patients: secondary analysis of a large international nutrition database. Crit Care 2014;18(1):R29.

8. Compher C, Chittams J, Sammarco T, et al. Greater Protein and Energy Intake May Be Associated With Improved Mortality in Higher Risk Critically Ill Patients: A Multicenter, Multinational Observational Study. Crit Care Med 2017;45(2):156-163.

9. Allingstrup MJ, Esmailzadeh N, Wilkens Knudsen A, et al. Provision of protein and energy in relation to measured requirements in intensive care patients. Clin Nutr 2012;31(4):462-468.

10. Faisy C, Candela Llerena M, Savalle M, et al. Early ICU energy deficit is a risk factor for Staphylococcus aureus ventilator-associated pneumonia. Chest 2011;140(5):1254-1260.

11. Villet S, Chiolero RL, Bollmann MD, et al. Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients. Clin Nutr 2005;24(4):502-509.

12. Wei X, Day AG, Ouellette-Kuntz H, et al. The Association Between Nutritional Adequacy and Long-Term Outcomes in Critically Ill Patients Requiring Prolonged Mechanical Ventilation: A Multicenter Cohort Study. Crit Care Med 2015;43(8):1569-1579.

13. Casaer MP, Van den Berghe G. Nutrition in the acute phase of critical illness. N Engl J Med 2014;370(25):2450-2451.

14. Preiser JC, van Zanten AR, Berger MM, et al. Metabolic and nutritional support of critically ill patients: consensus and controversies. Crit Care 2015;19(1):35.

15. Doig GS, Simpson F, Finfer S, et al. Effect of evidence-based feeding guidelines on mortality of critically ill adults: a cluster randomized controlled trial. JAMA 2008;300(23):2731-2741.

16. Heyland DK, Murch L, Cahill N, et al. Enhanced Protein-Energy Provision via the Enteral Route Feeding Protocol in Critically Ill Patients: Results of a Cluster Randomized Trial. Crit Care Med 2013.

17. Fivez T, Kerklaan D, Mesotten D, et al. Early versus Late Parenteral Nutrition in Critically Ill Children. N Engl J Med 2016;374(12):1111-1122.

18. Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med 2011;365(6):506-517.

19. Casaer MP, Wilmer A, Hermans G, et al. Role of disease and macronutrient dose in the randomized controlled EPaNIC trial: a post hoc analysis. Am J Respir Crit Care Med 2013;187(3):247-255.

20. Vanhorebeek I, Gunst J, Derde S, et al. Insufficient activation of autophagy allows cellular damage to accumulate in critically ill patients. J Clin Endocrinol Metab 2011;96(4):E633-645.

21. Choi AM, Ryter SW, Levine B. Autophagy in human health and disease. N Engl J Med 2013;368(7):651-662.

22. Arabi YM, Aldawood AS, Haddad SH, et al. Permissive Underfeeding or Standard Enteral Feeding in Critically Ill Adults. N Engl J Med 2015;372(25):2398-2408.

23. Needham DM, Dinglas VD, Bienvenu OJ, et al. One year outcomes in patients with acute lung injury randomised to initial trophic or full enteral feeding: prospective follow-up of EDEN randomised trial. BMJ 2013;346:f1532.

24. Rice TW, Wheeler AP, Thompson BT, et al. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. JAMA 2012;307(8):795-803.

25. Deane AM, Little L, Bellomo R, et al. Outcomes Six Months after Delivering 100% or 70% of Enteral Calorie Requirements during Critical Illness (TARGET). A Randomized Controlled Trial. Am J Respir Crit Care Med 2020;201(7):814-822.

26. Marik PE, Hooper MH. Normocaloric versus hypocaloric feeding on the outcomes of ICU patients: a systematic review and meta-analysis. Intensive Care Med 2016;42(3):316-323.

27. Marik PE, Rice TW. Feeding the Critically Ill: More Questions Than Answers! Am J Respir Crit Care Med 2017;195(5):555-556.

28. Preiser JC. High protein intake during the early phase of critical illness: yes or no? Crit Care 2018;22(1):261.

29. Singer P, Cohen J. Nutrition in the ICU: proof of the pudding is in the tasting. Intensive Care Med 2015;41(1):154-156.

30. Iwashyna TJ, Ely EW, Smith DM, et al. Long-term cognitive impairment and functional disability among survivors of severe sepsis. JAMA 2010;304(16):1787-1794.

31. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med 2017;43(3):304-377.

32. Artinian V, Krayem H, DiGiovine B. Effects of early enteral feeding on the outcome of critically ill mechanically ventilated medical patients. Chest 2006;129(4):960-967.

33. Harvey SE, Parrott F, Harrison DA, et al. Trial of the route of early nutritional support in critically ill adults. N Engl J Med 2014;371(18):1673-1684.

34. Reignier J, Boisrame-Helms J, Brisard L, et al. Enteral versus parenteral early nutrition in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2). Lancet 2018;391(10116):133-143.

35. Reignier J, Mercier E, Le Gouge A, et al. Effect of not monitoring residual gastric volume on risk of ventilator-associated pneumonia in adults receiving mechanical ventilation and early enteral feeding: a randomized controlled trial. JAMA 2013;309(3):249-256.

36. Poulard F, Dimet J, Martin-Lefevre L, et al. Impact of Not Measuring Residual Gastric Volume in Mechanically Ventilated Patients Receiving Early Enteral Feeding: A Prospective Before-After Study. JPEN J Parenter Enteral Nutr 2009.

37. Reignier J, Dimet J, Martin-Lefevre L, et al. Before-after study of a standardized ICU protocol for early enteral feeding in patients turned in the prone position. Clin Nutr 2010;29(2):210-216.

38. Gacouin A, Camus C, Gros A, et al. Constipation in long-term ventilated patients: associated factors and impact on intensive care unit outcomes. Critical care medicine 2010;38(10):1933-1938.

39. van der Spoel JI, Schultz MJ, van der Voort PH, et al. Influence of severity of illness, medication and selective decontamination on defecation. Intensive Care Med 2006;32(6):875-880.

40. Brisard L, Le Gouge A, Lascarrou J, et al. Impact of early enteral versus parenteral nutrition on mortality in patients requiring mechanical ventilation and catecholamines: study protocol for a randomized controlled trial (NUTRIREA-2). Trials 2014;15(1):507.

41. Chastre J, Fagon JY. Ventilator-associated pneumonia. Am J Respir Crit Care Med 2002;165(7):867-903.

42. Hubmayr RD, Burchardi H, Elliot M, et al. Statement of the 4th International Consensus Conference in Critical Care on ICU-Acquired Pneumonia--Chicago, Illinois, May 2002. Intensive Care Med 2002;28(11):1521-1536.

43. Favier C, Bonneau HP, Tran Minh V, et al. Endoscopic diagnosis of regressive ischemic colitis. Endoscopic, histologic and arteriographic correlations. Nouv Presse Med 1976;5(2):77-79.

44. Wright SE, Thomas K, Watson G, et al. Intensive versus standard physical rehabilitation therapy in the critically ill (EPICC): a multicentre, parallel-group, randomised controlled trial. Thorax 2017.

45. Bittner EA, Martyn JA, George E, et al. Measurement of muscle strength in the intensive care unit. Crit Care Med 2009;37(10 Suppl):S321-330.

46. Sharshar T, Bastuji-Garin S, Stevens RD, et al. Presence and severity of intensive care unit-acquired paresis at time of awakening are associated with increased intensive care unit and hospital mortality. Crit Care Med 2009;37(12):3047-3053.

47. Santamaria JD, Duke GJ, Pilcher DV, et al. The timing of discharge from the intensive care unit and subsequent mortality. A prospective, multicenter study. Am J Respir Crit Care Med 2015;191(9):1033-1039.

48. Ware J, Jr., Kosinski M, Gande B. SF-36® Health Survey Manual & Interpretation Guide. : Lincoln, RI: Quality Metric Incorporated; 2005.

49. Oeyen SG, Vandijck DM, Benoit DD, et al. Quality of life after intensive care: a systematic review of the literature. Crit Care Med 2010;38(12):2386-2400.

50. Anthon CT, Granholm A, Perner A, et al. No firm evidence that lack of blinding affects estimates of mortality in randomized clinical trials of intensive care interventions: a systematic review and meta-analysis. Journal of clinical epidemiology 2018;100:71-81.

51. Li G, Taljaard M, Van den Heuvel ER, et al. An introduction to multiplicity issues in clinical trials: the what, why, when and how. Int J Epidemiol 2017;46(2):746-755.

AUTHORS' CONTRIBUTIONS:

ALG and JR prepared the first draft of the manuscript.

JR, JBL, DM, ALG, and BGi wrote the manuscript.

JR, JBL, ALG, DM, and BGi participated in designing the NUTRIREA-3 study.

ALG and BGi wrote the statistical analysis plan and performed the sample size estimation.

JR and DM obtaining funding for the study.

JR, JBL, DA, LA, YH, PA, JB, MAN, NVB, LB, HNB, DC, LC, AC, CC, MD, VD, MD, AD, JD, SV, NAB, LMD, JO, OG, SG, BGu, SJ, FL, CL, PL, BM, JM, OM, FM, EM, JPM, SN, WP, GPi, GPl, JPQ, AR, LG, JR, JPR, FS, DS, MS, BS, FR, FT, NT, DT, GT, NTR, JFT, FT, PT, TV, IV, and CV contributed to acquire the study data.

All authors revised the manuscript for important intellectual content and read and approved the final version of the manuscript.

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COMPETING INTEREST STATEMENT

JR had travel and accommodation expenses to attend scientific meetings covered by Baxter and Fresenius.

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FIGURE LEGENDS

Figure 1: Study interventions

Figure 2: Study diagram

Table 1: Criteria for readiness for ICU discharge

A patient will be considered ready for ICU discharge when he/she meets all of the following criteria:

- No longer in need of, or at risk for needing, invasive mechanical ventilation
- No longer in need of, or at risk for needing, vasoactive support
- No agitation or altered consciousness requiring close monitoring and management
- No severe acute metabolic or haematologic disorder requiring close monitoring and management

Table 2: Mobilisation scale

Remains in bed	▪ no mobilisation, ▪ turned in bed, ▪ sitting position in bed with the head of the bed elevated
Mobilised in the bed	▪ passive mobilisation of the legs in bed ▪ active mobilisation of the legs in bed ▪ cycling motions in bed
Mobilised out of bed	▪ sits on the edge of the bed with the feet on the floor ▪ sits in a chair ▪ stands ▪ marches in place ▪ walks

Table 3: Study flow chart of patient follow-up

	Inclu-sion	D0*	D1 to Dn	End of study proto-col	Ready for ICU discharge	D28	D90	One year End of follow-up **
Eligibility: check inclusion and exclusion criteria	X							
Patient information and consent	X							
Randomisation		X						
Demographic characteristics		X						
Vital signs		X						
Weight		X	X					
Ventilation		X	X					
Laboratory tests		X	X*					
SOFA		X	X					
Nutritional evaluation		X	X					
Treatments used		X	X					
Daily nutritional intake		X	X					
Fluid intake		X	X					
Nosocomial infections			X					
Final extubation				X				
Final discontinuation of nutritional support				X				
Health status					X			
MRC score					X			
Survived / died					X	X	X	X
SF-36							X	X

* from time of inclusion to 11:59 pm

** Information will be collected by phone contact with patients or relatives.

Figure 1: **Study interventions**

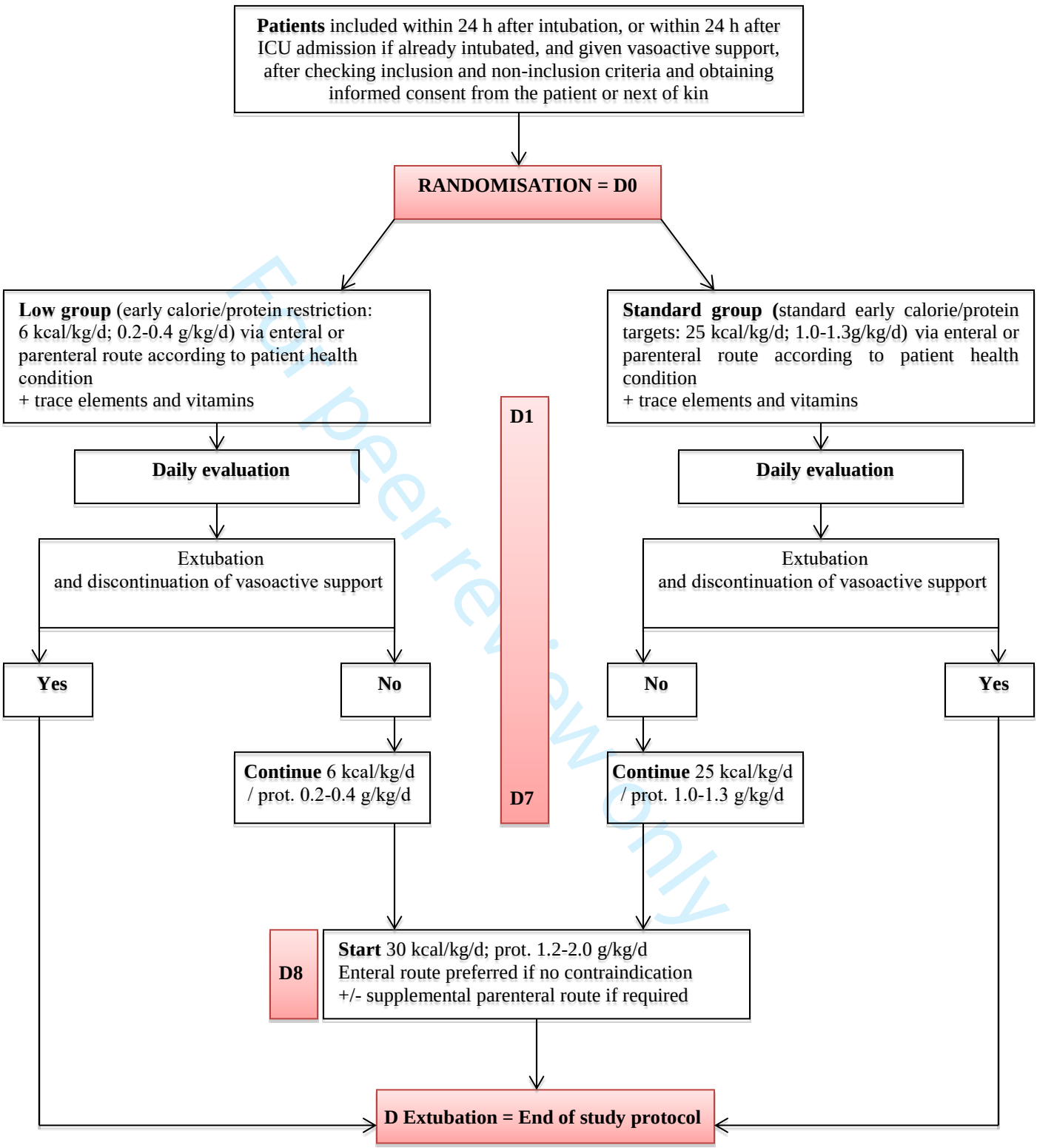
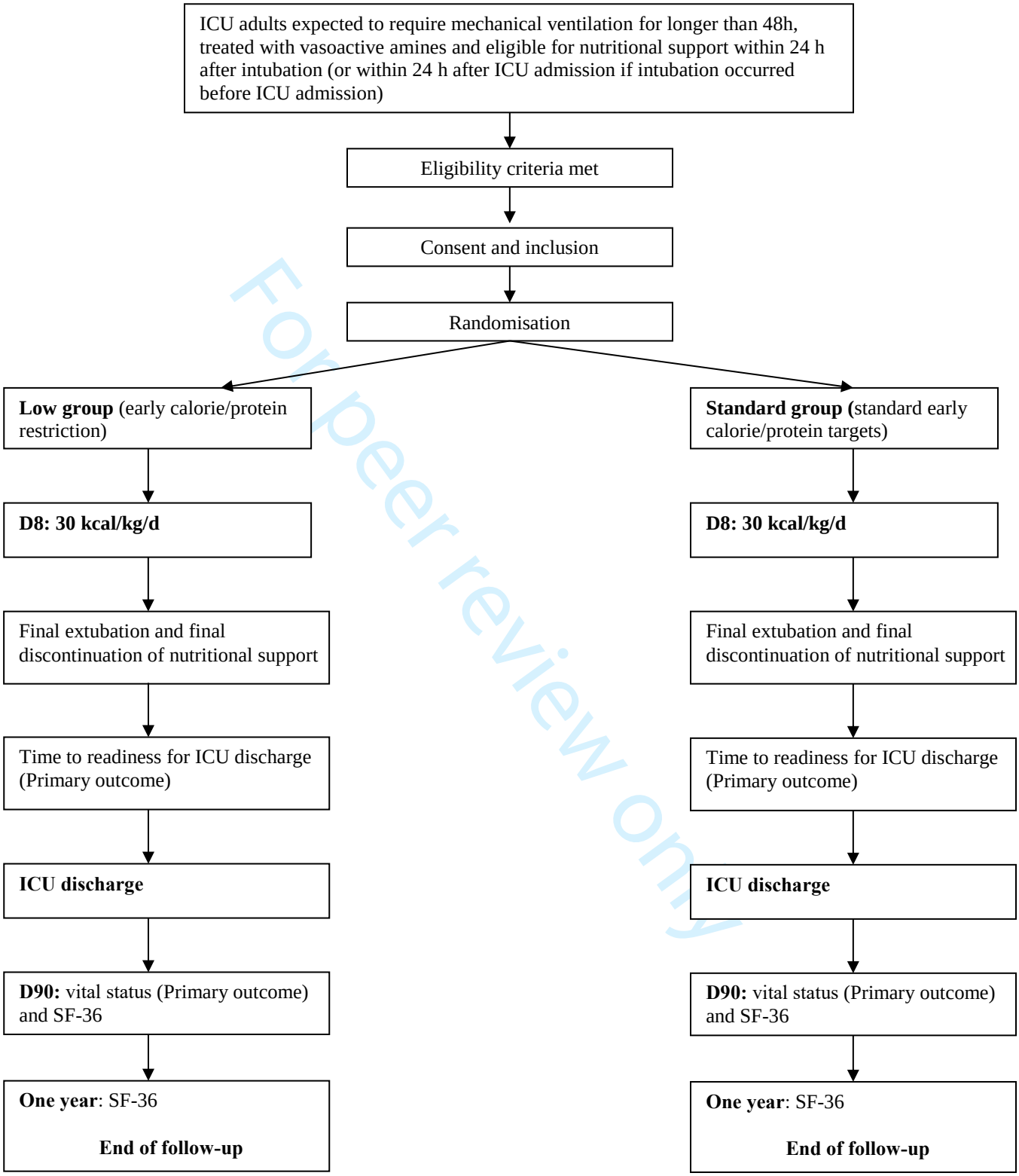


Figure 2: Study diagram



SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Page	Description
Administrative information			
Title	1	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	9	Trial identifier and registry name. If not yet registered, name of intended registry
	2b		All items from the World Health Organization Trial Registration Data Set
Protocol version	3	NA	Date and version identifier
Funding	4	29	Sources and types of financial, material, and other support
Roles and responsibilities	5a	29	Names, affiliations, and roles of protocol contributors
	5b	NA	Name and contact information for the trial sponsor
	5c	29	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	NA	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction			
Background and rationale	6a	11	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	12	Explanation for choice of comparators
Objectives	7	12	Specific objectives or hypotheses
Trial design	8	13	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes			
Study setting	9	13	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10	13	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a	14	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	14-17	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	14-17	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	14-17	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	18	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	21, 25	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	22	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	21	Strategies for achieving adequate participant enrolment to reach target sample size
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	22	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

Allocation concealment mechanism	16b	22	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	22	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	22	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	NA	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis			
Data collection methods	18a	25	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	25	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	26	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	24	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	24	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	23-24	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring			
Data monitoring	21a	NA	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

	21b	23	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	NA	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	NA	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination			
Research ethics approval	24	26	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25		Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	27	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	NA	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	27	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	NA	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	27	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	27	Authorship eligibility guidelines and any intended use of professional writers
	31c	NA	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials	32		Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	NA	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.