JRMO Research Protocol for Interventional Studies

Full Title	Prevention of acute muscle wasting in critically ill adults using enteral ketogenic feeding: Alternative Substrates In the Critically Ill Subject II (ASICS–II) trial
Short Title	ASICS-II Trial
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List of participating sites: For a list of participating sites please refer to the IRAS application.

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The Sponsor and funders have not played, nor will play a role in the study design, conduct, data analysis and interpretation, manuscript writing, and/or dissemination of results.

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1. Contents

2. Glossary

30STS	30-Second Sit-To-Stand test
AE	Adverse Event
BIA	Bioimpedance Analysis
CI	Chief Investigator
CRF	Case Report Form
DMEC	Data Monitoring and Ethics Committee
GCP	Good Clinical Practice
GRV	Gastric Residual Volume
HRA	Health Research Authority
HRQol	Health Related Quality of Life
ICU	Intensive Care Unit
IRAS	Integrated Research Application System
ISF	Investigator Site File
JRMO	Joint Research Management Office
MPB	Muscle Protein Breakdown
MPS	Muscle Protein Synthesis
NG	Nasogastric
PCTU	Pragmatic Clinical Trials Unit
PI	Principal Investigator
PIS	Patient Information Sheet
R&D	NHS Trust R&D Department
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RF_{CSA}	Rectus Femoris cross-sectional area
SAE	Serious Adverse Event
SOFA	Sequential Organ Failure Assessment
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee
USS	Ultrasound Scan
ATP	Adenosine Triphosphate
TCA	Tri-Carboxylic Acid

3. Signature page

Chief Investigator Agreement

The study as detailed within this research protocol will be conducted in accordance with the principles of Good Clinical Practice, the UK Policy Framework for Health and Social Care Research, the Declaration of Helsinki, and the current regulatory requirements, including the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and all subsequent amendments. I delegate responsibility for the statistical analysis and oversight to a qualified statistician (see declaration below).

Chief Investigator: Zudin Puthucheary

Signature: 

Zudin Puthucheary

Digitally signed by Zudin Puthucheary
Date: 2025.08.27 10:48:12 +01'00'

Date: 03/06/25

Statistician's Agreement

The study as detailed within this research protocol plan will be conducted in accordance with the principles of Good Clinical Practice, the UK Policy Framework for Health and Social Care Research, the Declaration of Helsinki, and the current regulatory requirements, including the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and all subsequent amendments, and ICH E9 - Statistical principles for Clinical Trials and ICH E10 - Choice of Control Groups.

I take responsibility for ensuring the statistical work in this protocol is accurate, and for the statistical analysis and oversight of this study.

Statistician name: Tom Hamborg

Signature:

Date:

Principal Investigator Agreement

The clinical study as detailed within this research protocol **(version 2.0, dated 22/04/25)**, or any subsequent amendments, involves the use of an investigational medicinal product and will be conducted in accordance with the UK Policy Framework for Health and Social Care Research , the World Medical Association Declaration of Helsinki (1996), Principles of ICH-GCP, and the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and any subsequent amendments of the clinical trial regulations.

Principal Investigator:

NHS site:

Signature:

Date:

4. Summary and synopsis

Short title	ASICS-II
Study design	Double-blind randomised controlled superiority trial
Objectives	**Primary objective** • To assess and draw inference on the efficacy of a 10-day ketogenic enteral feeding regimen compared with standard enteral feeding in increasing the number of sit-to-stand repetitions performed in 30 seconds, 30 days after randomisation in critically ill patients. **Secondary objectives** • To assess and draw inference on the difference between the 10-day ketogenic enteral feeding regimen and standard enteral feeding for the Core Outcome Set measures of functional recovery (mortality, SF-36, Barthel Index) 30 days after randomisation. • To provide safety data on the use of a 10-day ketogenic enteral feeding regimen in critically ill patients compared with standard enteral feeding during the intervention period. **Mechanistic objectives** • To collect routinely measured daily serum urea and creatinine data during the 10-day intervention period as biochemical markers of catabolism. • To examine alterations in the causal pathway between trial arms (differential ketone and amino acid flux, urea cycle flux and tricarboxylic acid cycle intermediate generation) using serum metabolomics from samples on day 1 and 7 post-randomisation. • To confirm the induction of ketosis at seven days post-randomisation.
Number of participants	282 patients
Inclusion and exclusion criteria	**Inclusion criteria** Adults (≥18 years) admitted to critical care units who are EITHER: • Hospitalised with acute respiratory failure (PaO_2/FiO_2 ratio of ≤39.9 KPa)* AND

	• Expected to require advanced respiratory support (High-Flow Nasal Oxygen, non-invasive or invasive ventilation for >48 hours)[$] AND • C-reactive Protein ≥75 mg/l indicating systemic inflammation* AND • Nasogastric feeding planned for >48 hours[$] OR • In multi-organ failure (Sequential Organ Failure Assessment Score [SOFA] Score ≥2 in two or more domains)* AND • Nasogastric feeding planned for >48 hours[$] **Exclusion criteria** • Pre-existing inability to perform a sit-to-stand test (e.g., significant cognitive impairments that would impact their ability to engage in physical activity testing, Clinical Frailty score of ≥6, amputations, acute or chronic disability expected to preclude the sit-to-stand test at 30 days. amongst others)[$] • New (pre-randomisation) inability to perform a sit-to-stand test. e.g., Primary neuromyopathy, acute intracerebral pathology, new or existing weight bearing restrictions or new neurological impairment amongst others)[$] • Deemed unlikely to survive to 30 days OR presence of a treatment limitation[$] • Contraindications to nasogastric feeding^ • Clinical need for specialist feeds^ • Patients with known inborn errors of metabolism^ * Most recent recording from the first 24 hours of hospital admission [$] as confirmed by the treating clinician ^ absence of these criteria in the medical notes will be considered to indicate no concern
Statistical methodology and analysis	The primary outcome analysis is a survivor analysis. The treatment effect is the difference in the mean 30-Second Sit-To-Stand among participants who survive to 30 days follow-up under intervention and control. The treatment effect will be estimated using a linear mixed model adjusted for site (random effect), age and functional co-morbidity index. The main analyses of primary and secondary outcomes will be conducted using multiple imputation under a missing at random assumption for those

	participants lost to follow-up. Controlled multiple imputation analysis using a δ-based imputation approach will be performed as sensitivity analyses. We will estimate the survivor average causal effect and assess consistency with the main primary outcome treatment effect estimate.
Study duration	48 months

5. Introduction

Our overarching aim is to prevent muscle wasting which affects the majority of the 16000 patients admitted daily as emergencies to NHS hospitals in England, helping them regain the quality of life and physical independence they enjoyed before hospital admission.[1] Every month 50000 patients stay for >7 days in hospital, losing muscle mass, developing new physical impairment and need for social care support, delaying their discharge.[1-4] The most seriously ill patients, those in intensive care, lose muscle rapidly. A 70-kilogram patient in intensive care will lose 1-2 kilograms of muscle every day.[5] Of the 120,000 patients a year that survive critical illness, 98% develop physical functioning impairments, resulting in loss of physical independence.[6-8] At 12 months, 70% of survivors have substantial functional limitations and 30% remain carer-dependent.[8,9] Exercise can only increase or maintain muscle mass in conjunction with effective nutrition.[10,11] Many high-quality trials have failed to yield an intervention that improves physical independence.[12,13] The lack of successful interventions is felt by patients. One of our PPI members stated in regard to our planned trial, "*I wish there was something like this in place rather than throwing endless prescription calorie drinks at me*". One third of previously employed critically ill patients do not return to work within five years.[14] The estimated UK annual excess cost of muscle weakness across health and social care is £25 billion per year.[15] While NICE identified this as a growing public health issue, no specific interventions are recommended due to lack of efficacy data.[16] Patients ranked prevention of muscle wasting in the top three priorities for critical care research in the James Lind Alliance research priority setting exercise.

Carbohydrates, fat or protein cannot maintain muscle mass in critically ill patients

Muscle mass is maintained by a balance between synthesis and breakdown.[17] Muscle protein synthesis is a very highly energy dependent process and is low in critically ill patients, and does not respond to increased protein delivery.[5,18] Muscle protein breakdown is increased in an attempt to use protein for energy.[5,19] Current medical nutrition therapy is ineffective as carbohydrates, fats and protein cannot be utilised effectively to produce energy because of tissue inflammation and hypoxia, leading to rapid muscle wasting. [20-22]

Ketogenic feeds may help patients regain independence by maintaining muscle mass

Ketogenic feeding involves stimulating hepatic synthesis of ketone bodies. Hepatic metabolism of medium-chain triglycerides (MCTs) can yield ketone bodies such as beta-hydroxybutyrate and acetoacetate and is not affected by hypoxia or inflammation.[23]

Ketogenic feeding represents a frame shift in critical care nutritional research. Ketone derived energy would increase muscle protein synthesis and decrease muscle protein breakdown. Ketones are used for energy in high-intensity exercise and starvation, sparing muscle.[24-27]. Ketogenic diets have been used to treat epilepsy and are being investigated for use in traumatic brain injury, neurodegenerative diseases, non-alcoholic fatty liver disease, diabetes and heart failure.[28-33]

A proof-of-concept trial demonstrated safety, feasibility and a signal for efficacy

We performed a randomised controlled trial to determine the feasibility and safety of delivering a ketogenic enteral feed in critically ill patients as step-change intervention to prevent muscle wasting and loss of physical independence.[34] This was necessary for a number of reasons. Ketoacidosis might occur if ketones were not metabolised, exacerbating pre-existing systemic and cellular acidosis that carries a mortality risk to critically ill patients. Ketogenic diets minimise exogenous glucose delivery, which might predispose patients to hypoglycaemia, which is harmful to patients[35]. Lastly, a ketogenic high lipid feed might increase the risk of vomiting (and therefore pulmonary aspiration), diarrhoea and pancreatitis. [36]

Ketosis was achieved within 48 hours and sustained for the 10-day intervention period. Ketogenic feeding was demonstrated to be safe. Ketogenic feeding resulted in less hypoglycemia (0.0% vs. 1.6% events) and hyperglycemia (26.9% vs. 57.5% events), lower glucose co-efficient of variation (9.4% vs. 14.8%), and lower cumulative insulin use (0IU (IQR 0-16) vs.78 IU (IQR 0-412)). The trial process was considered acceptable and feasible. A mean score of 8/10 (with 10 scored as the most positive response) was obtained for the question '*How keen would you be to work on another similar study*?'. A signal that ketogenic feeding may reduce muscle wasting was seen in the metabolomic data (decreased muscle protein breakdown) and clinical markers of catabolism such as urea were lower in the ketogenic arm by day eight and persisted until the end of the study period (8.7 (95%CI 6.4-19) vs. 12(95%CI 10-19), as was the Urea-to-Creatinine ratio (117 (95%CI 93-206) vs. 168 (95%CI 102-235). Lastly the median Chelsea Critical Care Physical Assessment score at hospital discharge was higher in the ketogenic feeding arm ((34 (95%CI 22-45) vs. 25 (95%CI 8-46).

6. Risks and benefits

6.1 Summary of potential risks

Participants allocated to receiving the ketogenic feed could be susceptible to ketoacidosis if the ketones are not metabolised. This could exacerbate pre-existing systemic and cellular acidosis that carries a mortality risk to critically ill patients. There is a possibility that ketogenic diets can also minimise exogenous glucose delivery, predisposing patients to hypoglycaemia, which is harmful.[35] Lastly, ketogenic enteral feeds with a high lipid content could increase the risk of vomiting (and therefore pulmonary aspiration), and diarrhoea. However data from previously studies including our recently published trial (ASICS) does not support concerns of acidosis, hypoglycaemia or vomiting, indicating that the feed is safe.[34,37-45] It may be that ketogenic feeding reduces glucose variability and hypoglycaemia, decreasing harm to patients, an observation also seen in other ketogenic feeding trials in the critically ill.[34,46,47] The signal for increased diarrhoea is unclear, as diarrhoea is extremely common in critically ill patients.[36]

6.2 Summary of potential benefits

The signal for efficacy is consistent across carbohydrate, lipid and amino acid metabolism, biochemical signatures of muscle protein homeostasis and clinical physical function. If this is confirmed in this trial, the novel ketogenic enteral feed will decrease muscle wasting in the sickest of patients and may mitigate the muscle loss seen in early critical illness, providing a new treatment to improve function and well-being in critical care survivors. Further, if the decrease in hypoglycaemia and insulin therapy is confirmed, ketogenic feeding may represent a lower risk of harm to patients than conventional enteral feeding.

7. Trial objectives, endpoints and estimands

7.1 Primary objective

- To assess and draw inference on the efficacy of a 10-day ketogenic enteral feeding compared with standard enteral feeding in increasing the number of sit-to-stand repetitions performed in 30 seconds, 30 days after randomisation in critically ill patients.

7.2 Secondary objectives

- To assess and draw inference on the difference between a 10-day ketogenic enteral feeding regimen compared with standard enteral feeding for the Core Outcome Set

measures of functional recovery (mortality, SF-36, Barthel Index) 30 days after randomisation.

- To provide safety data on the use of a 10-day ketogenic enteral feeding regimen compared with standard enteral feeding during the 10-day intervention period in critically ill patients.

7.3 Mechanistic objectives

- To collect routinely measured daily serum urea and creatinine data during the 10-day intervention period as biochemical markers of catabolism.
- To examine alterations in the causal pathway between arms (differential ketone and amino acid flux, urea cycle flux and tricarboxylic acid cycle intermediate generation) using serum metabolomics from samples on day 1 and 7 post-randomisation.
- To confirm the induction of ketosis by the 10-day ketogenic enteral feeding regimen at seven days post randomisation.

7.4 Primary outcome measure

- The number of sit-to-stand repetitions performed in 30 seconds 30 days after randomisation. [48]

7.5 Secondary outcome measures

- Core Outcome Set measures: [48]
    - All-cause mortality within 30 days of randomisation
    - All-cause mortality within 90 days of randomisation
    - Barthel Index at 30 days after randomisation
    - Short Form 36 quality of life questionnaire at 90 days after randomisation
- PICUPS or PICUPS community questionnaire Index at 30 days after randomisation

7.6 Safety outcome measures

- New (post initiation of intervention) metabolic acidosis (Base Excess of >4 mEq/l) not in keeping with the clinical condition, in the opinion of the treating clinician within 10 days of randomisation.
- Hypoglycaemia episodes not in keeping with the clinical condition (normoglycaemia defined as 4.0-10.0 mmol/l), assessed from routine blood monitoring within 10 days from randomisation.

- Hyperglycaemia episodes not in keeping with the clinical condition (normoglycaemia defined as 4.0-10.0 mmol/l) assessed from routine blood monitoring within 10 days from randomisation.
- Days when an episode of diarrhoea (defined as a Bristol School Score ≥5) is recorded on nursing observation charts during the first 10 days from randomisation.
- Days where an episode of vomiting is recorded on nursing observation charts during the first 10 days from randomisation.
- Nausea defined as when an anti-emetic is given for patient-reported nausea assessed daily during the first 10 days from randomisation.

7.7 Mechanistic outcome measures

- Daily serum urea and creatinine concentrations, for the first 10 days after randomisation.
- Plasma metabolomic profiling at day one and day seven after randomisation.
- Ketone body generation at day one and day seven after randomisation.

7.8 Estimands

7.8.1 Primary outcome estimand

Amongst hospitalised, critically ill, adult patients at risk of acute muscle wasting who do not die and do not experience limp amputation or a intracerebral event within 30 days of treatment assignment, what is mean difference in functional ability, as measured by the 30-second sit-to-stand test, 30 days after treatment assignment between 10-day ketogenic enteral feeding regimen compared with standard enteral feeding regardless of whether alternative treatment(s), rescue medication(s), incorrect treatment dose, or the opposing treatment were received or adverse event or further illness experienced. The objective is to demonstrate statistical superiority of ketogenic enteral feeding relative to standard feeding for this estimand.

Table. Estimand Framework (Primary Outcome)

Domain	Definition	Description
Target population	Patients targeted by the research objective	Adults ≥18 years old, who don't die or experience limp amputation or a intracerebral event within 30 days of treatment assignment, admitted to hospital critical care units with: • Acute respiratory failure during first 24 hours of ICU admission; • Expected to require advanced respiratory support for >48 hours; • Evidence of inflammation, and; • Nasogastric feeding planned for >48 hours **OR** • Multi-organ failure during first 24 hours after ICU admission, and; • Nasogastric feeding planned for >48 hours
Treatment conditions	Experimental and control interventions administered to patients in different trial arms	**Intervention arm** Ketogenic enteral feeding (75% Fats, 20% Protein, & 5% Carbohydrates) administered via nasogastric tube for 10 days unless no longer indicated **Control arm** Standard enteral feeding administered hours in critical care

			via nasogastric tube for 10 days unless no longer indicated
Endpoint	Outcome variable to be measured for each patient		30-second Sit-to-Stand test (i.e., the number of sit-to-stand repetitions performed in 30 seconds) 30 days after treatment assignment
Population-level summary measure	Quantitative measure used to compare and summarise difference between trial arms		Mean difference between trial arms
Intercurrent events	Post-randomisation events that affect that measurement, interpretation, and/or existence of an outcome		<u>Strategies to account for intercurrent events</u>
	• Develops adverse event & discontinues assigned treatment	Outcome-modifying event	Treatment policy
	• Receives alternative treatment and continues assigned treatment	Outcome-modifying event	Treatment policy
	• Takes rescue medication **and** discontinues assigned treatment	Outcome modifying event	Treatment policy
	• Discontinuing intervention or control treatment before end of 10-day duration	Outcome-modifying event	Treatment policy
	• Randomised treatment not received or opposing treatment received (i.e., opposite to the trial arm to which the participant was randomly allocated)	Outcome-modifying event	Treatment policy

•		
• New events that prevent delivery of the treatment (i.e., feeding): - new indication for parenteral nutrition - patient becomes nil per oral - other	Outcome-modifying events	Treatment policy
• Receives wrong dose of intervention	Outcome-modifying event	Treatment policy

7.8.2 Survivor average causal effect estimand

The survivor average causal effect (SACE) analysis is a sensitivity analysis for the primary outcome analysis estimating the average treatment effect in those patients who did not and would not die.[49] Outcome truncating intercurrent events will be handled using a principal stratum intercurrent event strategy articulated in detail in the statistical analysis plan.

Table. Estimand Framework (SACE)

Domain	Definition	Description
Target population	Patients targeted by the research objective	Adults ≥18 years old admitted to hospital critical care units with • Acute respiratory failure during first 24 hours of ICU admission; • Expected to require advanced respiratory support for >48 hours;

		• Evidence of inflammation, and; • Nasogastric feeding planned for >48 hours **OR** • Multi-organ failure during first 24 hours after ICU admission, and; • Nasogastric feeding planned for >48 hours
Treatment conditions	Experimental and control interventions administered to patients in different trial arms	**Intervention arm** Ketogenic enteral feeding (75% Fats, 20% Protein, & 5% Carbohydrates) administered via nasogastric tube for 10 days unless no longer indicated **Control arm** Standard enteral feeding administered via nasogastric tube for 10 days unless no longer indicated
Endpoint	Outcome variable to be measured for each patient	30-second Sit-to-Stand test (i.e., the number of sit-to-stand repetitions performed in 30 seconds) 30 days after treatment assignment
Population-level summary measure	Quantitative measure used to compare and summarise difference between trial arms	Mean difference between trial arms
Intercurrent events	Post-randomisation events that affect that measurement, interpretation, and/or existence of an outcome	Strategies to account for intercurrent events

• Develops adverse event & discontinues assigned treatment	Outcome-modifying event	Treatment policy
• Receives alternative treatment and continues assigned treatment	Outcome-modifying event	Treatment policy
• Takes rescue medication **and** discontinues assigned treatment	Outcome modifying event	Treatment policy
• Death within 30 days after treatment assignment	Outcome-truncating event	Principal stratum
• Discontinuing intervention or control treatment before end of 10-day duration	Outcome-modifying event	Treatment policy
• Randomised treatment not received or opposing treatment received (i.e., opposite to the trial arm to which the participant was randomly allocated)	Outcome-modifying event	Treatment policy
• New events that prevent the collection of the primary outcome: - new limb amputation - new intracerebral event precluding physical function testing - other	Outcome-truncating events	Principal stratum
• New events that prevent delivery of the treatment (i.e., feeding):	Outcome-modifying events	Treatment policy

- new indication for parenteral nutrition - patient becomes nil per oral - other		
• Receives wrong dose of intervention	Outcome-modifying event	Treatment policy

8. Trial methodology

8.1 Study design

Multi-centre, double-blind, randomised, controlled, superiority trial.

8.2 Study population

Patients aged 18 years and older admitted to Critical Care Units

8.3 Inclusion criteria

Adults (≥18 years) admitted to Critical Care who are:

EITHER:

- Hospitalised with acute respiratory failure (PaO2/FiO2 ratio of ≤39.9 KPa) *

  AND
- Expected to require advanced respiratory support (High-Flow Nasal Oxygen, non-invasive or invasive ventilation for >48 hours) $

  AND
- C-reactive Protein ≥75 mg/l indicating systemic inflammation*

  AND
- Nasogastric feeding planned for >48 hours$

OR

- In multi-organ failure (Sequential Organ Failure Assessment Score [SOFA] Score ≥2 in two or more domains) *

  AND
- Nasogastric feeding planned for >48 hours$

8.4 Exclusion criteria

- Pre-existing inability to perform a sit-to-stand test (e.g., significant cognitive impairments that would impact their ability to engage in physical activity testing, significant neurological conditions such as Parkinsons Disease, Parkinsonism, Clinical Frailty score of ≥6, amputations, vascular mobility problems, acute or chronic disability expected to impair or preclude the sit-to-stand test at 30 days, amongst others) $
- New (i.e., pre-randomisation) inability to perform a sit-to-stand test (e.g., primary neuromyopathy, acute intracerebral pathology, new or existing weight-bearing restrictions or new neurological impairment, amongst others) $
- Deemed unlikely to survive to 30 days OR presence of a treatment limitation$
- Contraindications to nasogastric feeding^

- Need for specialist elemental feeds^
- Patients with known inborn errors of metabolism^

* Most recent recording from the first 24 hours of hospital admission

$ as confirmed by the treating clinician

^ absence of these criteria in the medical notes will be considered to indicate no concern

8.5 Safety population

The safety population will be the per-protocol population. Per-protocol is defined as being analysed according to the feeding regimen received (rather than the feed randomised to) and having received at least one feed.

9. Trial Procedures

9.1 Screening and recruitment

Potential participants will be screened by the direct care team at participating sites within 48 hours of Critical Care admission. In this trial, the member of the research team conducting the screening activity will be considered as part of the direct care team in accordance with local hospital policy. All patients that undergo screening and meet the eligibility criteria will be recorded on the screening log. Only anonymised screening data will be collected by the central trial coordinating team for publication purposes. Once the patient has been randomised, they will also be recorded on the study enrolment log.

9.2 Informed consent

Informed consent will be obtained prior to the patient undergoing trial specific procedures at a participating site. All consent procedures will be documented in detail in the patient's medical notes. Patients admitted to critical care are frequently unable to consent for themselves due to severity of illness, neurological impairment, sedation, delirium, trauma, etc. Similarly, having a relative in an emergency clinical situation often causes profound distress for the next of kin of the patient. It would be unethical and inappropriate to add to this stressful and emotional situation by asking them to decide on trial enrolment on behalf of the patient. Therefore, in cases where a patient is unable to provide consent, we will adopt a "research with deferred consent" model, where eligible patients will be enrolled initially through written informed consent from a Professional Legal Representative (independent clinician with clinical responsibility for patient care not involved in the trial). After professional consent is received, and the patient still does not have the capacity to consent, then a Personal Legal Representative (a family member, partner or close friend) will be

approached. This is an accepted model of consent in adult emergency and critical care research where participants are likely to lack capacity to consent and where the distress and burden on the Personal Representative should be minimised.[50] This model is used in a variety of other studies recruiting patients from the Adult Critical Care Unit. [51-53]

The Principal Investigator (PI) has overall responsibility for the informed consent of participants at their site and will ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained, and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP), and Declaration of Helsinki. If delegation of consent occurs, then details will be provided in the site delegation log. Delegation can only be to members of the research team (which include research nurses, doctors).

9.2.1 Immediate patient informed consent

If patients have full capacity as deemed by the treating clinician to provide fully written informed consent they will be approached directly by a delegated member of the site research team. This process will include provision of the Patient Information Sheet (PIS) accompanied by the ICF, and an explanation of the trial. Patients will be given a minimum of 24 hours as long as this does not fall outside the inclusion criteria window (as intervention needs to start within 48 hours of adult critical care admission) to make an informed decision. If patients feel they are unable to make an informed decision during this timeframe they will not be included in the trial.

If a participant is unable to read or sign the informed consent form but has full capacity to give consent, this can be provided on the participant's behalf by a witness. A statement will be included in the consent form explaining that the participant understood the information and informed consent was given freely.

9.2.2 Deferred consent procedure

Professional Legal Representative consent

If the patient does not have capacity to consent, a Professional Legal Representative will be approached in the first instance to obtain informed consent on behalf of the patient. The Professional Legal Representative will be fully informed about the trial by a member of the research team. They will be given a copy of the Professional Legal Representative Information Sheet and sign a Professional Legal Representative Consent form. If the Professional Legal Representative declines participation of the patient, no further attempts for consent will be made. The Professional Legal Representative can stop the trial treatment

at any point. In this scenario the trial treatment will be stopped (if ongoing) immediately and a protocol deviation logged. Data collection from medical notes review will continue unless the Professional Legal Representative declines. Blood samples and data collected up to this point will be retained.

Personal Legal Representative consent

As soon as appropriate and after Professional Legal Representative consent, the Personal Legal Representative will be approached if available and fully informed about the trial by a member of the research team. They will also receive a copy of the Personal Legal Representative Information Sheet. Judgement on when the approach is appropriate is situation dependent and will be made by the PI or the Research Nurses. The Personal Legal Representative will also be informed that the patient has currently been enrolled in the trial through Professional Legal Representative Consent and they will be asked to provide their opinion on whether the patient would object in taking part in medical research. If the Personal Legal Representative decides that the patient would not object to taking part in research, they will provide consent either written or via a witnessed phone consent (in the latter setting the PIS will be posted to them). If a Personal Legal Representative advises that, in their opinion, the patient would choose not to participate in the trial, the trial treatment will be stopped (if ongoing). Data collection from medical notes review will continue unless the Personal Representative declines. Blood samples and data collected up to the point of withdrawal will be retained. If no Personal Legal Representative can be approached, or they feel unable to decide, the Professional Legal Representative Consent will remain in place until the patient regains capacity. This will be documented in the patient's medical record.

Patient informed deferred consent

The patient will be informed of their participation in the study as soon as possible when they have return of full capacity to provide informed deferred consent. It is anticipated that this first approach will occur within 24-48 hours of regaining capacity during their hospitalisation, however this will depend on the patient's condition and will be left to the discretion of the clinical team. This process will include provision of a PIS accompanied by the ICF, and an explanation of the trial. Participants will have time to consider their ongoing participation, to discuss with friends and family and to have their questions answered. The participant will then be asked whether they would like to continue participating in the study. If they decide to participate, the patient will sign a copy of the ICF. If participants decline to continue participating in the trial, treatment will be stopped (if ongoing), and all blood samples and

data collected up to the point of withdrawal will be retained. Data collection from reviewed medical notes will continue unless the participant declines.

If the patient does not regain capacity during their hospital stay and is transferred to another hospital without providing consent, a cover letter notifying them of their participation in the trial, PIS and ICF will be sent with their medical notes. The letter will direct the patient to the PIS for detailed information on the trial and provide contact details if the patient wishes to discuss the trial further. A prepaid return envelope will be included to receive the signed ICF. If no response is obtained from the patient, the 30-day follow-up phone call will be conducted, and the participant will be asked at this time to confirm their willingness to participate, prior to follow-up data collection, and if so, to return the consent form or provide witnessed(a separate member of the trial team will witness the taking of consent) telephone consent. If no consent is received, blood samples and data that has already been collected will be retained under the Legal Representative Consent.

For those patients that have regained capacity and were discharged before being approached by the research team, they will be contacted by phone in the first instance. If the research team does not get a response to the phone call, the patient will be approached by post. In either case, the patient will be sent a covering letter and a copy of the PIS and ICF. The letter will direct the patient to the PIS for detailed information on the trial including contact details if they wish to discuss the trial further. A prepaid return envelope will be included to receive the signed ICF. If no response is obtained from the patient, the 30-day follow-up phone call will be conducted, and the participant will be asked at this time to confirm their willingness to participate, and if so, to return the ICF or provide witnessed telephone consent. Additionally, the letter will also confirm that if no consent is received within four weeks from the time of the letter being sent, then the participant's data will be included in the trial under the Legal Representative Consent and no further contact will be attempted to obtain consent.

Patients will be given the opportunity to opt out of on-going data collection. A decision to opt out during the telephone call will be documented by the person seeking consent. For the postal approach, the patient can actively opt out by returning the consent form declining participation or using the telephone contact details provided on the PIS, at any point during the trial.

Consent considerations

The right of a participant to refuse participation without giving reasons will be respected. There will be no financial penalty, and the participant will continue to receive their treatment

as standard care without prejudice. If the participant decides to withdraw from the study, further information about next steps can be found in the trial procedures section. This will be clearly specified in the PIS. A signed copy of the respective ICF will be retained by the patient or legal representative, if applicable; one copy goes in the participant's medical notes along with the PIS, and the original will be filed in the ISF. Patients who are consented but not enrolled in this study should be recorded (including reason non-enrolment) on the screening log in the ISF. The ICFs will be countersigned by the PI or medical delegate, in a timely manner, if the consent is not taken by a medical qualified person. Where a participant is required to re-consent (for example if new Research Safety Information becomes available during the study, or following an amendment that affects the participant, or new information needs to be provided to a participant) it is the responsibility of the PI to ensure this is done in a timely manner and prior to the next dose of IMP (where applicable). Patient withdrawal and refusal for continuous data collection will be documented in patient's medical records.

9.3 Vulnerable participant considerations

The study involves participation of vulnerable participants, as adult patients admitted to critical care are frequently not able to consent for themselves. The PI is responsible for ensuring that all vulnerable participants are protected and participate voluntarily in an environment free from coercion or undue influence. Consent procedure for vulnerable patients is described above.

9.4 Randomisation procedures

A bespoke web-based system with 24-hour availability will be developed for randomisation. Randomisation will use a 1:1 allocation ratio between arms and be stratified by site. Random permuted blocks of sizes 4 and 6 will be used within strata.

Patients will be randomised by a delegated member of the research team. The database is accessible via the NHS computers on site, with access only given to delegated members of the research team. Following randomisation, confirmation e-mail will be sent to the member of the research team randomising. This will be included in the patient's medical records and in the ISF.

9.5 Blinding

Our industry partner will use their existing packaging and logistical infrastructure to ensure bespoke colour packaging of the intervention and control feeds ensuring blinding is robust. Research teams, patients, and clinicians will be blinded to arm allocation.

9.6 Unblinding

Blinding is critical to the integrity of the trial. However, it is understood that on rare occasions unblinding will be required (e.g., for medical or safety reasons if it will alter clinical management). For the purposes of this trial, if a patient experiences refractory acid-base abnormalities, hypo or hyperglycaemias, or vomiting that cannot be attributed to the clinical setting and causes concern to the responsible intensive care consultant (in regards to this affecting patient treatment or outcome), the intervention should be stopped. If this and/or conversion to standard feeding regimen does not resolve, unblinding may be required to change clinical management. The rescue treatment (being either cessation of the trial feed or conversion to a standard clinical feed) should not depend on the treatment group allocation, so unblinding requests are expected to be rare. Where unblinding is being considered, the PI (or assigned delegate) should have determined that the information is necessary, i.e., that it will alter the participant's immediate management. Site teams are encouraged to contact the study coordinating team if they wish to discuss this further, but they will always have the ability to unblind via the trial database.

Treatment identification information should be kept confidential and should be disseminated only to those individuals involved with the medical management of the participant. The CI will be kept informed of all instances of unblinding but should remain blinded to treatment allocations them self. The trial manager and the site staff will maintain a record of all unblinding events including patient trial ID, the date code break was performed, the person who broke the blind, and reason for it. The breaking of the code and the reasons for doing so will also be captured on the electronic case report form (eCRF), in the site file and medical notes. The code break for the trial will be held by the trial coordinator until the end of the trial when it will be filed in the Trial Master File (TMF). The CI will ensure any unblinding is documented at the end of the study in any final study report and/or statistical report. The information will also be disseminated to the Data Monitoring and Ethics Committee (DMEC) for review in accordance with the DMEC Charter.

9.7 30-Second Sit-To-Stand test (primary outcome)

Proximal muscle wasting occurs differentially in critically ill patients, decreasing proximal muscle strength.[54] The 30STS test is a measure of proximal muscle strength, and therefore as an outcome measure is mechanistically linked to interventions to preserve muscle mass.[55] The 30STS test has normative data, has been extensively used across a wide

spectrum of chronic diseases and maps to complex measures such as the Barthel Index and the SF-36.[56-59] The STS movement is fundamental to independence of function and activities of daily living (e.g., getting out of bed or going to the toilet). The methodology of performing the STS test is highly standardised by the Centre for Disease Control and Prevention (CDC) and has been safely and reliably applied by video conference in the community.[60-62] Our data shows the STS has excellent reliability, construct validity and responsiveness and a lack of floor and ceiling effects at hospital discharge.[63] ICU survivors experience profound disability with previous work demonstrating that only 40% could ambulate at 7 days post-ICU discharge.[64] The lack of floor and ceiling effects at hospital discharge makes the 30STS test an appropriate measure of physical function from ICU admission to recovery. One patient commented, "*it is very straightforward, other than a dining room/kitchen chair no equipment is needed. Any little improvements can mean a big deal in the early stages of recovery.*"

9.7.1 Performing a 30-Second Sit-to-Stand Test

The 30-second sit-to-stand (30STS) test involves recording the number of stands a person can complete in 30 seconds rather than the amount of time it takes to complete a pre-determined number of repetitions. That way, it is possible to assess a wide variety of ability levels with scores ranging from 0 for those who cannot complete 1 stand to greater than 20 for more fit individuals.

The participant is encouraged to complete as many full stands as possible within 30 seconds. The participant is instructed to fully sit between each stand. While monitoring the participant's performance to ensure proper form, the tester silently counts the completion of each correct stand. The score is the total number of stands within 30 seconds (more than halfway up at the end of 30 seconds counts as a full stand). Incorrectly executed stands are not counted. The modified 30STS can be used for those unable to stand without the use of armrests, a task which many patients at point of discharge from critical care will find difficult to perform.[63]

Prior to the trial study commencement, the research team will be given a 30-minute education session and a written protocol to facilitate the standardised and safe performance of the 30-STS test. Patients will also be asked to perform the 30STS at discharge from the critical care unit, to ensure they are familiar with the test prior to repeating it 30 days after randomisation. While it is likely that patients will still be in hospital at 30 days after randomisation (median hospital length of stay was 40 days in our pilot study), the 30STS test can also be performed via video and/or teleconferencing if patients are discharged home.[34,65]

Whilst on the call, the tester will screen for safety using the Australia-modified Karnofsky Performance Status (AKPS≥50%) and the Clinical Frailty Score (CFS<6) to determine suitability for performing the 30STS in this manner.[65] This will be accompanied by a short screening questionnaire: [65]

- Do you have someone at home who can supervise you while completing this test?
  -If CFS >4 and no-one to supervise test completion, do not complete the test.
- Are you wearing study shoes that don't slip and have support at the heel?
  -If "no" and no shoes are available, do not complete the test.
- Have you had a recent fall?
  -If "yes", do not complete the test.
- Are you feeling dizzy, cold, or sweaty?
  -If "yes", do not complete the test.
- Have you experienced any new onset chest pain since last seeing your doctor?
  -If "yes", do not complete the test.

The tester will instruct the participant to set up their environment to ensure safety, including asking the participant to place their chair securely against a wall to avoid movement. If patients and relatives do not have access to videoconferencing, telephone-based assessment will be performed.[66]

9.8 Functional and health-related quality of life measures

9.8.1 Barthel Index

The Barthel index measures the extent to which somebody can function independently and has mobility in their activities of daily living.[67] The index also indicates the need for assistance in care and is a widely used measure of functional disability. The 10-item form of the index consists of 10 common activities of daily living including: feeding, bathing, grooming, dressing, bowel control, bladder control, toileting, chair transfer, ambulation, and stair climbing. Items are rated in terms of whether individuals can perform these independently, with some assistance, or are dependent. Items are weighted according to the level of care required. This will be performed at day 30 post-randomisation via telephone or in-person if the patient is still in hospital.

9.8.2 Short form-36 score

The 36-Item Short Form survey is a self-reported outcome measure often used as a measure of a person or population's quality of life. This outcome measure comprises 36

questions covering eight domains: physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain, and general health. The total score can be used to indicate a range of low to high quality of life, as well as looking at two component scores: the physical component score (PCS) and the mental component score (MCS), which can be calculated via an online calculator (https://orthotoolkit.com/sf-36/ or equivalent). The PCS has been widely used as a measure of physical function in the critical care population and is included in the Core Outcome Set for metabolic and nutritional trials in critically ill patients.[48] This will be performed at 90 post randomisation via telephone or in-person if the patient is still in hospital.

9.8.3 Post Intensive Care Presentation and Screening (PICUPS) and PICUPS community

The PICUPS tool can be used to inform the rehabilitation needs after treatment in the critical care environment by identifying areas that are likely to require further assessment/treatment by members of the multi-disciplinary team.[68] It can be used at an individual patient level to guide decision making and inform rehabilitation plans, as well as at population level to enable understanding of shortfalls in service provision and aid future planning. It covers five main domains (with three additional in the PICUPS plus items): 1) medical care; 2) breathing/nutrition; 3) physical movement; 4) communication / cognition, and; 5) psychosocial (upper airway, physical and activities of daily living and symptoms that interfere with daily activities).[68] An adaptation of this tool is the PICUPS-Community which works off the same foundations but is a self-reported measure to be used with the critical care population once they have been discharged into the community. It covers a similar area but groups questions into four main domains: 1) breathing; 2) upper airway nutrition; 3) symptoms that interfere with daily activities, and; 4) communication, cognition, and psychosocial. An additional domain is applied if the patient is a wheelchair user. Each of the 24 PICUPS items is rated on a 6-point ordinal scale that describes the patient's level of function ranging from 0 (most dependent) to 5 (near-normal). This will be performed at day 30 days post randomisation, face-to-face if the patient is in hospital (using the PICUPS) or by telephone if they have been discharged (using the PICUPS community).

9.9 Clinical data

The medical records of participants will be reviewed during the intervention period of 10 days and for up to 30 days, to collect data on secondary outcomes. Where use of an indirect

calorimeter (e.g., Q-NRG system https://www.cosmed.com/en/products/indirect-calorimetry/q-nrg or an equivalent system of standard of care) is possible, energy expenditure data will be recorded. To determine whether patients are receiving their prescribed target level of enteral feed, total energy and total protein received will be recorded along with the prescribed energy and protein for the first ten days after randomisation.

9.10 Muscle ultrasound

Rectus Femoris cross-sectional area (RF_{CSA}) is associated with physical strength and physical activity[69] and has been validated (against muscle biopsies) in the critical care setting as a true measure of muscle mass[5]. RF_{CSA} will be assessed by muscle ultrasound on days one, seven and 10, using B-mode ultrasonography (using a 6-15 MHz 6cm linear transducer array or similar, or a 5-10MHz curvilinear probe if necessary).[5,70] The transducer will be placed perpendicularly along the superior aspect of the thigh, with special care taken to ensure a 90^{o} angle between the transducer and patients' legs for all measurements to minimize any risk of bias. The patient will be supine with a 30^{o} upward incline at the head unless clinical condition makes this inappropriate. The transducer will be placed two thirds of the distance between the anterior superior iliac crest and the superior border of the patella. Ultrasound gel will be used to optimize transmission of ultrasound and reduce distortion. The derived RF_{CSA} will be taken as the average of three consecutive measurements within 10% of one another. To ensure measurements occur at the same position on the leg the position of the probe on the thigh will be marked using a surgical marking pen and then covered with a 10 x 12 cm dressing (3M™ Tegaderm™ Transparent Film Dressing Frame Style 1626W or similar). To assess differential muscle wasting in different body areas, we will also image and collect data on Parasternal muscle (between 2nd and 3rd rib, mic clavicular line) and the Oral and Suprahyoid muscles (between hyoid and mandible) using a similar technique.

9.11 Body Impedance analysis

Whole-body impedance data will be obtained using multi-frequency impedance plethysmography using the Seca mBCA 525 which will be provided to all participating sites for data acquisition on the day of randomisation and at day seven. BIA evaluates characteristics of tissues in response to an application of alternate current and is a quick, non-invasive and relatively inexpensive, making it ideal for bedside use.[71] Electrolyte-rich tissues are highly conductive to electrical current, while anhydrous tissues (like fat) resist the

current flow. The opposition to the flow of a current is called resistance (R), while the opposition to a current change due to a capacitor (tissue) is defined as reactance (X). The total opposition to an electrical current by both resistance and reactance is the impedance dimension (I). Using the participant's height, age and sex in the regression equations, BIA can estimate fat free mass from impedance values and body water content. These machines also offer Phase Angle data, based on the relationship between reactance and resistance, named from a phase shift caused by resistance to flow determined by capacitors (i.e., healthy cell membranes) that delay the current's flow. High phase angle correlates with large quantities of intact cell membranes and body cell mass. By using phase angle and length of the impedance vector, changes in body cell mass can be examined, independent of regression equations or body water. To collect data, the skin is cleaned to ensure good electrode contract and electrodes are attached to the patient, who would be lying still with arms separated from trunk by about 30° and legs separated by about 45° for at least five minutes to ensure good electrode contact.

9.12 Blood sampling

Samples will be taken on days one and seven for measurements of ketone generation, metabolomic analyses and saved for future whole blood leukocyte gene expression analyses. Further details are given below in the sample collection and preparation section.

9.13 Schedule of assessment

Event/Visit	Within 48 hours of critical care admission	Day one feed	Day two – Day 10 feed	Critical care discharge	Follow-up 30 days post randomisation	Follow-up 90 days post randomisation
Eligibility review	X					
Patient informed consent or by Professional/ Personal Legal Representative *	X					
Medical history	X					
Randomisation	X					
Feed administration		X	X			
30STS				X	X	
Barthel index	X				X	
SF-36	X					X
PICUPS/ PICUPS Community					X	
Clinical data		X	X			
Muscle ultrasound		X	X			
Bioimpedance analysis		X	X			
Blood sampling		X	X			

Medical record review	X	X	X	X	X	X
Follow-up phone call					X	X
Review of AE/SAE			X			

SF-36 – The 36 item short form survey; BIA: Body Impedance Analysis; 30STS: 30 Second Sit to Stand; PICUPS: Post Intensive Care Unit Presentation Screen

9.14 End of trial (EOT) definition

The EOT is defined as the date the last patient sample analysed. The CI is delegated the responsibility of submitting the EOT notification to REC once reviewed by sponsor. The EOT notification must be received by REC within 90 days of the end of the trial. If the study is ended prematurely, the CI will notify the Sponsor and REC, within 15 days, including the reasons for the premature termination.

9.15 Participant withdrawal

All trial participants are free to withdraw from the study at any time. It is always within the remit of the clinician with the clinical responsibility of patient care to withdraw the participant from the study for appropriate medical reasons. This can be (but is not limited to) individual AEs, new information gained about a treatment, or if it is felt to be in the participant's best interest.

If a patient or their Personal Legal Representative withdraws consent at any time during the trial - this decision will be respected and will be abided by. Treatment will be stopped (if ongoing). All data up to the point of this decision will be retained in the trial. Data collection from medical records for this trial will continue unless declined by the patient or their legal representative. This is mentioned in the respective Information Sheets.

If a participant or their Legal Representative withdraws consent, they will be asked to provide a reason for withdrawal, although it is not necessary to provide this. Withdrawal from the trial will be documented in the patient's medical records, in the enrolment log and the database.

10. Trial Intervention

10.1 Feed administration

Following consent, participants will be randomised to either receiving the ketogenic enteral feed or control enteral feed within 48 hours of critical care admission. Local protocols will be followed for all participants in both feeding arms with the only difference being the feed. Nestle Health Sciences will produce and package both the ketogenic and control enteral feed (equivalent in volume, energy and protein). Within the individual groups the feed will be tailored depending on the patient's clinical requirements, specifically the use of propofol which provides additional fat to the patient. Therefore, one feed will be used when patients receive propofol and one when patients stop receiving propofol. Feeding bags will be differentiated by colour to allow for a double-blind randomisation protocol. The control feed will be eucalorific to the intervention feed.

Ketogenic feed

1) Ketogenic enteral feed with propofol: Fat 75% (MCT 47%), Carbohydrates 5% Protein 20%

2) Ketogenic enteral feed without propofol: Fat 75% (MCT 75%), Carbohydrates 5%, Protein 20%

Nestle Health Sciences will produce and package the control (equivalent in volume, energy and protein) in parallel for the control arm prior to site delivery, allowing a double-blind randomisation protocol to be used with maximal financial efficiency. Enteral feed packages will be colour coded for randomisation, quality control and allocation purposes. Both arms will switch to a second, separately coloured enteral feed bag once propofol is stopped, preserving blinding. Enteral feeding will be delivered continuously over 24 hours. If patients are discharged to the ward, enteral feeding will continue for a total of 10 days unless no longer indicated (adequate oral intake established). Patient co-applicants were keen on continuing the enteral feed, citing comments from focus groups that "*the nutrition plan should follow through with a patient from ICU to High Dependency to ward to home* ".

10.2 Participant management during the study intervention period

10.2.1 Nasogastric tubes

Nasogastric (NG) tubes will be inserted in all patients as is routine on the critical care unit. To ensure safe administration of feed the position of the tube tip in the stomach will need to be confirmed prior to commencing enteral feed. This will be carried out according to each site's local policy.

10.2.2 Delivery of Enteral Nutrition

After randomisation and confirmation of NG tube tip, enteral feeding can be commenced once a clinical decision is made to feed the patient. The feed rate will commence progressively providing no more than 20 kcal/kg bodyweight over the first 72 hours of critical care admission, to not delay the feed start. Each patient will then have an individual feeding regimen calculated by the dietitian within 72 hours. While this is standard of care, if no dietetic review occurs, feed rate will be increased to 25kcal/kg over 24 hours until a dietetic review occurs or until the end of the intervention period. Catch-up rates should be used if necessary to ensure enteral feed delivery meets at least 80% of energy targets. Trial enteral feeding will continue for the duration of the 10-day trial period unless oral intake is established, before reverting to standard enteral feed, as per the clinical team responsible for the patient's care. If patients are discharged to the ward before the end of the intervention period, enteral feeding will continue and follow local ward protocols or dietetic recommendations.

The end of the intervention is defined as either 1) completion of the 10-day feeding period, 2) enteral feeding no longer indicated or 3) hospital discharge. For patients still in hospital beyond the intervention period, the feeding regimen will revert to standard of care.

10.2.3 Management of Gastric Residual Volumes

Absorption of enteral feeds will be assessed by measurement of gastric residual volume as per usual practice. Management of consecutive high gastric residual volumes (defined by local guidelines) will be managed as per local guidelines.[72] Guidelines include the use of prokinetic drugs, but ultimately their use will be at the discretion of the treating clinicians, as is the case for routine clinical care.

10.2.4 Blood Glucose Control

Enteral feeding in critically ill patients can result in elevated blood glucose levels, and research has shown that moderate rather than intensive blood sugar control improves patient outcomes[73]. Intravenous glucose (including crystalloid replacement) will not be administered except for the emergency treatment of hypoglycaemia (≤3.9mmol/l). In our previous trial, glucose control was improved by the ketogenic enteral feed, with hypoglycaemia occurring in the control arm only.[34] This is in keeping with other ketogenic trials in critically ill patients.[46]

10.2.5 Administration of Drugs

Intravenous considerations

Intravenous medication will need to be diluted in 0.9% sodium chloride as opposed to 5% glucose. This practise varies across ICUs and will be standardised for the trial.[74] The pharmacist at each site will advise on the use of 0.9% sodium chloride alternatives to 5% glucose solution administration of specific medication to limit the effect on achievement of ketosis from dextrose-containing medication. In patients where sodium and/or chloride administration may raise issues (e.g., severe hypernatremia), please liaise with ICU pharmacist or ASICS-II trial team for mitigation.

Enteral considerations

Patients who are receiving enterally administered drugs (e.g. phenytoin) will need a period of 'feed free' time prior to administration of the drug to ensure optimal absorption though in many clinical scenarios (e.g., status epilepticus) or failure to reach therapeutic serum levels the parenteral route of administration is required.[75] In these instances, the dietitian will provide an appropriate feeding regimen for patients in both arms. Oral medication suspended in Maltitol (levetiracetam, Senna, Ibuprofen) or Sucrose (Rifampicin, Carbocysteine) are to be avoided. If any such medications are required for a patient safety or clinical purpose, we will explicitly state that they should be given as per our pilot study and would not be considered a protocol violation. In our pilot study, amiodarone (diluted in 5% glucose) was given to several patients with no appreciable effect on ketogenesis.

10.2.6 Stopping enteral Feed for Interventions

Critically ill patients may require procedures or interventions that require fasting e.g. airway management or surgery. In such cases enteral feeding will be stopped as required by local guidelines and restarted as soon as possible following the procedure, with a catch-up rate prescribed if possible. All cases of missed enteral feed will be recorded.

10.2.7 Refeeding Syndrome

Patients who are deemed at risk of refeeding syndrome will be assessed individually for eligibility into the study by the dietitian.

11. Assessment and management of risk

11.1 Study intervention risks

Published data on our ASICS trial that specifically set out to assess safety does not support worries of acidosis, hypoglycaemia, or vomiting.[34] The signal for increased diarrhoea is unclear, as diarrhoea is extremely common in critically ill patients. For ASICS-II, pre-defined safety data will be collected on acid-base balance, glucose control, and gastrointestinal intolerance (specifically on vomiting and diarrhoea). All such side effects would occur during the acute inpatient stay and therefore detected directly by the study team. Furthermore the Data Monitoring and Ethics Committee (DMEC) will monitor safety data throughout the trial and will routinely meet to assess safety analyses.

11.2 Data collection risks

Critically ill patients have an increased mortality in the first-year post hospital discharge. To ensure families are not contacted to provide data following a death, all available electronic records will be checked for recordings of death prior to contact being performed at day 30. If new medical or social issues arise from telephone contact the study team will advise patients and families accordingly. For example, advising patients to contact their primary care practice or attending emergency departments.

11.3 Risks to researchers

The only study-related possible harm to the study team is from needle stick injuries during collection of blood samples. Members of the research team and critical care nurses taking blood samples will have received training and will abide by the standard precautions for the prevention of needle stick injuries.

12. Statistical Considerations

12.1 Statistical analysis

The primary outcome analysis is a survivor analysis: The treatment effect is the difference in the mean 30STS among participants who survive to 30 days follow-up under intervention and control. The treatment effect will be estimated using a linear mixed effects model adjusted for site (as a random effect), age, and Functional Co-morbidity Index. The main analyses of primary and secondary outcomes will be conducted using multiple imputation under a missing at random assumption for those participants lost to follow-up. Controlled multiple imputation analysis using a δ-based imputation approach will be performed as

sensitivity analyses.[76] In this approach an offset term, δ, is added to values imputed under MAR to assess the impact of unobserved participants having a worse or better outcome than those observed. We will furthermore estimate the survivor average causal effect and assess consistency with the main primary outcome treatment effect estimate.[49]

In the primary outcome analysis it is assumed that neither feeding regimen influences mortality in the population of interest so that participants who survive under ketogenic feeding and standard feeding are not inherently different and the estimated causal effect of treatment on those patients who would always survive regardless of feeding regimen is the most relevant. In support of this statement, a systematic review of 212 trials provided no conclusive evidence of any single pharmacology intervention translating to mortality benefit.[77] However, there is debate on the ability of nutritional interventions to alter mortality in critical illness, with large randomised trials of increased protein or energy not demonstrating efficacy in altering mortality.[13,78] Mortality will be closely monitored by the DMEC and formally assessed at the end of the trial using a non-inferiority test.

Given (i) 80% statistical power, (ii) a 10% alpha level, (iii) a trial sample size of 282 participants, (vi) a 75% 30-day survival probability in the control arm, (v) no survival difference between trial arms, and (vi) the proportional hazards assumption, the non-inferiority margin identified comprises a hazard ratio of 1.83 (HR=1.83). This equates to a 30-day survival probability non-inferiority margin of 0.59. A 10% alpha level is selected given that, for mortality, committing a Type I error is considered less concerning and identifying a difference between intervention and control arms if a difference truly exists is prioritised.

Table 1: Non-inferiority margins* identified for survival & binary outcomes

Outcome metric ≥	Statistical power	
	80%	**90%**
Survival outcome		
Hazard ratio (HR)	1.83	2.05
30-day survival probability	0.59	0.55
Binary outcome		
Absolute risk difference (ARD)	0.11	0.13

*Assuming a 10% alpha level, a trial sample size of 282 participants, a 75% 30-day survival probability,
no difference in survival between trial arms, and proportional hazards

A causal mediation analysis will be conducted to assess whether the effect of receiving the intervention treatment on the primary outcome is mediated through metabolite panels traits considered as Principal Components.[79] The traits included in the panel will be determined in the mechanistic outcomes analysis. Participant baseline characteristics will be summarised using suitable descriptive statistics for central tendency and variability.

An unmatched win ratio approach will be used as a secondary analysis to assess net clinical benefit. The win ratio treatment effect will be estimated using hierarchically (in this order) the outcomes 30-day mortality (yes/no), 30STS, and Barthel Index 30 days after randomisation. More emphasis will be placed on the win ratio analysis if relevant differences in mortality are observed. A full statistical analysis plan will be prospectively developed.

12.2 Sample size calculation

The 30STS at 30 days post-randomisation is the primary outcome, a recommended outcome from our co-designed Core Outcome Set.[48] An international collaborative analysis of 451 critically ill patients from 5 studies, the STS mean (SD) at hospital discharge was estimated as 5.98(4.06).[63] A two repetition increase represents a minimal clinically important difference.[80] To detect this difference with 90% power at 5% significance level and assuming a common SD of 4.06 requires a total of 176 patients. Data from the Intensive Care national audit and research centre shows hospital mortality over the last three years to be 19.1%, 23.1% and 24.2%, and we have used 25% as a worst case scenario.[6] In our previous eight-centre nutritional intervention trial we saw withdrawal related to clinical decisions, loss to follow-up and arm cross over, in 11 out of 121 patients (9%).[81] Rounding these proportions up to be cautious, we have inflated the sample size to allow for 25% mortality, 10% loss to follow-up and 2% unplanned cross over. This yields a total number of **282** participants to recruit.

12.3 Metabolic data

In our pilot trial, untargeted metabolomic profiling was used in an exploratory fashion, to generate potential panels for future targeted work, coupled with targeted ketone and medium chain fatty acid analyses. The advantage of this approach was seen in the identification of panels separate from those that we would have used a priori e.g., energetic intermediate pathways such as TCA Cycle metabolites and NAD Metabolites. We are therefore in a position to apply both untargeted (to confirm our preliminary findings) and targeted metabolomics.

12.3.1 Ketone Flux, TCA cycle and Fatty Acid analysis

We will assess both routes of synthesis and metabolism of ketones through analyses of ketone precursors; plasma free fatty acids (C2-C24), ketone bodies and metabolites; Acetyl CoA, Acetoacetyl CoA, HMG-CoA, Malonyl-CoA, Mevalonate, as well as linked energetic intermediate pathways such as TCA Cycle metabolites and NAD Metabolites.

12.3.2. Amino acid and urea cycle flux

We will assess amino acid homeostasis through analysis of branch chain amino acids, glucogenic amino acids, ammonia, glutamine and their metabolites. Urea cycle flux will be assessed through analysis of 4-hydroxy-proline, ornithine, urea, and N-acetylornithine, citrulline, Aspartate, arginosuccinate, fumarate, arginine and their metabolites.

These targeted metabolite panels will be assessed using stable isotope labelled internal standard based concentration measurements using UHPLC-MS for each panel of metabolites, and metabolic modelling techniques such as stoichiometric metabolic flux anaylsis.[82]

Data matrices of relative metabolite abundances will be log transformed, centered and scaled and exploratory visualisations generated using PCA/ PLSDA. To determine differences in metabolite abundance (both targeted panels and untargeted) as a result of the intervention, across time and interactions between intervention and time – analyses will be performed using a moderated empirical Bayesian mixed effects model approach with the limma R package.[83] For each comparison, False Discovery Rate correction will be applied using the Benjamini-Hochberg approach. Data sets will be reduced to only those metabolites important in differentiating temporality and intervention, relationships between changing metabolites and clinical variables determined using a combination of sparse redundancy analyses and canonical correlative analyses.[84,85]

13. Ethics

The CI must ensure that the study is conducted in accordance with the guidelines of the International Conference on Harmonisation, Good Clinical Practice (GCP) and UK legislation. All study documentation will be reviewed and approved by the research ethics committee prior to start of recruitment. Research Ethics Committee, Health Research Authority and Sponsor approvals will be in place before patient recruitment commences. The study will be sponsored by Barts Health NHS Trust. Additionally, each participating site will ensure that the approval of the relevant trust Research & Development department and Ethics Committee is in place and a written confirmation is provided to the Sponsor.

14. Patient and Public Involvement

Patients and the Public have been actively involved in identifying the research topic, prioritising the research questions and in application preparation. Patient members have been drawn from nationwide critical care survivors support charities and local East London support groups. Both patient co-applicants and ICUsteps (Home - ICUsteps) reviewed the lay summary. Patients and relatives participated in the co-design of the Core Outcome Set. Patient focus groups have further informed and refined our application (focus on monitoring of diarrhoea) and reviewed our response to first stage comments (continuation of the intervention for 10 days regardless of ICU discharge). Patient members will help prepare the ethics submission and review patient information sheets and consent forms. A representative will attend trial steering group meetings, and review data on adverse events and outcomes. Panel members will interpret, analyse and frame safety and adverse events data especially in regard to the relevance and tolerability of diarrhoea. Panel members will be central to dissemination of findings both with the lay media and in professional education to ensure that these data reach the widest audience possible.

15. Data handling and record keeping

15.1 Data Management

Pseudonymised trial data will be transcribed onto the electronic CRF (eCRF) on the secure data entry web portal. All data will be pseudonymised at site, and a trial ID generated by the database. Age, patient initials and the trial ID will be used to identify the participants The CRF will be designed by the database manager in the Critical Care and Perioperative Medicine Research group with input from the CI in accordance to Sponsor requirements. Only trial data related to the outcomes and data including safety events that will be used for statistical analysis will be collected. For participants that are withdrawn, data collected up to the point of withdrawal will be retained. Handling of withdrawal in terms of statistical analysis will be fully detailed in the statistical analysis plan.

Submitted data will be reviewed for completeness and consistency by authorised users within the trial coordinating team. Direct access to eCRF will be restricted, with only delegated and authorised users will be issued with (trial role related and defined) access to the eCRF. Each user will be assigned specific user roles and rights, and this will be reflected on the respective delegation log. Final sign-off by the site PI will be undertaken. Following data cleaning, a single final data lock will prevent changes to protect the final data set and will be exported from the study database for analysis by the trial statistician.

Storage and handling of confidential trial data and documents will be in accordance with the Data Protection Act 2018 (UK). A trial specific Data Management Plan will be developed by the coordinating team detailing all key methods of data management for collecting, recording, handling and storing of trial data. Transfer of patient identifiable information between @nhs.net accounts and those used in Wales @wales.nhs.uk will be secure and meet appropriate IT encryption and data protection requirements.

15.2 Source data

Source data is defined as all information in original patient records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the clinical investigation. Only members of the direct care team are entitled to have access to patients' medical records before consenting to the trial. Direct access will be granted to authorised representatives from the sponsor, host institution, and the regulatory authorities to permit study-related monitoring, audits, and inspections. Source data verification will be conducted in the eCRF.

15.3 Confidentiality

The PI has a responsibility to ensure that participant anonymity is protected and maintained. They must also ensure that their identities are protected from any unauthorised parties. The Sponsor will ensure that all participating partner organisations will maintain the confidentiality of all subject data and will not reproduce or disclose any information by which subjects could be identified, other than reporting of serious adverse events. In the case of special problems and/or competent authority queries, it is also necessary to have access to the complete trial records, provided that patient confidentiality is protected. Information with regards to study participants will remain confidential and managed in accordance with the Data Protection Act, NHS Caldicott Guardian, The UK Policy Framework for Health and Social Care Research Ethics Committee Approval. The CI and the study team will adhere to these parameters to ensure that the participant's identity is protected at every stage of their participation within the study. Patients will be anonymised with regards to any publications relating to this study.

15.4 Record retention and archiving

During the course of research, the CI has full responsibility of all study records which must be kept in secure conditions at all times. The UK Policy Framework for Health and Social Care Research and Sponsor SOP, requires that research records are kept for 25 years after

the study has completed. Archiving will be authorised by the Sponsor following submission of the end of study report. The Sponsor is responsible for maintaining and archiving the study TMF. The study database will be stored according to the Sponsor's policies. Electronic data sets will be stored indefinitely. The sites are responsible for maintaining and archiving all local records including the ISF and CRFs. These records should be archived together once authorisation has been given by the Sponsor. It is the responsibility of the PI to ensure a full set of records is collated and documented.

16. Laboratories

Samples will be stored centrally at the William Harvey Institute at Queen Mary University of London, until sent out as batches to laboratories for analyses.

16.1 Central laboratories

Study specific sample analysis will be performed as follows:

1) Beta-hydroxybutyrate and lactate analysis will be performed at Laboratory of Clinical Chemistry, University College London, Institute of Child Health.

2) Metabolomic analysis will be performed at Centre of Metabolism, Ageing and Physiology, University of Nottingham Medical School at Derby

3) Whole blood leucocyte gene expression analysis will be performed at Wellcome Trust Centre for Human Genetics, Henry Wellcome Building of Genomic Medicine.

4) Leucocyte gene expression analysis will be performed at Harris laboratory, University of Exeter Medical School.

16.2 Sample collection, labelling and logging

The following blood samples will be collected for all participants:

- 2x 6ml EDTA tubes will be collected for plasma separation for metabolomics and ketone body analysis at day one and day seven from point of randomisation.
- 1x 2.5ml whole blood will be collected for extra study specific bloods for leucocyte gene expression analysis at day 1 and day 7.
- 2x 10ml Whole blood will be collected for future study of immunological and metabolic assessments on days 1 and 7.

All blood samples will be pseudo-anonymised. Samples collected at each participating site will be labelled with the participant's corresponding trial ID and kept in a hospital freezer. The samples will be routinely collected and transferred to William Harvey Research Institute prior

to transfer to the different central laboratories by an approved courier company. The full sample, collection, labelling, logging and transfer procedure will be documented in the study laboratory log. The trial coordinating team will provide sites with a SOP on sample collection, processing and storage.

16.3 Sample receipt/ chain of custody/ accountability

Handling of the samples upon arrival at the local and central laboratory will be documented. All samples will be logged upon receipt and the laboratory will ensure that the physical integrity of these samples have not been compromised in transit. If compromise has occurred, the trial coordinating team, as well as the Sponsor, will be informed of this. Upon receipt of samples, laboratory staff will ensure that all samples are accounted for as per the labelling.

16.4 Sample storage procedures

The samples will be stored in pseudo-anonymised form with the participant's trial ID written on the label in a local hospital freezer at an optimal temperature for the troponin assay until collection. The samples should be put in the freezer within two hours of preparation. The samples will not be destroyed if a patient withdraws from the study unless they specifically request so. If the patient requests for the samples to be destroyed the Tissue Custodian (CI), will inform the lab who will ensure the samples are destructed as per the Human Tissue Act. This will be documented in the TMF and ISF of the participating site.

16.5 Sample analysis procedures

16.5.1 Ketone and lactate generation

Plasma samples will be analysed (for beta-hydroxybutyrate and lactate) by electron impact ionization, with selected ion monitoring for BOHB at m/z 233, and 237 for13C4-BOHB.

16.5.2 Metabolomic analysis

Samples will be analysed for targeted and untargeted analyses using a combination of hydrophilic interaction liquid chromatography (HILIC) and Reverse Phase Ultra High-Performance Liquid Chromatography-mass spectrometry (UHPLC-MS) for polar and non-polar/lipid metabolites respectively.[86]

Sample preparation for each targeted panel of metabolites (FFA, AA, energy metabolite/organic acids) will be performed following standardised SOPs. For untargeted analyses metabolites will be extracted from plasma using a dual phase Bligh-Dyer extraction as previously described.[86] Both targeted and untargeted panels will be analysed using a combination of hydrophilic interaction liquid chromatography (HILIC) and Reverse Phase Ultra High-Performance Liquid Chromatography-mass spectrometry (UHPLC-MS) for polar and non-polar/lipid metabolites respectively.[86]

16.5.3 Whole blood leucocyte analysis

Whole blood will be collected into a tempus/PAxgene tube, and inverted and mixed with the preservative at the time of collection before freezing at -80°C. RNA extraction will occur at the central laboratory.

16.6 Sample and data recording/ reporting

Pseudonymised results will be shared on a password protected excel sheet with the CI and study team by secure electronic communication (email) after the last patient sample has been analysed.

16.7 Sample and data recording/ reporting

The samples will be stored beyond the end of the trial to be used for closely related studies in the future. After completion of any potential sub-studies the samples will be destroyed according to the Human Tissue Act Code of Practise.

16.8 Sample management at end of study

The samples will be stored beyond the end of the trial to be used for closely related studies in the future. After completion of any potential sub-studies the samples will be destroyed according to the Human Tissue Authority's Code of Practice. Consent will be obtained for the use of the leftover blood samples for closely related studies in the future.

17. Interventions and tools

17.1 Bioimpedence analysis

The Seca mBCA 525 (https://uk.secashop.com/products/seca-mbca/seca-mbca-525/5250021009) will be used for the bioimpedance analysis. Its use is contra-indicated in pregnancy and in patients with a permanent pacemaker. There are no additional risks attached to performing the analysis and the device is currently used in routine clinical care across hospitals in the UK.

17.2 Point of Care Ultrasound

Participating sites will use the ultrasounds machine that is available on the Critical Care Unit as part of standard of care.

17.3 Other biological or chemical products

Two ketogenic bespoke recipes will be used, depending on the clinical use of propofol infusions.

1) Ketogenic enteral feed with propofol: Fat 75% (MCT 47%), Carbohydrates 5% Protein 20%.
2) Ketogenic enteral feed without propofol: Fat 75% (MCT 75%), Carbohydrates 5%, Protein 20%.

Nestle Health Sciences will produce and package the control (equivalent in volume, energy and protein) in parallel for the control arm prior to site delivery, allowing a double-blind randomisation protocol to be used with maximal financial efficiency. Enteral feed packages will be colour and bar coded for randomisation, quality control and allocation purposes.

18. Safety Reporting

18.1 Adverse Events (AE)

An AE is any untoward medical occurrence in a subject to whom an intervention has been administered, including occurrences which are not necessarily caused by or related to that

intervention. An AE can therefore be any unfavourable and unintended sign, symptom or disease temporarily associated with study activities.

18.2 Adverse Reaction (ARs)

An AR is any untoward and unintended response in a participant to an intervention. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to the intervention qualify as adverse reactions. The expression 'reasonable causal relationship' means in general that there is evidence or an argument to suggest a causal relationship.

18.3 Notification and reporting of AEs and ARs

The AE will be documented in the participants' medical records and the electronic Case Report Form (eCRF). The participant will be followed up by the research team until the AE is resolved.

The following safety events will be required for daily reporting from the point randomisation until day 10 and recorded in the eCRF. These events won't be reported as AEs:

- Acid-Base balance disruption, defined as unexpected acidosis not in keeping with the clinical condition, in the opinion of the treating clinician. The absence of documentation in the medical notes will be considered to indicate no concern.
- Hypoglycaemia episodes (normoglycaemia defined as 4.0-10.0 mmol/l), assessed from routine blood monitoring. Where no routine blood monitoring occurs, normoglycaemia is assumed.
- Hyperglycaemia episodes (normoglycaemia defined as 4.0-10.0 mmol/l) assessed from routine blood monitoring. Where no routine blood monitoring occurs, normoglycaemia is assumed.
- Diarrhoea defined as a Bristol School Score ≥5.
- Vomiting defined as >10ml of vomitus.
- Nausea defined as when an anti-emetic is given for patient-reported nausea.

18.4 Serious Adverse Event (SAE)

A serious adverse event (SAE) is defined as an untoward occurrence that:

- Results in death,
- Is life-threatening,
- Requires hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability or incapacity,
- Consists of a congenital anomaly or birth defect, or

- Is otherwise considered medically significant by the investigator.

The recruiting site research team will only report SAEs if they meet the following criteria:

I. Related to the comparison intervention or procedures and
II. Unexpected (i.e. not listed in the protocol as an expected occurrence)

18.5 Considerations for critically ill participants

ASICS II is a trial of a nutritional intervention in critically ill participants. Considering that all eligible patients are critically ill and are at increased risk of experiencing multiple AEs due to the complexity and severity of their condition, with consequences up to and including death. Please see Appendix 1 for a list of AEs and/or SAEs possibly and definitely related to organ failure and critical illness which are exempt from regulatory reporting.[87,88]

18.6 Notification and reporting of SAEs

SAEs that are considered to be 'related' and 'unexpected' are to be reported to the Sponsor within 72 hours of learning of the event and to the REC within 15 days in line with the required timeframe. The PIs at the sites will submit a SAE form to the CI for any SAEs that are considered to be 'related' and 'unexpected' to the study intervention.

18.7 Urgent safety matters

The CI will take urgent safety measures if necessary to ensure the safety and protection of the clinical study participant from immediate hazards to their health and safety. The measures will be taken immediately. The approval of the REC prior to implementing urgent safety measures is not required. However the CI will inform the sponsor and REC (via telephone) of this event immediately.

The CI will inform the REC in writing within three days, in the form of a substantial amendment. The sponsor (Joint Research Management Office (JRMO)) will be sent a copy of the correspondence with regards to this matter.

18.8 Overview of the safety reporting responsibilities

The CI has the overall oversight responsibility. The CI will ensure that safety monitoring and reporting is conducted in accordance with the sponsor's requirements.

19. Monitoring and auditing

The Sponsor or delegate retains the right to audit any study, study site, or central facility. Any part of the study may be audited by the funders, where applicable.

20. Trial committees

20.1 Trial Management Group (TMG)

The TMG will consist of the CI, trial manager, trial statistician and other key collaborators. Meetings will be held monthly to ensure the progress of the study against milestones and to ensure effective communication across the team. The day-to-day trial team will meet regularly to discuss and monitor progress.

20.2 Trial Steering Committee (TSC)

The TSC will oversee the trial and will consist of several independent clinicians and trialists, sponsor representative, lay representation, co-investigators, and an independent Chair. Meetings will be held at regular intervals determined by need but not less than once a year. The TSC will take responsibility for:

- Major decisions such as a need to change the protocol for any reason
- Monitoring and supervising the progress of the trial
- Reviewing relevant information from other sources
- Informing and advising on all aspects of the trial
- Advising on issues of patient safety during the trial

20.3 Data monitoring and Ethics committee (DMEC)

The DMEC is independent of the trial coordinating team and comprises of a minimum of two clinicians with experience in undertaking clinical studies and a statistician. The DMEC functions primarily to periodically review overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis. The committee will also review relevant new external evidence and monitor the overall conduct of the study. The committee will agree conduct and remit, which will include the early termination process. The study will be terminated early if there is evidence of harm in the intervention group or if recruitment is futile. Generally, the CI identifies any relevant external evidence and passes this to the DMEC Chair for review by the DMEC. The DMEC will provide recommendations about stopping, modifying or continuing the study to the TSC. The DMEC may also make recommendations regarding selection, recruitment, or retention of participants, their management, protocol adherence and retention of participants, and

procedures for data management and quality control. The TSC will be responsible for promptly reviewing the DMEC recommendations, to decide whether to continue or terminate the study, and to determine whether amendments to the protocol or changes in study conduct are required.

21. Finance and funding

ASICS-II is funded by the National Institute of Health Research (**NIHR158620**). The proposal was peer reviewed by internal and external experts during the funding process. Since securing the award, the protocol has since been further reviewed during the study design process.

Nestle Health Sciences will be providing the feed preparation for the participants randomised to the intervention arm.

22. Indemnity

NHS indemnity scheme will apply. It provides cover for the design, management, and conduct of the study.

23. Dissemination of research findings

Responsibility for ensuring accuracy of any publication from this study is delegated to the CI. All publications should acknowledge the Sponsor. Data arising from this research will be made available to the scientific community in a timely and responsible manner. A detailed scientific report will be submitted to a widely accessible scientific journal on behalf of the ASICS-II trial group. All members of the writing committee will comply with internationally agreed requirements for authorship and will approve the final manuscript prior to submission. All publications will be sent to the Sponsor prior to publication. The clinical trial will be registered on a publicly accessible database. The full study report will be accessible via the public website within one year of the EOT Notification. The full study report will also be submitted to the funder.

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APPENDIX 1

AEs and/or SAEs possibly and definitely related to organ failure and critical illness which are exempt from regulatory reporting

- headaches, circulatory effects (e.g. hypotension /hypertension)
- rash
- abdominal pain
- rise in body temperature or fever
- shivering
- chills
- tiredness
- transient increase in liver function tests
- dyspnoea
- chest pain
- hypoxaemia
- rapid pulse
- rapid respiratory rate
- dizziness
- syncope
- altered mental status
- seizure
- confusion
- anxiety
- generalised weakness
- anorexia back pain
- constipation
- pneumonia
- skin infection
- cancer
- electrocardiography abnormalities
- elevated troponin level
- elevated BNP or NT ProBNP level
- high white cell count
- pulmonary infiltrate
- pleural effusion
- cardiomegaly

- shock
- worsening organ failure
- sepsis