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Protocol

The effect of an intervention of porcine protein versus maltodextrin supplement on CONvalescence of FUnCtional outcomes after IcU Stay (CONFUCIUS): Study protocol for a randomized controlled, single-center, double-blind trial

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SUMMARY

Background: Patients discharged from the Intensive Care Unit (ICU) frequently suffer from ICU-acquired weakness because of immobilization and massive inflammation-induced muscle mass loss. Consequently, rehospitalization, reduced quality of life (QoL), increased disabilities, and higher post-ICU mortality is observed. Exercise rehabilitation and optimal nutrition, particularly protein intake, are pivotal to regaining muscle mass and function. Studies have shown that protein requirements in the post-ICU phase are often unmet. Furthermore, protein supplementation in other patient groups has shown beneficial effects. However, a study on protein supplementation during the post-ICU period is lacking. This study aims to investigate the effect of a six-week intervention of daily porcine protein supplementation versus an isocaloric control (maltodextrin) on functional outcomes in the post-ICU period in patients with moderately severe ICU-acquired weakness.

Methods: 72 post-ICU patients with moderately severe ICU-acquired weakness of Hospital Gelderse Vallei will be randomly assigned to either the intervention or the control group (36 per arm). The intervention group receives a porcine protein supplement twice a day. The control group receives a maltodextrin supplement twice a day. The intervention starts on the first day in the general ward and lasts 42 days (6 weeks). The primary outcome is the between-group difference in physical function at hospital discharge ($t=2$), the end of the intervention ($t=3$, day 42), and the 3-month follow-up ($t=4$) expressed as a composite score consisting of handgrip strength, muscle strength leg, muscle strength arm and exercise capacity. Secondary outcomes encompass physical function, QoL, Activity of daily living (ADL), and plasma amino acids concentrations. Lastly, ICU readmission after ICU discharge, hospital readmission after hospital discharge, and overall survival status will be considered. Linear mixed models will be used to test the treatment effect for the primary and secondary outcome measures.

Discussion: This trial will be the first to investigate porcine protein supplementation compared with carbohydrate supplementation in the post-ICU period aiming to improve functional outcomes of ICU survivors with moderately severe ICU-acquired weakness.

Trial registration: The study has been registered at [ClinicalTrials.gov](https://clinicaltrials.gov). Number: NCT05405764.

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Background

Patients discharged from the Intensive Care Unit (ICU) frequently suffer from Post-Intensive Care Syndrome (PICS).

List of abbreviations

ARDS	Acute Respiratory Stress Syndrome
BCAA	Branched Chain Amino Acids
BIA	Bioelectric impedance analysis
CK	Creatine kinase
CPAx	Chelsea Critical Care Physical Assessment Tool
CRP	C-reactive protein
DNR	Do-not-resuscitate
EQ-5D	EuroQuol 5 Dimension
HADS	Hospital Anxiety and Depression Scale
Hb	Hemoglobin

HHD	hand-held dynamometer
ICU	Intensive Care Unit
LAPAQ	LASA Physical Activity Questionnaire
MMSE	Mini Mental State Examination
MRC-sum	Medical Research Council sum score
NHP-1	Nottingham Health Profile Part 1
PICS	Post-Intensive Care Syndrome
QoL	Quality of life
SF-36	Short Form Health Survey 36
TCST	Time Chair-Stand-Test
TSQ	Trauma Screening Questionnaire
6MWD	6-min walking distance

Around 50% of survivors still suffer from one or more PICS problems up to one year after ICU admission [1]. This syndrome is characterized by muscle weakness and physical disabilities besides neurocognitive and psychological disturbances. Post-ICU patients with acute respiratory distress syndrome (ARDS), for example, still have only 60% of the walking distance of their peers five years after ICU discharge [2]. Muscle weakness following ICU-admission is called ICU-acquired weakness [3]. The clinical diagnosis for ICU-AW is based on a Medical Research Council (MRC)-sum score <48, a MRC-sum <36 defines severe ICU-AW [4].

These functional disabilities frequently prevent living independently after discharge, hindering daily activities' performance or preventing post-ICU patients from returning to work. Consequently, the long-term sequelae of ICU stay confer marked healthcare, societal, economic, and financial effects. Moreover, most importantly, it may reduce patients' quality of life (QoL).

Over the last few years, ICU treatment has shifted from reducing ICU or hospital mortality to a new focus: achieving a better functional outcome for post-ICU patients while maintaining or improving survival performance. The two main factors potentially involved in functional rehabilitation are exercise and optimal nutrition intake.

Recent research has demonstrated that persistent protein and caloric underfeeding among patients who leave the ICU are frequently encountered and that energy and protein requirements are unmet [5,6]. These macronutrient deficiencies will likely affect functional recovery [7]. Adequate nutritional intake is essential, as hypocaloric and low protein feeding could lead to more complications, while, in contrast, an increased intake of energy and proteins during convalescence is associated with improved outcomes [8,9].

There is evidence that increased protein intake is associated with improved outcomes in other patient groups (i.e. in malnourished older adults (>65 years) and elderly with sarcopenia). However, research on protein supplementation during the post-ICU period is limited or absent [10,11]. Patients leaving the ICU suffer from muscle weakness and physical disabilities, similar to sarcopenia as seen in older adults and elderly patients, although some pathophysiological mechanisms involved may differ. Like post-ICU patients, individuals with sarcopenia suffer from loss of skeletal muscle mass and function [12]. These similarities between the elderly, the post-hospitalization populations studied, and the post-ICU population indicate that protein supplementation during the post-ICU period could potentially lead to better recovery.

Protein supplementation after ICU discharge is a promising intervention to improve the long-term functional outcome of post-ICU patients. Increased high-quality protein intake, like porcine protein, results in higher protein absorption, with more substrate availability for protein synthesis [13].

In the present study, we investigate the effect of porcine protein supplementation on functional outcomes after an ICU stay. Porcine

protein is high in arginine and glycine, substrates for creatine synthesis, providing essential building blocks for muscle protein synthesis [14]. Additionally, porcine protein contains branched-chain amino acids (BCAA) such as leucine, isoleucine, and lysine. These BCAA have been shown to exert anabolic effects. For example, leucine affects muscle protein synthesis by stimulating the mTOR pathway. Since the protein supplement is provided in powdered form, it can be easily added to a regular diet in a small volume [15].

As recovery after ICU treatment is not a reversible outcome, a parallel two-arm randomized, blinded controlled trial is designed to study the effect of porcine protein supplementation versus an isocaloric carbohydrate comparator (maltodextrin). The primary objective is to investigate the effect of a porcine protein supplement compared with carbohydrate supplementation in the post-ICU period on the physical function expressed as a composite score of functional tests among patients with moderately severe ICU-acquired weakness. It is hypothesized that protein supplements will result in improved recovery. Results of this first protein supplementation study in post-ICU patients may provide insights for improved care of ICU survivors.

Methods/design

Aims

The aim is to investigate the effect of 6 weeks of porcine protein supplementation compared with isocaloric carbohydrate supplementation in the post-ICU period on functional outcomes in patients with moderately severe ICU-acquired weakness.

Design

A parallel two-arm, randomized, double-blinded placebo-controlled trial. The isocaloric intervention will include six weeks twice daily intake of 22 g porcine protein supplement or 21 g control maltodextrin. Patients are discharged from the ICU department and followed up until three months after hospital discharge. In total, there will be four visits on which measurements will be performed: At baseline, at hospital discharge, at the end of the intervention (6 weeks after ICU discharge), and 3-months follow-up (3 months after hospital discharge). Each visit consists of multiple measurements, including a physiotherapist's physical function evaluation, blood sampling, questionnaires, and a body composition measurement. The study flow is depicted in Fig. 1. Fig. 2 shows a schedule of the enrollment, intervention, and measurements.

Participants

The study population comprises 72 adult patients with moderately severe ICU-acquired weakness discharged to a general ward

after an ICU stay of at least 72 h at Gelderse Vallei Hospital, Ede, The Netherlands. Patients can be enrolled in the study if they fulfil all the inclusion criteria and none of the exclusion criteria. The inclusion and exclusion are depicted in Table 1.

Randomization and blinding

If a patient meets all the inclusion and exclusion criteria, and consent is obtained, the patient will be randomly assigned in a 1:1 ratio to either the intervention or the control group. Nine random blocks of 8 (4:4) randomization will be performed to assign patients to both groups equally. A randomization list has been made with an online random number generator. Subsequently, closed opaque envelopes will be used to randomize each patient. Randomization will be performed after obtaining consent. Since the randomization list has been prepared in advance, the randomization process can be performed by the researcher and attending physician. The researcher is responsible for correct blinded group allocation. Since it is a double-blinded study, patients, physicians, dieticians, and outcome assessors are blinded for the assigned intervention. All

powders are packaged in identical sachets and sealed before delivery to the hospital.

Setting

The study will be conducted at Gelderse Vallei Hospital in Ede, The Netherlands. After hospital discharge, patients will be asked to return for the remaining study visits.

Interventions

Patients will be assigned to one of the two groups:

- The intervention group will receive a 22 g porcine protein supplement (20 g protein, 80 kcal) twice daily. Since the supplement also contains some remaining moisture and minerals/salts, which results in a slightly higher amount (22 g instead of 20 g) that is needed for the intervention. The porcine protein contains a wide range of amino acids; it contains almost all essential amino acids, except for tryptophan.

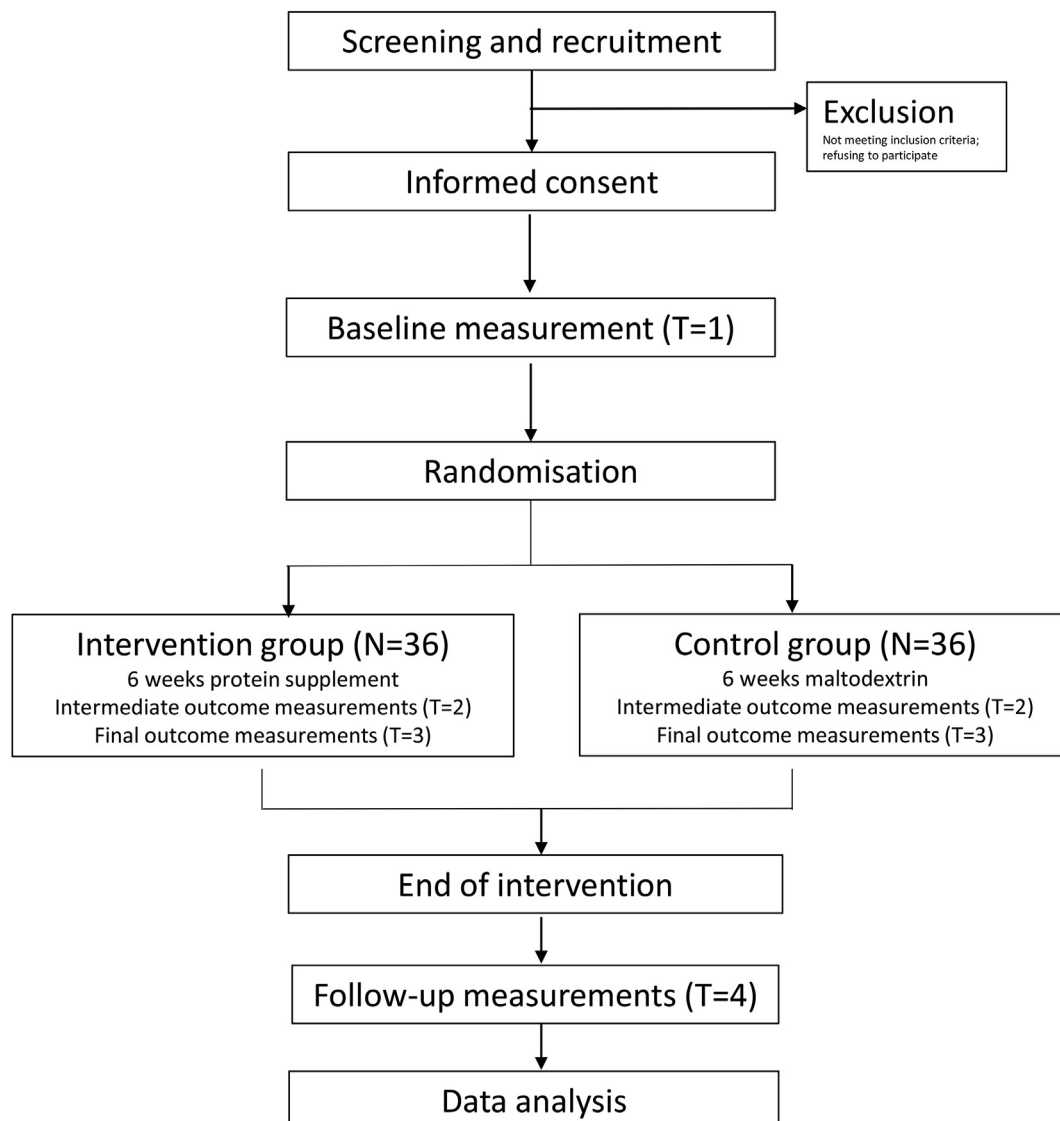


Fig. 1. Diagram of study flow.

	T=1		T=2	T=3	T=4
	ICU discharge	General ward	Hospital discharge	End of the intervention = end of week 6	3 month follow-up = 3 months after hospital discharge
Enrolment					
Screening	X				
Informed consent	X				
Baseline characteristics	X				
Randomization	X				
Intervention					
Intake supplements		●		●	
Questionnaires	X		X	X	X
LAPAQ				X	X
Functional tests	X		X	X	X
BIA	X		X	X	X
Barthel	X			X	
Rockwood Clinical Frailty Score	X			X	
Plasma AA profile	X			X	
Lab	X		X	X	X
24h recall (week 4,6,8,10)		●			●
ICU readmission after ICU discharge		●			●
Hospital readmission after hospital discharge			●		●
Overall survival status		●			●

Fig. 2. Schedule of the enrollment, interventions, and measurements.

- The control group will receive twice-daily a 21 g maltodextrin (0 g protein, 82 kcal).

The patients receive an absolute amount of protein/maltodextrin, the dosage is not based on kg bodyweight. Both products are provided in a powdered form. The powders have similar appearances, and the doses provided in the study are isocaloric. Both powders are freely soluble so that they can be dissolved in liquids. Multiple usage forms are present for taking the supplement; patients can combine the study products with various food products. However, it is essential that they do not heat the product itself and not add it to a heated product. Patients should not only mix the supplements with water to guarantee blinding.

Patients will be asked to take one supplement in the morning (breakfast) and the other in the afternoon (lunch) as research has shown that these meals have, in general, too low protein content in the elderly [16]. All patients will receive the same routine care concerning physical activity.

Visits

There are four study visits, starting on the day of ICU discharge. Patients must perform several physical function tests with the physiotherapist during these visits. Additionally, they must fill in questionnaires on cognitive status, mental wellbeing, health status, quality of life and physical activity. Moreover, body composition will be measured, blood samples will be taken, and the Barthel score and Rockwood Clinical Frailty Scale will be determined. Figure 3 shows an overview and planning of the study visits. At T=3 and T=4, the questionnaires, except for the Mini-Mental State Examination (MMSE), can be done at home.

Functional tests

Several tests will be performed under the supervision of a physiotherapist; the handgrip strength of the dominant hand will

Table 1
Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion criteria
<ul style="list-style-type: none"> • Age ≥ 18 years • Living at home before hospital admission • Minimum ICU stay of 72 h • Informed consent 	<ul style="list-style-type: none"> • MRC sum score ≤ 24 or ≥ 48 at ICU discharge • Barthel Index < 14 before ICU admission • Chronic home ventilation • Mitochondrial or muscle disease or pareses • Serum creatinine > 173 $\mu\text{mol/l}$ (renal dysfunction) • Treatment limitations: do-not-resuscitate (DNR), no ICU readmission or palliative care • Inclusion in another intervention trial since ICU admission • Intolerance or allergy (for study products) • People living in a nursing home before hospital admission • Chronic Organizing Pneumonia or Pulmonary Interstitial Fibrosis • Inflammatory Bowel Disease • Diabetes Mellitus pharmaceutical medication at ICU admission • Underlying disease in which, in the eyes of the attending physician, the protein or carbohydrate supplement could form a risk for the patient • Pregnancy

be measured with the Jamar dynamometer. Percentages of predicted values will be calculated using the reference values of Werle et al. [17].

Arm and leg muscle strength will be measured with a Handheld Dynamometer: the Microfet II [18]. These values are also expressed as a percentage of predicted values.

Exercise tolerance will be measured by a 6-min walking distance (6 MWD). According to Gibbons et al. [19], values will be compared to predicted values.

The lower extremity function will be tested with the Time Chair-Stand-Test (TCST) [20].

Furthermore, Medical Research Council (MRC)-sum score will be measured. This is an ordinal score that evaluates global muscle strength [21]. The strength of six muscle groups (shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension, and ankle dorsiflexion) is evaluated manually on both sides using the MRC scale. All individual scores combined give the sum score.

The Chelsea Critical Care Physical Assessment Tool (CPAx) allows holistic assessment to grading physical morbidity in the critical care population [22]. It is a numeric and pictorial composite of 10 commonly assessed components of physical function: respiratory function, cough, bed mobility, supine to sitting on the edge of the bed, dynamic sitting, sit to stand, standing balance, transferring from bed to chair, stepping, and grip strength.

Questionnaires

As multiple mental, cognitive, and other factors can be related to our study outcomes, patients must fill in several questionnaires during the four study visits.

These include the MMSE, Short Form Health Survey-36 (SF-36), EuroQuol 5 Dimension (EQ-5D), Nottingham Health Profile Part 1 (NHP-1), Trauma Screening Questionnaire (TSQ), LASA Physical Activity Questionnaire (LAPAQ) and Hospital Anxiety and Depression Scale (HADS) (see Table 2). The questionnaires must be filled out in this consecutive fixed order. The order of the questionnaires is based on the brain's functioning (from "now" to "4 weeks ago").

Blood samples

First, to guarantee safety, blood samples will be taken to analyze levels of creatinine, urea, Creatine kinase (CK), glucose, Haemoglobin (Hb), and C-reactive protein (CRP). At T_1 , these laboratory

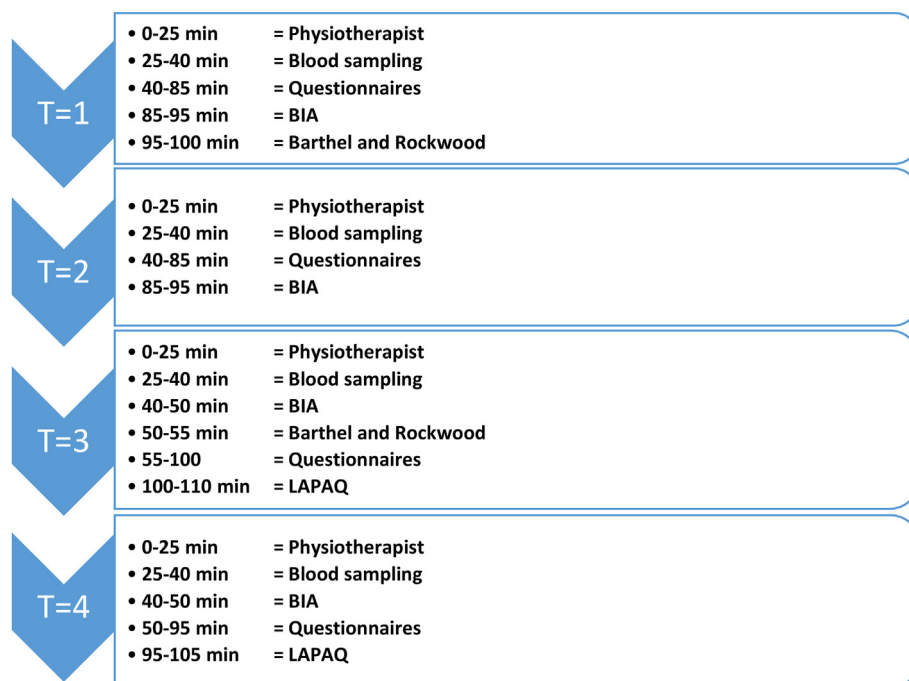
**Fig. 3.** Overview and planning of the study visits.

Table 2
Overview of the questionnaires; *only T₁=3 and T₁=4.

Questionnaire	Outcome
MMSE [21]	Cognitive function
SF-36 [22]	Patient-reported health status
EQ-5D [23]	Generic health status
NHP-1 [24]	Subjective health status
TSQ [25]	Traumatic stress
LAPAQ* [26]	Physical activity
HADS [27]	Anxiety and depression

parameters are baseline routine. At T₁=2, T₁=3 and T₁=4, three additional tubes are collected per study day to analyze these safety parameters. Second, at T₁=1 and T₁=3, one additional blood sample will be taken per study day to analyze the plasma amino acid composition. To observe whether the difference in protein intake between groups leads to a difference in plasma amino acid availability, essential for protein synthesis.

Body composition measurement

Body composition will be measured using bioimpedance analysis (Inbody S10 Body Composition Analyser®). The bioelectrical impedance analysis (BIA) can be performed in a supine or sitting position. Electrodes will be placed on both thumbs, middle fingers, and ankles.

Barthel index

The Barthel score measures the Activity of Daily Living (ADL). The Barthel Index consists of 10 items and focuses on functional independence [23]. The higher the score, the more independent.

Rockwood Clinical Frailty scale

The Rockwood Clinical Frailty Score is a tool to measure the level of fitness or frailty. It is a 7-point scale; the higher the score, the higher the frailty [24].

Nutritional intake

The nutritional intake (mostly energy and protein intake) of the patients post-ICU is estimated based on information from 24 h recalls. These will be completed in weeks 4 and 6 (during the intervention) and weeks 8 and 10 (post-intervention period). The 24 h recall will be combined with dietary food records, used as a memory aid. Patients must record their intake including meals, snacks and beverages. The 24 h recall will be carried out by a trained researcher or a dietician. Data from the recall will be entered in Compl-eat (Department of Human Nutrition, Wageningen University), a validated program that calculates nutritional intake based on the Dutch Food Composition Table (NEVO) for various nutrients. For each subject the protein intake in grams per day and energy intake in kilocalories per day will be calculated for both the intervention period and the post-intervention period. These nutrition data are essential to see whether the supplements lead to an increased protein intake and do not reduce the appetite for regular oral food intake. There is no need to monitor the nutritional intake daily, this will be too burdensome for the patients in the recovery period. As part of standard care, patients in both groups that need continuation of nutritional care from a dietician will receive this after hospital discharge. The nutritional therapy form the study patients will not differ from the other patients.

Cumulative protein/energy deficit and mean protein/energy deficit during the ICU stay will also be gathered to acquire

information on nutritional intake from ICU admission until ICU discharge.

Primary outcome

The primary outcome is the between-group difference in physical function at hospital discharge (t₁=2), the end of the intervention (t₁=3, day 42), and the 3-months follow-up (t₁=4) expressed as a composite score consisting of handgrip strength (Jamar dynamometer), muscle strength leg (hand-held dynamometer (HHD) musculus quadriceps femoris), muscle strength arm (HHD musculus biceps brachii) and exercise capacity (6 MWD).

Secondary outcomes

Secondary outcomes of this study include the separate physical function parameters (handgrip strength, arm strength, leg strength, 6 MWD, TCST) at the end of the intervention (t₁=3). Furthermore, CPAX will be determined at T₁=2 and MRC-sum at T₁=2, T₁=3, and T₁=4. QoL (as assessed with the EQ-5D) and body composition (measured with an Inbody S10 Body Composition Analyser® (Seoul, Korea)) will be analyzed at T₁=2, T₁=3, and T₁=4. Furthermore, the Barthel-Index, the Rockwood Clinical Frailty Scale, and plasma amino acid concentrations will only be analyzed at T₁=3. Finally, ICU readmission after ICU discharge, hospital readmission after hospital discharge, and overall survival status will be monitored throughout the study.

Sample size

A basic power calculation is complicated because the effect size is not known. Therefore, we based our sample size on estimated values. The study is powered based on unpublished data from the outpatient clinic on this study endpoint (Oral communication: Bert Strookappe). The control group's mean endpoint was estimated at 210 with an SD of 39. An improvement of 14% compared with the control group is expected, leading to an intervention group's mean endpoint of 238.

Considering a type I error rate of α ;=0.05 and a type II error rate of β ;=0.20 (statistical power;=80%), 60 patients are needed for the study to detect a significant difference. A study by Hermans et al. shows that the expected dropout rate in patients with an ICU MRC-sum score between 24 and 47 is around 15% during 90 days of follow-up [25]. Therefore, the aim is to include 72 patients in this study, 36 patients per study group.

Statistical analysis

Statistical analysis will be performed using SPSS 27. All study results will be analyzed using appropriate statistical tests and primarily based on the intention-to-treat principle. A per-protocol analysis will be performed among all patients with a minimum mean intake of 50% of the study products. P-values of <0.05 will be considered statistically significant.

A linear mixed model will be used to calculate the treatment effect for the primary and secondary endpoints. In this model, the treatment will be added as a fixed effect. Moreover, because repeated measurements at the different time points are clustered within patients, patients will be added as a random effect. Time will be added as a categorical variable with a treatment \times time interaction to observe whether there is a difference in treatment over time. Using this model, a crude analysis will be performed.

Subsequently, to determine whether different factors influence this effect over time, these factors will be added to the mixed models. The models will be built to adjust for known relevant

variables that may affect the outcome. The measurements' exact date (days after ICU discharge) will be registered, and this will be added to the model as a covariate. Adjustments will be performed for baseline characteristics and potential confounders: BMI (cut-off 27), age (cut-off 65 years), sex, NRS 2002 (cut-off <4 vs > 4), mNUTRIC (cut-off <4 and >4), APACHE-II, baseline composite score.

For the endpoint mortality, survival curves for both study groups will be made using the Kaplan Meier method and tested with a log-rank test. Additionally, Cox regression analysis will be performed to adjust for relevant covariates.

Data management and data protection

Data will be handled confidentially through coding. Patients will receive a unique code consisting of 3 numbers. Personal data will be stored in a digital database on an intern network, protected by a password. Data will be kept until 15 years after the end of the study. The investigator will ensure that patient's identity and information are not publicly available.

All study data will be stored in a CRF, which is created with Castor. The unique code will be used for the patients. Other study data will be stored in a locked environment in the hospital.

Adverse events

No severe harm is expected from the study products. However, all adverse events will be recorded and reported to the medical ethical committee. Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to [the investigational product/trial procedure/the experimental intervention]. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

Patients are asked to report their complaints such as diarrhea, vomiting, skin rash, lack of hunger and stomach ulcer, nausea or ischemia on a specific form. Researchers will ask for these complaints regularly during the hospital stay and during the study visits.

Discussion

The CONFUCIUS trial is the first study on protein supplementation post-ICU in patients with moderately severe ICU-acquired weakness.

Patients discharged from the ICU frequently suffer from ICU-acquired weakness, a significant PICS domain. This weakness is induced by muscle mass and function loss due to immobilization and inflammation during critical illness: ICU patients with MODS may lose up to 1 kg of muscle mass per day in the first ten days of ICU treatment [26].

tWhile the period after ICU discharge may be a crucial phase for nutrition rehabilitation, energy and protein intake is often <50% of the requirements with oral nutrition only [27]. These deficits must likely be replenished because it has been shown that an increase in energy and protein intake is associated with decreased mortality, and better feeding in the ICU phase is associated with less ICU-acquired weakness [8,28]. Previous studies have already investigated the effect of protein supplementation in other groups; for example, the NOURISH study showed that high protein (40 g) oral nutrition supplements decreased mortality compared with placebo and improved indices of nutritional status during hospital discharge follow-up in malnourished older adults (>65 years) [10]. Additionally, another study showed that protein supplementation improves body composition (muscle mass), muscle strength, and function in the elderly [11]. While protein

supplementation is expected to yield improvements in functional recovery in the post-ICU period, actual studies on the post-ICU period are lacking.

Therefore, this will be the first study to investigate this intervention. To balance the caloric effect of the protein intervention, the non-protein control product will be isocaloric. Maltodextrin powder seems to be the best control product as it is a carbohydrate that provides an equivalent energy dose in a similar volume.

Previous studies often investigated the effect of proteins in combination with exercise [29]. However, the benefits of exercise may be limited in this post-ICU patient group. Both study groups receive routine care, including physical activity, starting from ICU discharge. The current study will focus on the additional effect of protein supplementation twice daily. No specific exercise intervention will be done, although general recommendations on the importance of exercise will be provided.

Patients discharged from the ICU suffer from mild to severe muscle weakness. This study will select a more homogeneous group of patients with an intermediate muscle weakness severity (excluding MRC-sum scores <24 or >48 at ICU discharge). It is expected that in this specific group, the effects of the intervention should be visible.

Considerations

Since this is the first trial to investigate the effect of protein supplementation in the post-ICU period, the optimal dose for protein supplementation is still unknown. Based on the Nourish study, 40 g of protein per day will be used [10]. Assuming that the patients are likely to have a dietary protein deficit, it is expected that every supplement will elicit a response. The protein dose used in this study will substantially contribute to the daily protein target (expressed in g/kg BW/day), depending on patient requirements according to dieticians' judgement, combined with the regular diet. The porcine protein supplement is available in powdered form and could be easily added to the diet.

Another consideration is that the second measurement is at hospital discharge. This visit depends on the patient's hospital stay duration and may be unbalanced when comparing groups. Therefore, these measurements are secondary endpoints, and the primary endpoint is at the end of the intervention (T₃=3, identical for both study groups). From T₂=2, patients leave the hospital, so we must rely on the patients' compliance. To assess data about supplement compliance, a compliance calendar showing all intervention days will be provided to the patients. Patients will mark off each time the supplement is consumed, and they must write down how they take the supplement (e.g. with orange juice or apple juice) and at what time. A record list will be provided to the patients to write down all the information needed. If the patient is not able to take the supplement, they must mention the reason. Patients must take all the empty sachets and the remaining sachets to the 3-months follow-up visit. These will also be counted. Furthermore, patients will be closely monitored by the study team by a weekly phone call.

In conclusion, the Confucius trial is the first randomized controlled study designed to evaluate the effects of protein supplementation compared with an isocaloric carbohydrate supplement in the post-ICU phase. It will provide insights into nutrition therapy for ICU survivors to improve functional outcomes and QoL.

Trial status

The recruitment of the study started in April 2022. Completion is expected for August 2024. Protocol Version 5, February 2022.

Ethics approval and consent to participate

The medical ethical committee Oost-Nederland has approved this study with number NL79158.091.21. All study participants will provide informed consent before the study intervention.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Authors' contributions

Yente Florine Niké Boelens contributed to the conception of the research and writing of the manuscript. Bert Strookappe contributed to the conception of the research and revision of the final manuscript. Marco Mensink contributed to the conception of the research and revision of the final manuscript. Emmelyne Vasse contributed to the conception of the research. Arthur Raymond Hubert van Zanten contributed to the conception of the research and revision of the final manuscript and has the principal investigator's role.

Declaration of Competing Interest

The authors declare no competing interests.

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Not applicable.

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