JRMO Research Protocol for MHRA Regulated Studies

Full Title	Hospital-acquired Infection Prevention with Parenteral Omegaven
Short Title	HIPPO
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I. Contents

II. Glossary of terms and abbreviations

AR	Adverse Reaction
APR	Annual Progress Report
BOIN	Bayesian Optimal Interval
CI	Chief Investigator
CPIS	Clinical Pulmonary Infection Score
CCPMG	Critical Care and Perioperative Medicine Group
CTCAE	Common Terminology Criteria for Adverse Events
DHA	Docosahexaenoic Acid
DLT	Dose-limiting toxicity
DMEC	Data Monitoring and Ethics Committee
DSUR	Development Safety Update Reports
eCRF	Electronic Case Report Form
EOT	End of Trial
EPA	Eicosapentaenoic Acid
ESPEN	European Society for Clinical Nutrition and Metabolism
FA	Fatty Acids
GCP	Good Clinical Practice
HAI	Hospital-Acquired Infection
IMP	Investigational Medicinal Product
ISF	Investigator Site File
JRMO	Joint Research Management Office
MHRA	Medicines and Healthcare Products Regulatory Agency
NICE	National Institute for Health and Care Excellence
PI	Principal Investigator
PPI	Patient and Public Involvement
QMUL	Queen Mary University of London
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SOFA	Sequential Organ Failure Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee

III. 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 name: **Zudin Puthucheary**

Signature: Zudin Puthucheary Digitally signed by Zudin Puthucheary Date: 2025.02.14 13:34:23 Z

Date: _____

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's name: **Jo Haviland**

Signature: Jo Haviland Digitally signed by Jo Haviland Date: 2025.02.14 14:00:55 Z

Date: _____

Principal Investigator Agreement

The clinical study as detailed within this research protocol (Version 2.0, dated 21/01/2025), 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 name: **Zudin Puthucheary**

Principal Investigator affiliation: **Barts Health NHS Trust**

Signature:

Date: _____

IV. Synopsis

Full title	Hospital-acquired Infection Prevention with Parenteral Omegaven
Short title and / or acronym	HIPPO
Sponsor	Queen Mary University of London
MHRA Risk level	Type B, licenced product in the EU, used for new indication and in a new patient population
Phase of the trial	Phase I/II
Medical condition or disease under investigation	Patients admitted to Adult Critical Care Unit
Study design and methodology	Single-centre randomised controlled dose-escalation trial
Planned number of participants	36 participants
Objectives	Primary objective • To determine the maximum tolerable dose of Omegaven that can be administered in critically ill patients. Exploratory objectives • To measure omega-3 index and fatty acid profile • To characterise immune profiles and function • To characterise metabolic profiles
Inclusion and exclusion criteria	Inclusion criteria: • Patients aged 18 years and over. • Patients requiring intubation and ventilation OR requiring two or more other organ systems support (Sequential Organ Failure Assessment (SOFA) score ≥2 in >2 domains) without requiring intubation and ventilation. • Patients predicted to remain in critical care unit for at least 72 hours as determined by the Intensive Care Consultant with clinical responsibility for patient care. Exclusion criteria (as defined in the patient's medical notes): • Patients requiring total parenteral nutrition at time of enrolment or during the first 10 days • Palliative care admission for end-of-life care or withdrawal of active therapy as determined by the Intensive Care Consultant with clinical responsibility for patient care

	• Neutropaenia (<1x10^9/l) on admission to the Adult Critical Care Unit • Lymphopenia (<0.25x10^9/l) on admission to the Adult Critical Care Unit • Primary immune deficiency • Bone marrow transplant recipient • All immunosuppressive drug therapy (with the exception of corticosteroid use for acute illnesses in the preceding five days) • Recorded or reported allergy to fish, or egg protein or to any of the active ingredients or excipients • Known inborn errors of lipid metabolism • Recorded or reported severe hyperlipidaemia or severe disorders of lipid metabolism (Electronic health record documentation ± clinical concern and if available with serum triglycerides >400 mg/dl on admission to the Adult Critical Care Unit • Enrolment in any other study with an IMP or a study that may have similar primary outcome • Therapeutic anti-coagulation therapy • Pregnancy The absence of the above criteria in the medical notes will be considered to indicate no concern
Investigational Medicinal Product(s)	• Patients in the intervention arm will receive intravenous Omegaven in three different doses (dose-escalation: 0.2, 0.4 and 0.6 g/kg/day) • Patients in the control arm will receive standard care
Treatment duration	10 days or hospital discharge, whichever happens sooner
Follow-up duration	30 days from start of intervention
End of trial definition	This is defined as the date when the last patient's blood sample has been analysed

1.0 Introduction

1.1 Background

Hospital-acquired infections (HAI) are new infections that are typically not present at admission and manifest 48 hours after hospital admission. HAIs include central line-associated bloodstream infections, catheter-associated urinary tract infections, surgical site infections, hospital-acquired pneumonia, ventilator-associated pneumonia, and *Clostridium difficile* infections.[1]The National Institute for Health and Care Excellence (NICE) estimates 300,000 patients a year in England acquire a HAI as a result of care within the NHS, with an estimated cost of £1 billion/year (NICE CG139).[2] HAIs are not only a public health issue but also a major, patient safety concern, monitored by the National Care Quality Commission.[3 4] Europe wide, 2.5 million HAIs are reported yearly with > 90,000 attributed deaths.[5]

Critically ill patients (with or without COVID-19) are more susceptible to HAIs with an incidence of ventilator acquired pneumonia in non-COVID-19 patients of approximately 15-20%.[6-8] This proposal seeks to prevent HAI in critically ill patients using administration of omega-3 fatty acids (FAs). Critically ill patients are often in a catabolic state, with intense metabolic changes, leading to energy deficits, malnutrition, and impaired immune system function.[9] Therefore, medical nutrition therapy needs to be considered for all patients staying in the critical care unit for more than 48 hours. Although oral or enteral nutrition is preferred, often patients will receive parenteral nutrition or total parenteral nutrition. Lipid emulsions should generally be part of parenteral nutrition in critical care but should not exceed 1.5 g lipids/kg/d, according to the latest European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines.[10] Emulsions solely based on soybean oil, rich in omega-6 FAs, should be avoided due to their likely pro-inflammatory effects. Currently, there is no specific recommendation for lipid emulsions containing omega-3 FAs; however, the guidelines allow parenteral lipid emulsions enriched with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (fish oil dose 0.1 - 0.2 g/kg/d) to be used, indicating that they are safe to use and well tolerated. Therefore, omega-3 FA containing lipid emulsions can be part of the parenteral feeding scheme; however, they can also be used as an additional “drug”. In the LIPIDS-P trial, a similar intravenous lipid emulsion containing 15% fish oil was tested for the first time as therapeutic intervention in patients with sepsis and septic shock, rather than as a nutritional intervention.[11]

1.2 Rationale for study design

Several studies highlight the potentially beneficial effects of using omega-3 FAs in critically ill patients. A systematic review from 2012 investigating the effect of omega-3 FA supplementation on inflammatory biomarkers concluded that dietary omega-3 FAs are

associated with lower plasma levels of inflammation and endothelial activation.[12 13] However, the quality of the included studies was deemed low. A few trials including 159 medical and surgical patients across 17 Spanish critical care units found a significant reduction in nosocomial infections and predicted time free of infections in patients receiving total parenteral nutrition prepared with a lipid emulsion containing 10% fish oil (0.1 g fish oil/kg/d).[14] A recent (2020) systematic review with meta-analysis concluded that omega-3 FA enriched lipid emulsions should be preferred over standard lipid emulsions, due to the reported benefits of shortening the length of hospital stay and length of critical care stay by two days, and reducing the risk of sepsis. Similar results were found for critically ill patients.[15 16]

Due to the anti-inflammatory properties, omega-3 FAs may be useful as a therapeutic agent in critically ill patients, preventing them from HAIs. These immunomodulatory effects have been shown in clinical trials in critically ill and surgical patients. However, the acceptable dose that needs to be administered and is tolerated by patients' needs to be determined. This will be clarified in a dose-escalation randomised controlled trial. Inclusion of a control (standard care) group will provide information on expected baseline levels of the outcomes.

1.3 Assessment and management of risk

This trial is categorised as Type B (studies that testing authorised medicinal products according to treatment regimens outside the marketing authorisation) hence this is somewhat higher than the risk of standard medical care.

The investigational medicinal product (IMP) for the HIPPO trial is Omegaven, a licensed product in the EU used for parenteral nutritional supplementation (MA34164.00.00), with long chain omega-3 fatty acids, when oral or enteral nutrition is impossible, insufficient or contraindicated. In the USA Omegaven is also used in paediatric patients with parenteral nutrition-associated cholestasis.

Previously, Omegaven has been used nutritionally in critically ill patients (0.15 g/kg/d – 0.2 g/kg/d) in the EU. [17 18] In the UK, Omegaven has also been used therapeutically in clinical trials to improve clinical outcomes in critically ill patients with sepsis [19] and patients with severe advanced esophagogastric adenocarcinoma receiving palliative chemotherapy, [20] and perioperatively in patients undergoing liver surgery. [21] In Taiwan, Omegaven has also been used therapeutically in critically ill patients with sepsis (10 g/d for 5 days) [22]. In this trial, it will be used for a new indication (therapeutic intervention instead of nutritional support) in a new population (critically ill patients). Therefore, this trial will determine the maximum tolerable dose, across three pre-specified doses, in the critically ill patient population. For most parts, the current Summary of Product Characteristics (SmPC) will be followed, however, patients

with life-threatening conditions, which are listed as contraindication in the SmPC, will not be excluded, since this trial seeks to specifically test the safety of Omegaven in this new patient population. To minimise any risks, all patients enrolled in HIPPO will be inpatients during the intervention and will be monitored throughout their hospital stay.

The route of administration (intravenous; central or peripheral) is defined in the SmPC for the IMP. The lowest proposed dose (0.2 g/kg/d of Omegaven) is based on the ESPEN guidelines.[10] A dose of 0.4 g/kg/d of Omegaven was chosen as a step wise change. The rationale for using 0.6 g/kg/d of Omegaven as the highest dose is that it has been used previously in a clinical trial in critically ill patients in Turkey.[23] This dose is also to prevent lipid overload syndrome or parenteral nutrition-associated liver disease.

For safety reporting all patients receiving the IMP will be assessed at least until five hours after the last infusion has stopped. This is based on 1) the triglyceride half-life for Omegaven being 54 minutes according to the SmPC and 2) the Council for International Organisations of Medical Sciences recommendation to collect Adverse Events (AEs) for at least an additional five half-lives of the IMP, after IMP administration.[24]

2.0 Trial objectives

2.1 Primary objective

- To determine the maximum tolerable dose of Omegaven that can be administered in critically ill adults

2.2 Exploratory objectives

- To measure Omega-3 Index and fatty acid profile
- To characterise immune profiles and function
- To characterise metabolic profiles

2.3 Primary outcome measure

- The primary outcome measure is the maximum tolerable dose of Omegaven, across three pre-specified doses (0.2, 0.4, 0.6 g/kg/d) which will be calculated after the completion of the dose-escalation (see section 2.6 and 7.0 for further details).

2.4 Exploratory laboratory data

Exploratory laboratory data will be collected to characterise the following in comparison to control blood samples:

- The immune profiles (proportion of T-cells, B-cells, monocytes, natural killer cells and neutrophils) and function (including cytotoxicity and antibody production) using flow cytometry before the start of intervention and on day five, 10 and 20 after the start of intervention
- The metabolic profiles (i.e. cytokine production using electro-chemiluminescence and cell metabolic analysis using Seahorse) after treatment with Omegaven in comparison to control blood samples before the start of intervention and on day five, 10 and 20 after the start of intervention.
- Omega-3 Index (% Eicosapentaenoic Acid + Docosaheaxaenoic Acid of total fatty acids) and Fatty Acid (FA) profile (Myristic, Palmitic, Palmitelaidic, Palmitoleic, Stearic, Elaidic, Oleic, Linoelaidic, Linoleic, Arachidic, gamma-Linolenic, Eicosenoic, alpha-Linolenic, Eicosadienoic, Behenic, Dihomo-g-linolenic, Arachidonic, Lignoceric, Eicosapentaenoic, Nervonic, Docosatetraenoic, Docosapentaenoic-n6, Docosapentaenoic n3, and Docosahexaenoic acid) will be measured in blood samples collected before the start of intervention and on day five, 10 and 20 after the start of intervention to be measured at an external laboratory (OmegaQuant).

These data are not part of the core objectives for the HIPPO trial but will provide mechanistic data that would inform a future efficacy trial.

2.5 Objectives and end points summary

Primary Objective	Primary Outcome Measures
• To determine the maximum tolerable dose of Omegaven that can be administered in critically ill adults.	• Maximum tolerable dose calculated after the completion of the dose-escalation

2.6 Trial design

To improve transparency, completeness, reproducibility and trial usefulness of this early phase dose-finding trial, the Standard Protocol Items: Recommendations for Interventional Trials Dose-finding Extensions (SPIRIT-DEFINE) guideline [25] has been followed. This is a dose-escalation, randomised controlled trial, where critically ill patients will receive either Omegaven or standard care for 10 days or until hospital discharge, whichever is sooner. The Bayesian Optimal Interval (BOIN) design is being used to specify the dose-escalation/ de-escalation decision strategy whereby the observed dose-limiting toxicity (DLT) at each dose level is

compared with a pair of escalation and de-escalation boundaries optimised to minimise the risk of patients receiving overly toxic or subtherapeutic doses.[26] The BOIN design implemented in HIPPO is similar to the traditional 3+3 design but provides more flexibility and possesses superior operating characteristics that are comparable to those of more complex model-based designs.[27]

Dose-limiting toxicity assessment

DLT events and assessments will be treated separately from the overall pharmacovigilance described in section 13.0.

Patients will be screened for DLT events once a day (this can be at any point during a 24-hour period) from the start of the intervention until five hours after the completion of the last dose or hospital discharge, whichever occurs first. DLT event screening will also occur in control patients from days 1-11 to compare the event rates with the intervention arm. Screening for DLT events will occur by reviewing routinely collected clinical laboratory tests and clinical examination in the first place. Blood tests include electrolytes, glucose, serum creatinine, liver enzymes (serum ALT, AST, ALP, y-glutamyl transpeptidase) and total serum bilirubin, serum triglycerides, blood count (leukocytes, platelets, red blood cells, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and nucleated red blood cell count) and coagulation measures (prothrombin time, PTR/INR, activated partial thromboplastin time), and acid-base metabolism. If these measures are not available routinely, they will be mandated by the research team. Similarly, daily vital sign measurements (heart rate, blood pressure, body temperature, fluid balance and respiratory rate) will be taken by the research team, if not performed as part of routine care. These results will be noted in the Case Report Form (CRF).

The DLT assessment will be performed by a three-member panel comprising of two independent assessors (Consultant Gastroenterologists) and the Chief Investigator (CI) after the completion of each dosing phase. The panel will be blinded to study arm allocation (intervention or control). In the event that the CI does become unblinded, the delegated sub investigator will replace the CI on the adjudication panel.

Potential DLT events are defined as either a pre-specified AE or serious adverse event (SAE) attributable to Omegaven, as listed in **Table 1.**[28 29] The pre-defined AEs and SAEs have been taken from the “undesirable effects” section in the SmPC for Omegaven, considering effects deemed unacceptable. Thrombophlebitis has also been added to this list and the range for hyper-triglyceridaemia adjusted based on previously published data.[30] To make provision to address any undesirable effects not listed in the SmPC, “Other” has been added to Table 1 as well. These are medical events of concern to the consultant in charge of direct patient care

with potential to be related to Omegaven. Patients will be monitored by senior clinicians at least twice a day as part of standard care. On occurrence of a medical event of concern, the research team will be notified and will assess the event against the US National Cancer Institute guidance document of Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [31], and will record a potential DLT event, if the event is determined as Grade 3 or higher (Figure 1). Following the identification of an event listed in **Table 1**, relatedness to Omegaven will be assessed to determine if the event will be classified as a DLT event.[32] This will be based on a tiered assessment (WHO-UMC causality categories, **Table 2**).[33] If the pre-defined AEs and SAEs in **Table 1** are deemed as definitely or probably/likely related to the intervention, they will be counted towards the DLT assessment.

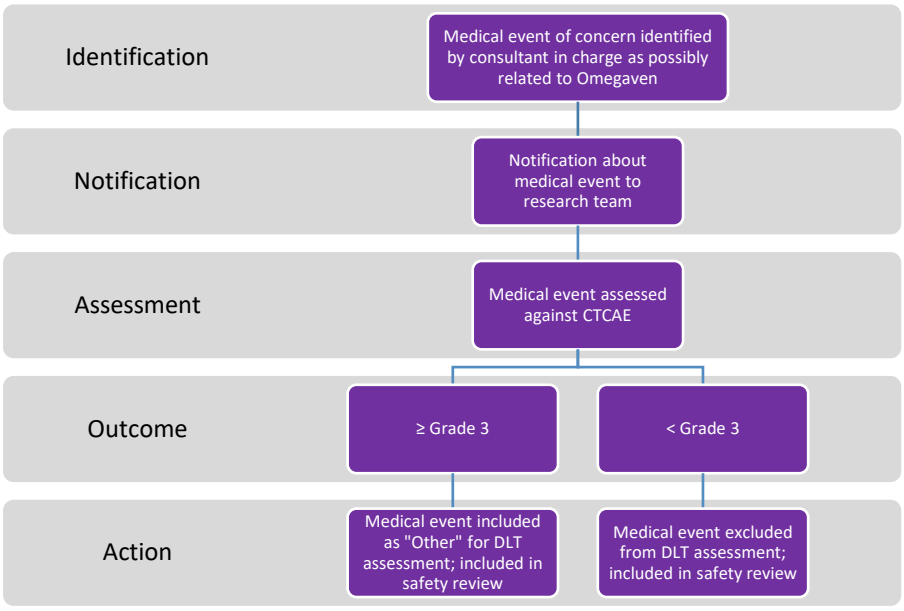

Figure 1 Flow diagram for "Other" DLT identification: *The figure describes the steps of identification of an "Other" DLT for the HIPPO trial.*

CTCAE: Common Terminology Criteria for Adverse Events

Table 1: DLTs defined for the HIPPO trial

DLT events	Description	Initial identification	Criteria	Time scale for consideration	Action (related to trial)
Haemolysis	Widespread erythrocyte cell membrane destruction	- Haemoglobin measured daily. - Treating clinician requests haemolysis screen if indicated. -	- Laboratory evidence of haemolysis (e.g., direct antiglobulin test; schistocytes; decreased haptoglobin) AND - Loss of > 2 g haemoglobin within 24 hours (2 blood tests closest to 24 h apart) AND - Transfusion or medical intervention (i.e. steroids) indicated AND - No other potential cause than the intervention	- Evidence of haemolysis within 24 hours of Omegaven infusion - Transfusions that occur within 24 hours of diagnosis of haemolysis	- Document and contact CI
Hyper-triglyceridaemia	Elevated levels of triglycerides in blood	- Measured daily..	- Triglycerides > 530.97 mg/dl (6 mmol/l)[30]	- If occurs at any point during the infusion or within five half-lives (5 hours) of finishing the infusion	- Stop infusion - Document and contact CI
Reticulocytosis	Increase in circulating reticulocytes (immature red blood cells) as sign of accelerated erythrocyte production	- Measured daily.	- Reticulocytes >100 x10^9 /l [34] AND - No other potential cause than the intervention AND - Need for transfusion within 24 hours of diagnosis	- Need for transfusion within 24 hours of diagnosis	- Document and contact CI
Thrombocytopenia	Deficiency of blood platelets	- Measured daily.	- Platelets <50 x10^9 with requirement of platelet transfusion AND	- Within 24 hours of infusion - Transfusions that occur within 24 hours	- Document and contact CI

			- Absence of other causes of thrombocytopenia such as therapeutic agents (e.g. heparin), chronic diseases	of diagnosis of thrombocytopenia	
Thrombophlebitis	Inflammation in the vein in the presence of an intravenous catheter	- Identified on clinical examination by staff or by patient if conscious. - Absence of documentation will be considered to indicate no concern.	- Grade 3 (Pain at the puncture site with erythema, hardening and a palpable venous cord) OR - Grade 4 (Pain at the puncture site with erythema, hardening and a palpable venous cord that is > 1 cm, with purulent discharge)	- If occurs within 24 hours of any Omegaven infusion, specific to the cannula used to infuse Omegaven.	- Document and contact CI
Urticaria	A skin reaction/rash with itchy welts	- Identified on clinical examination by staff or by patient if conscious. - Absence of documentation will be considered to indicate no concern.	- > 30% body surface area AND - Requiring IV intervention	- Diagnosis within one hour of Omegaven infusion	- Document and contact CI
Other	Medical event of concern to the consultant with clinical responsibility to patient possibly related to Omegaven	- Concern to the consultant in charge and notification of research team	- ≥ Grade 3 event in CTCAE[31]	- If occurs at any point during the infusion or within five half-lives (5 hours) of finishing the infusion	- Document and contact CI

CTCAE: Common Terminology Criteria for Adverse Events v 5.0

Table 2: WHO-UMC Causality Categories[33]

Causality term	Assessment Criteria*
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/ Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not require
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

**Validity of criteria should be judged by independent adjudicator panel*

Dose-escalation plan

The BOIN intervention algorithm for the HIPPO trial is shown in **Figure 2**.[35 36] Cut-offs for the escalation and de-escalation boundaries for the DLT rate were obtained using software available at www.trialdesign.org, using the following input parameters:

- three doses
- target toxicity rate for the maximum tolerable dose 0.30 (30%)
- patients recruited in cohorts of nine,
- maximum sample size is 27
- 0.80 probability cut-off for overdose control

Upon the completion of each dosing phase (defined as at least five hours after the last patient in the phase has finished the last dose of Omegaven), the DLT rate will be computed as follows, and compared with the cut-offs shown in **Figure 2** before treating the next cohort of patients:

$$DLT\ rate = \frac{Number\ of\ patients\ who\ experienced\ DLT\ at\ current\ dose}{Total\ number\ of\ evaluable\ patients\ treated\ on\ current\ dose}$$

Following the DLT assessment and based on the DLT rate, the next nine intervention patients will either:

1) receive the next highest dose if the observed DLT rate on the current dose is ≤0.236
2) remain on the same dose if the observed DLT rate is >0.236 and ≤0.359
3) de-escalate to the next lowest dose if the observed DLT rate is >0.359

If de-escalation is indicated on the lowest dose, the next cohort of patients will continue at the lowest dose. If the probability of the observed DLT rate being greater than the target DLT is >0.80 and if at least three patients are treated at the current dose, the dose is too toxic. Therefore, this dose and any higher doses will be eliminated. If the lowest dose is too toxic, the trial must be terminated.

After the panel meeting that will be held following completion of each dosing phase, a report will be drafted and agreed on by all panel members in a timely manner. The report which will include the recommended dosing plan for the next cohort of patients will be signed off by the trial statistician within two weeks of receipt. Once these approvals are in place, the next cohort of patients will be recruited. These approvals will be filed in the ISF and TMF. Each DLT assessment report will also be reported to the Data Monitoring and Ethics Committee (DMEC) for information only.

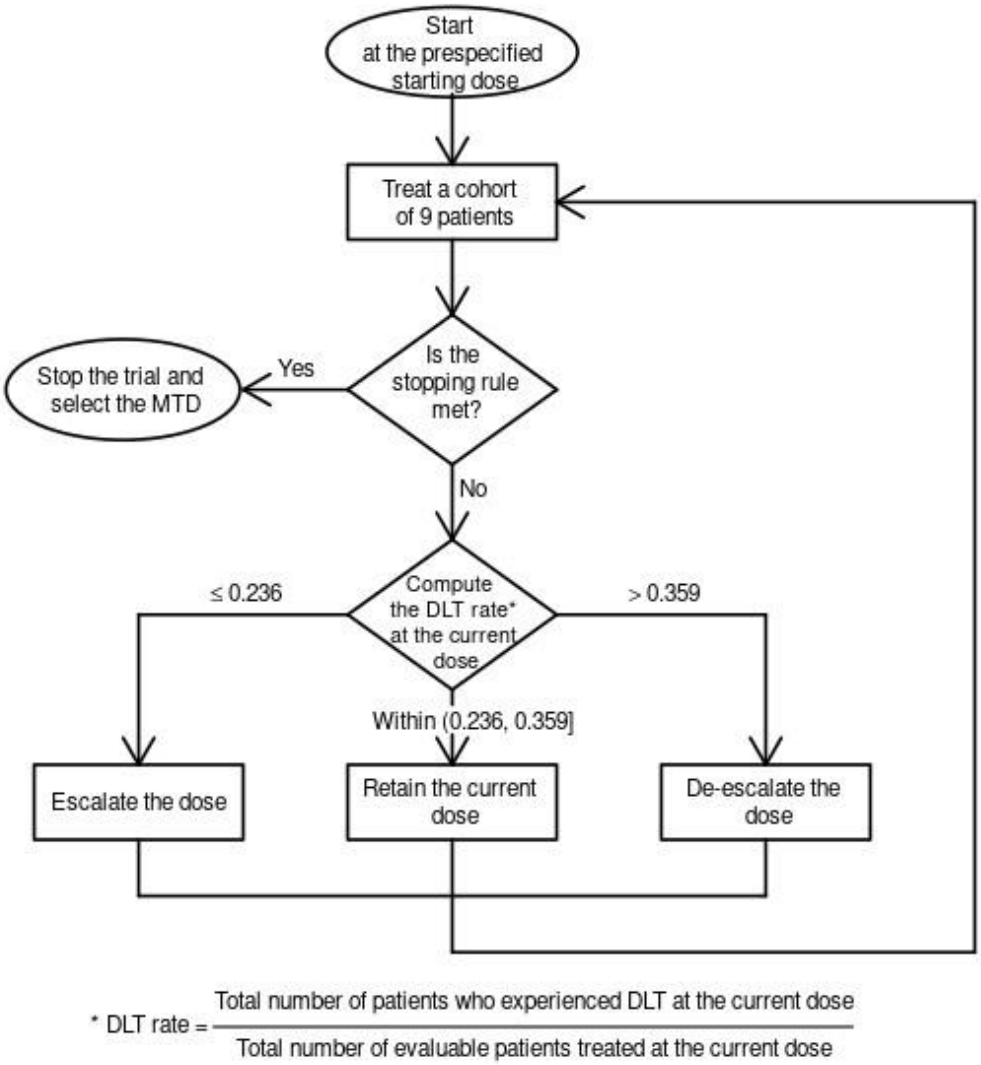

Figure 2 Intervention algorithm: *The figure describes the BOIN dose-escalation and de-escalation plan for the HIPPO trial. At each stage, the DLT events rate will be used to assess whether the dose will be escalated, retained, or de-escalated. The stopping rule at each dosing phase is defined as "Is the maximum sample size reached?". After the stopping rule is met, the maximum tolerable dose (MTD) will be calculated, which is the primary outcome of the trial. Note: If the lowest dose is eliminated due to toxicity the trial is stopped, and no maximum tolerable dose can be obtained.*

DLT = Dose-limiting toxicity, from a list of pre-specified adverse or serious adverse events attributable to Omegaven (Table 1).

BOIN design implementation

The following steps detail the BOIN design implementation plan for the HIPPO trial.

1. Treat patients in the first cohort (nine patients) at the lowest dose (0.2 g/kg/d) of Omegaven
2. Perform DLT assessment as described above
3. Calculate DLT rate

$$DLT\ rate = \frac{Number\ of\ patients\ who\ experienced\ DLT\ at\ current\ dose}{Total\ number\ of\ evaluable\ patients\ treated\ on\ current\ dose}$$

4. Assign a dose to the next cohort of patients:
   Conduct dose-escalation/de-escalation according to the rule displayed in **Table 3**. Notes for using Table 3:
   a. "Eliminate" means eliminate the current and higher doses from the trial to prevent treating any future patients at these doses because they are overly toxic.
   b. When a dose is eliminated, the next cohort is automatically de-escalated to the dose on the next lower level. When the lowest dose is eliminated, the trial is stopped for safety. In this case, no dose should be selected as the maximum tolerable dose.
   c. If none of the actions (i.e., escalation, de-escalation or elimination) is triggered, the new cohort of patients are treated at the current dose.
   d. If the current dose is the lowest dose and the rule indicates dose de-escalation, the new cohort of patients should be treated at the lowest dose unless the number of DLT events reaches the elimination boundary, at which point the trial is stopped for safety.
   e. Number of DLT events in **Table 3** is the number of patients with at least one DLT events, therefore a patient will only be counted once for DLT events assessment, independent of the number of DLT events the patient experiences.

5. Repeat step four until the maximum sample size of 27 patients receiving the intervention is reached, or stop the trial early if the number of patients experiencing DLT events at the lowest dose level reaches the elimination boundaries listed in **Table 3**. In the latter case, no dose should be selected as the maximum tolerable dose.

Table 3 Escalation/De-escalation Rule for the HIPPO trial: *The table details the rules when to escalate, retain, de-escalate or eliminate a treatment dose in the HIPPO trial, based on number of patients with DLT events (Table 1), considering the total number of patients treated with that dose. For HIPPO, cohorts of nine (highlighted columns) are treated. The last row represents the number of patients with DLT events at which the dose is deemed too toxic, and that dose and any higher dose will be eliminated.*

Escalation/De-escalation Rule

Number of evaluable patients treated	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**
Escalate if # of DLT <=	0	0	1	1	1	1	2	2	2	2	3	3	3	3	4	4	4	4	4	5	5	5	5	6	6
Stay if # of DLT =	1	1	NA	2	2	2	3	3	3	3-4	4	4-5	4-5	4-5	5-6	5-6	5-6	5-7	5-7	6-7	6-8	6-8	6-8	7-9	7-9
De-escalate if # of DLT >=	2	2	2	3	3	3	4	4	4	5	5	6	6	6	7	7	7	8	8	8	9	9	9	10	10
Eliminate if # of DLT >=	2	2	3	3	3	4	4	5	5	5	6	6	6	7	7	7	8	8	8	9	9	9	10	10	10

DLT = dose-limiting toxicity
# of DLT is the number of patients with at least 1 DLT
NA = not applicable (no rule available for staying on same dose in this scenario – plan is to either escalate or de-escalate)

Further notes:

Dose-escalation will occur if applicable, to the second (0.4 g/kg/d Omegaven) and third dose (0.6 g/kg/d Omegaven). If no dose-escalation can be performed, another nine participants will either be treated at the same or the lower dose, guided by the dose-escalation plan, leading to 27 patients receiving the intervention, and an additional 9 patients in the control group, to reach the maximum sample size of 36 patients.

The trial will stop if the stopping rule is met (once the maximum sample size for the trial has been reached), irrespective of which doses have been tested; or if the elimination rule is met on the lowest dose (the lowest dose is found to be too toxic) (lowest row in **Table 3**). The maximum sample size for this trial is 36 patients (27 patients receiving the intervention in cohorts of 9 patients, plus 9 control patients).

*For example, after treating nine patients in one phase of the dose-escalation trial the DLT events rates in **Figure 2** translate to the following, as described in **Table 3**:*

- *If ≤2 patients experience DLT events, the dose can increase to the next higher dose*
- *If 3 patients experience DLT events, another nine patients will be treated with the same dose*
- *If ≥4 patients experience DLT events, the current dose and higher doses are eliminated, and the dose has to be de-escalated to the next lower dose.*

2.7 Study setting

A single-centre study, conducted at The Royal London Hospital, Barts Health NHS Trust.

3.0 Patient Evaluability and Replacement

3.1 Target Accrual

36 patients aged 18 years and over admitted to the Adult Critical Care Unit at The Royal London Hospital, Barts Health NHS Trust (27 participants randomised to Omegaven arm and nine participants randomised to standard care).

3.2 Participant identification

Potential participants accepted for admission or admitted to Adult Critical Care at Royal London Hospital will be screened by the direct care team at the site. 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.

4.0 Informed consent procedures

Informed consent will be obtained prior to the participant undergoing trial specific procedures at a participating site. All consent procedures will be documented in detail in the patient's medical notes. The consent procedure is the same for patient's randomise to the standard of care arm or the intervention arm.

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 make a decision on trial enrolment on behalf of the patient. Therefore, in cases where a patient is unable to provide consent, HIPPO will adopt a "research with delayed patient 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.[37] This model is used in a variety of other studies recruiting patients from the Adult Critical Care Unit. [37-39]

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).

Immediate patient informed consent:

If patients have full capacity as deemed by the treating clinician to be able to give 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 PIS accompanied by the ICF, and an explanation of the trial. Patients will be given up to 36 hours depending on the time of approach (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.

Delayed patient consent procedure:

Professional Legal Representative consent

A Professional Legal Representative will be approached in order 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. If the Professional Legal Representative withdraws the patient, the trial treatment will be stopped (if ongoing) immediately. 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.

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 make a decision, 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 delayed 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 delayed consent. It is anticipated that this first approach will occur within 24-48 hours of regaining capacity during their hospitalisation at The Royal London Hospital, 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 or not they would like to continue participation 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 medical notes review will continue unless the participant declines.

If the patient does not regain capacity during their stay at The Royal London Hospital and is transferred to another hospital without providing consent, a covering 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, and if so, to return the consent form or provide witnessed 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.

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 in the patient's medical records by the person seeking consent. This will also be recorded on the eCRF. 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 section 9. 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 entered into this study should be recorded (including reason not entered) 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.

4.1 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.

4.2 Writing, reading, and translation considerations

If verbal translation is needed, an NHS hospital interpreter will be provided as per local trust policy.

4.3 Participants lacking capacity

The consent process for patients temporarily lacking capacity is described above.

5.0 Participant allocation

Since the trial involves an IMP that is unlicensed in UK, the PI or delegated doctors will be required to confirm eligibility of patients identified by the research team in the medical notes prior to approach. Following written informed consent, the patient will be randomised to either the standard care or Omegaven arm in blocks of 12 patients per dose-escalation phase. All randomised patients will be recorded on the study enrolment log with their trial ID.

6.0 Participant eligibility criteria

6.1 Inclusion criteria

- Age 18 years and over
- Patients requiring intubation and ventilation OR two or more other organ systems support (Sequential Organ Failure Assessment (SOFA) score ≥2 in >2 domains) without requiring intubation and ventilation.[40]
- Patients predicted to remain in critical care for at least 72 hours as determined by the Intensive Care Consultant with clinical responsibility for patient care.

6.2 Exclusion criteria

We are specifically not excluding patients with acute life-threatening conditions such as collapse or shock, recent cardiac infarction, stroke, embolism, undefined coma status, severe haemorrhagic disorders or severe liver or renal insufficiency as indicated in the SmPC. We seek to test the safety of Omegaven in critically ill patients (who suffer from these conditions) as part of a new set of indications. The SmPC notes that some of these are considered contraindications as a result of lack of experience, which we seek in this safety trial to inform. In previous studies, Omegaven has been given therapeutically to critically ill patients before, in the UK [19 20], and in- and outside the EU[17 18 22 23], but safety data are scarce. A safety trial such as the one we are proposing is necessary prior to a larger efficacy trial.

Exclusion criteria (as defined in the patient's medical notes):

- Patients requiring total parenteral nutrition at time of enrolment or during the first 10 days.
- Palliative care admission for end-of-life care or withdrawal of active therapy as determined by the Intensive Care Consultant with clinical responsibility for patient care.
- Neutropaenia ($<1x10^9$/l) on admission to the Adult Critical Care Unit
- Lymphopenia ($<0.25x10^9$/l) on admission to Adult Critical Care Unit
- Primary immune deficiency
- Bone marrow transplant recipient
- All immunosuppressive drug therapy (with the exception of corticosteroid use for acute illnesses in the preceding five days)
- Recorded or reported allergy to fish, or egg protein or to any of the active ingredients or excipients
- Known inborn errors of lipid metabolism

- Recorded or reported severe hyperlipidaemia or severe disorders of lipid metabolism
- Electronic health record documentation ± clinical concern and if available: serum triglycerides >400 mg/dl on admission to the Adult Critical Care Unit
- Enrolment in any other study with an IMP or a study that may have similar primary outcome
- Therapeutic anti-coagulation therapy
- Pregnancy

The absence of the above criteria in the medical notes will be considered to indicate no concern.

To verify fish or egg allergies, the electronic patient record will be checked when confirming eligibility. Clinical decision making will also be utilised. If patients are receiving standard enteral feed (Fresubin Original), containing fish oil they are deemed not to have a fish allergy. We will also talk to the clinician with clinical responsibility for patient care asking if there is any concern of an egg or other allergy from any communications from relatives or friends.

Patients in ICU are continuously monitored by the bedside nurse, who will pick up and react to possible signs of allergic reactions. Additionally, the research nurses administering Omegaven will stay at the patient's bedside and monitor the patient every 5 minutes for the first half an hour after the first administration of Omegaven, to make sure administration is of no concern.

7.0 Trial intervention

Following consent, the intervention will start within 48 hours of critical care admission and continue for 10 days or until hospital discharge, whichever is sooner. Participants will receive either standard care or Omegaven.

Standard care arm

Patients in the standard care group will be managed by clinical staff according to local policy and guidelines until hospital discharge. Standard care includes receiving enteral nutrition according to the dietitian's advice.

Intervention arm

Participants will be randomised sequentially in three dosing phases (0.2, 0.4, 0.6 g/kg/d Omegaven) according to the BOIN dose-escalation plan (**Figure 2,** and section below).[35 41] Omegaven will be provided based on bodyweight in kg, except in cases of morbidly obese patients (actual bodyweight > 200% of the ideal bodyweight). In this case, adjusted body weight will be used for Omegaven dosing, using the following formula:

Adjusted bodyweight = ideal body weight + (0.4 x (actual body weight – ideal bodyweight)).[11]

Patients will receive intravenous Omegaven to be administered daily (at any time within a 24-hour period) until day 10 or hospital discharge, whichever is sooner. Omegaven will be administered via a central line if available and if this is not possible it will be given peripherally. The timing of Omegaven administration will be determined in conjunction with the direct care team to ensure intervention delivery can be integrated with direct clinical care. Omegaven will be administered by an appropriately trained and qualified member of the research team, named on the delegation log. Treatment breaks are permitted for clinical reasons, with delivery of <80% of the intervention being considered a deviation.

The infusion rate of Omegaven will be initially set at 0.5 ml Omegaven/kg body weight/hour as specified in the SmPC (maximum infusion rate). For example, a 100 kg patient receiving 0.6 g/kg/d Omegaven would require a 12-hour infusion. The rate can be reduced if there is a clinical indication (e.g. small-bore peripheral canula, or uncontrolled diabetes mellitus (defined as diabetic ketoacidosis, or hypoglycaemic hyperosmolar state, as decided by the critical care consultant with responsibility for patient care)). Further guidance will be provided in the trial specific SOP.

8. Study Schedule

8.1 Schedule of treatment and assessments for each visit

The trial intervention period will commence on the day of randomisation and finish with the 30-day follow-up.

Assessment/ investigations	Within 48 hours of critical care admission/ Day 1 of intervention	Days from start of intervention											
		2	3	4	5	6	7	8	9	10	11	20	30
Eligibility review	x												
Patient informed consent or by Professional/ Personal Legal Representative *	x												
Randomisation	x												
Omegaven administration	x	x	x	x	x	x	x	x	x	x			
DLT events and safety review	x	x	x	x	x	x	x	x	x	x	x		
Trial blood sample	x[#]				x					x		x	
Follow-up in ward/telephone call													x
Medical record review	x	x	x	x	x	x	x	x	x	x	x		x

* Patient consent will be obtained when the patient regains the capacity to consent

[#] before intervention begins

8.2 Trial and follow-up assessments

The following assessments will be done in all participants:

Eligibility

- Screening for inclusion and exclusion criteria
- Medical history
- Informed consent

Randomisation (within 48 hours of admission to critical care)

- Participant Initials
- Trial ID (generated automatically at the point of randomisation)

Baseline data

- Age
- Sex at birth
- Medical history

Day 1-Day 10 or hospital discharge

- IMP administration and details (intervention arm only)
- Safety review

DLT assessment

- Day one continuing daily until day 11

Blood samples

- Before start of intervention (within 48 hours of admission to critical care)
- Day five from start of intervention
- Day 10 from start of intervention
- Day 20 from start of intervention; censured at hospital discharge

Routinely collected data

- Medical note review for
    - Infections
    - Clinical Pulmonary Infection Score
    - Antibiotic free days
    - Ventilator free days

- Mortality
- Length of critical care stay
- Length of hospital stay
- Length of hospital stay before Adult Critical Care Unit admission
- Critical care level received
- Steroid free days
- Renal replacement therapy free days
- Enteral feed intake
- Bristol Stool Score
- SOFA score
- Laboratory values
- Blood transfusions
- Hospital admission

Follow-up phone call at 30 days

- Antibiotic prescriptions after hospital discharge
- Use of omega-3/nutritional supplements in the 3 months prior to hospitalisation
- Ethnicity

8.3 Randomisation method

Once enrolled in the study (provision of informed consent), patients will be randomised to standard care or Omegaven in a simple randomisation (1:3 allocation ratio) in each dosing phase. Randomisation will be performed using an electronic randomisation system embedded within the bespoke online trial database. Please see section 16.6 for more details regarding database.

8.4 Randomisation procedure

Patients will be randomised by a delegated member of the research team using the bespoke trial database. 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. As this is an open label study, allocation is known to medical care team, since it is documented on the patient's medical record.

8.5 Blinding

This is an open label study. Therefore, no unblinding procedure is necessary. However, the independent adjudicators for DLT events will be blinded to study arm allocation. There is no requirement to unblind the independent adjudicators, as this is their only involvement in the trial.

8.6 Unblinding

As described above, no unblinding procedure are required due to the open label approach to this trial.

9.0 Participant, Study, and Site discontinuation

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.

If a patient is withdrawn from the study, up to three patients per treatment phase will be replaced. A patient who has withdrawn from the study cannot re-enter the study, as treatment should be provided on 10 consecutive days.

10.0 Laboratories and samples

10.1 Central laboratories

William Harvey Research Laboratory

This is an academic laboratory at QMUL. Immunological and metabolic assessments will be performed here. These are not standard diagnostic tests; they are performed for research purposes only and are exploratory.

Commercial laboratory for omega-3 Index and FA profile

A Clinical Laboratory Improvement Amendments-certified external laboratory (OmegaQuant) will be used to measure the omega-3 index and the FA profile. Results of these tests are an exploratory outcome and will not impact trial progression. These are not standard diagnostic tests performed for research purposes only and are exploratory.

Barts Health NHS Trust Pathology laboratory

Routine clinical samples from which data will be collected (via Electronic Health Records) will be processed as per usual care.

10.2 Sample collection, labelling, and logging

Where possible, blood sample collection (approximately 40 ml of whole blood) will be at the time of routine blood sampling to minimise discomfort for the participant. All blood samples will be pseudo-anonymised with the participant's trial ID. Samples will be stored in the site's hospital fridge and freezer depending on the subsequent analysis.

The full sample, collection, labelling, logging and transfer will be documented in the study sample log. The trial coordinating team will provide a Sample Management SOP Optional consent will be obtained for leftover blood samples from the blood tubes taken to be stored for future closely related studies and analysis carried out once ethical approval is obtained. A section for 'optional consent' for this purpose has been included in the ICFs.

10.3 Sample transfer, chain of custody, and accountability

Samples will be routinely transferred from Barts Health NHS Trust to QMUL where they will be stored prior to analysis or transferred to contracted laboratories (OmegaQuant). A Material Transfer Agreements or equivalent will be in place for all material transfers, as well as contracts with couriers and laboratories. Sample transfer will be at a temperature required for sample storage and analysis and temperature will be monitored as per Sample Management SOP. Handling of the samples upon arrival at the laboratories 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 sample log provided with the transfer.

10.4 Sample analysis procedures

Immunological and metabolic assessments will be performed in the laboratory at QMUL, procedures will be detailed in the laboratory manual. Omega-3 index and FA profile will be

analysed from dried blood spots at OmegaQuant using a proprietary methodology. To confirm the laboratory assessments are not standard diagnostic tests; they are performed for research purposes only. For further details, please see study specific laboratory manual. Samples used for these analyses will be destroyed during analysis (i.e. samples transferred to OmegaQuant will be destroyed during analysis there; samples transferred to QMUL for immunological and metabolic assessments will be destroyed during the analysis there).

10.5 Sample Storage Procedures

The samples will be stored in pseudo-anonymised form with the participant's trial ID written on the label. Samples will be stored at the appropriate temperature, please see the Sample Management SOP. Samples already collected will not be destroyed if a patient withdraws from the study. Samples not destroyed during analysis will be retained for a further 6 months after the EOT, in case data analysis prompts reanalysis of any samples.

10.6 Sample and result recording and 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.

10.7 Sample Management at End of study

Most samples will be destroyed during analysis. At the end of the study, remaining samples will be destroyed in accordance with the Human Tissue Authority's Code of Practice, unless a further ethics application will be made for any surplus samples. The Consent Form contains a section to ask for consent for surplus samples to be used in closely related future studies that are approved by regulatory bodies.

11.0 Trial medication

11.1 Name and description of investigational medicinal product(s) (IMPs)

The IMP is Omegaven emulsion for infusion (containing fish oil 10 g) in 100 mL vial and further details about the IMP can be found in the SmPC.

11.2 Legal status of Omegaven

Omegaven is an EU only licenced product. For the HIPPO trial, the drug will be imported from Germany as a German marketed product (MA34164.00.00), with a German commercial label

from the manufacturer's facility to Royal London Hospital Clinical Trial Pharmacy in the UK for the purposes of a clinical trial. Annex 13 compliant label will be applied at Royal London Clinical Trial Pharmacy.

11.3 Summary of Product Characteristics (SmPC)

The SmPC used for this trial is for the 10 g/100 ml Omegaven provided by Fresenius Kabi.

11.4 Drug storage and supply

EU-QP released finished marketed product with German marketed labels will be supplied by Fresenius Kabi directly to Clinical Trials Pharmacy, Royal London Hospital UK. Shipments to sites will be initiated and managed by the trial management team who will monitor Omegaven stocks at site and subsequently initiate re-supplies. Upon receipt of a shipment, Clinical Trials Pharmacy will check the condition of the contents, and whether the temperature during transit was acceptable. Thereafter, Omegaven will be transferred to and stored at the agreed out-of-pharmacy location in the Research room, which has restricted access and appropriate temperature monitoring. Please see IMP Management Plan for more details.

11.5 Supplier/ Manufacturer

Omegaven supply will be arranged by Fresenius Kabi via a sub-contracted third-party specialised logistics company, that will handle the customs clearance process for distributing the drug (shipment documentation, pick up, shipper packaging, temperature monitoring, and delivery to pharmacy at site). Upon MHRA approval, the final consignee which is site Clinical Trials Pharmacy will be able to receive and handle the Omegaven product. Since the product received by Barts Health NHS Trust is unaltered, QP certification within the UK would not be required.

The application of a trial specific clinical label (that comply with annex 13 requirements) to the German commercial product will be done by clinical trial site pharmacy via the regulation 37 exemption (MHRA). Therefore, no UK MIA(IMP) is involved and neither UK QP verification nor UK QP certification is required for labeled IMPs.

Once the product has been labelled as per Annex 13 guidelines it will become an IMP and will be transferred to the appropriate site location. Please see Table 4 for the HIPPO-Supply chain diagram.

Sponsor will ensure that IMPs are provided to study site(s) only after regulatory green light and formal regulatory release by Sponsor for use in a study (= Site Initiation & IMP release for use in a study by Sponsor).

Table 4: HIPPO-Supply chain diagram

Name	Function	Location
Fresenius Kabi	Manufacturer of Bulk Drug Product and primary packaging of Drug Product with German label. EU QP release in Germany/EU in primary packaging (commercially available German marketed finished drug product with German marketed labels) Provision of Transmissible Spongiform Encephalopathy Statement, Certificate of Analysis and Certificate of Conformity Ship the Drug Product from Germany to UK via third party specialised logistic company	Fresenius Kabi Deutschland GmbH Else-Kröner-Straße 1 61352 Bad Homburg, Germany
Third party specialised logistics company	Subcontracted by Fresenius Kabi. Pickup of product from Fresenius Kabi, Germany. Oversee and execute customs clearance (shipment documentation, pick up, temperature monitoring) and delivery of the drug to Barts Health Clinical Trial Pharmacy.	Safe GmbH Mergenthalerallee 73 - 75, 65760 Eschborn, Germany and/or Marken Time Critical Express GmbH Mönchhofallee 13, 65451 Kelsterbach, Germany
Royal London Hospital Clinical Trials Pharmacy	Receipt and labelling of drug product to comply with Annex 13 requirements (using the regulation 37 exemption) Releasing drug product for transfer to research team	Clinical Trials Pharmacy 5th Floor, Pathology and Pharmacy Building 80 Newark Street London E1 2ES
ACCU Research Team	Storage of Drug Product for HIPPO trial Dispensing of Drug Product to participants	ACCU Research Offices 4th Floor, Office 14 Royal London Hospital Whitechapel London E1 1FR

11.6 How the drug should be stored

The storage conditions for Omegaven as per the SmPC are specified as follows:

1) Do not store above 25°C
2) Do not freeze

11.7 Accountability

The site Clinical Trials pharmacy/trial management team will maintain the IMP accountability records, including, but not limited to, quantity of vials received, quantity of vials dispensed and to which participant, batch number, expiry date, and quantity of vials destroyed. A patient specific dosing schedule will also be completed with date, batch number, expiry date, quantity of vials dispensed and initials of person dispensing. The IMP Management Plan will specify this in further detail.

11.8 Prescription and Dispensing of IMP(s)

The trial medication must only be used to treat participants in the HIPPO trial and should be taken from the HIPPO trial stock only. Only the PI or a person appropriately trained and assigned on the delegation log, will be allowed to prescribe the drug to the participant.

The exact procedures for dispensing Omegaven will be agreed with the Sponsor prior to site activation and clearly documented in the investigator site file and the Pharmacy Site File. Trial-specific working practices will be agreed with the Trust pharmacist in the IMP Management Plan. Each member of staff who dispenses the IMP will sign the accountability logs to document appropriate IMP tracking.

11.9 Administration of IMP(s)

Omegaven will be administered intravenously, as per description in the SmPC. Administration will be via central access as a first choice if available, and via peripheral access as a second choice. The Omegaven vial should be shaken before use as per guidelines on SmPC. Omegaven should not be given in the same intravenous line as heparin, calcium, potassium and magnesium. IMP administration will be by an appropriately trained member of the research team assigned on the delegation log.

11.10 Assessment of compliance

The dose and the duration of the drug administered will be recorded on the participant's medical notes and the electronic case report form (eCRF). If an incorrect dose is administered,

a dose is missed, or <80% of a dose is administered, a protocol deviation form should be completed.

11.11 Destruction, return, and recall of IMP(s)

Any dispensed drug will be destroyed in accordance with Barts Health Trust waste management policy. Expired or unusable drugs (e.g. due to temperature deviation) will be returned to the clinical trials pharmacy for destruction.

11.12 Management of Omegaven specific adverse events

On the occurrence of AEs which specifically relate to Omegaven, the infusion rate can be reduced or stopped if deemed necessary at the discretion of the direct care team. In case of hyper-triglyceridemia (see definition in **Table 1**) the Omegaven infusion will be stopped as soon as possible.

11.13 Concomitant medication

The infusion of Omegaven can cause a prolonged bleeding time and an inhibited platelet aggregation. Therefore, Omegaven should be administered with caution to patients requiring anticoagulant therapy, even with regard to a possible reduction of anticoagulants. Incompatibilities may also occur through the addition of polyvalent cations, e.g. calcium, especially when combined with heparin. Full details of interaction with medicinal products and other forms of interaction can be found in the SmPC. Patients will be closely monitored for any harms during the course of the intervention.

11.14 Recommended concurrent treatment

No specific concurrent treatment is necessary. Patients should receive standard care as concurrent treatment.

11.15 Prohibited medication

There are no prohibited medication and please refer to the SmPC for further details.

11.16 Study restrictions

There are no study restrictions.

11.17 Precautions regarding contraception

Patients enrolled in HIPPO will be admitted to the adult critical care unit and it would be acceptable to say there is no chance of the participant falling pregnant during the trial intervention. Due to the short half-life of the IMP, no precaution needs to be taken after the first 11 days of IMP administration.

11.18 Management of overdose

No antidote available.

12.0 Equipment and Devices

This study includes no equipment or device.

13.0 Pharmacovigilance

13.1 General definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an IMP which is related to any dose administered to that participant. The phrase "response to an IMP" means that a causal relationship between a study medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the study medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: Results in death. Is life-threatening. Requires inpatient hospitalisation or prolongation of existing hospitalisation <may define what constitutes hospitalisation – e.g. A&E admission, day cases may not be considered hospitalisation> Results in persistent or significant disability/incapacity. Consists of a congenital anomaly or birth defect.

	Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator or medical assessor, believed with reasonable probability to be due to one of the study treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the Reference Safety Information (RSI): In the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product. In the case of any other IMP, in the investigator's brochure (IB) relating to the study in question.

13.2 Site investigator assessment

The PI, who is also the CI for this trial, is responsible for the care of the participant, or in their absence an authorised medic within the research team is responsible for assessment of any event for:

Seriousness

Assessing whether the event is serious according to the definitions given in section 13.1.

Causality

Assessing the causality of all SAEs and SARs in relation to the study treatment according to the definition given. If the SAE is assessed as having a reasonable causal relationship, then it is defined as a SAR.

Expectedness

Assessing the expectedness of all SARs according to the definition given. If the SAR is unexpected (as per the reference safety information), then it is a SUSAR.

Severity

Assessing the severity of the event according to the following terms and assessments. The intensity of an event should not be confused with the term "serious" which is a regulatory definition based on participant/event endpoint criteria.

Mild: Some discomfort noted but without disruption of daily life

Moderate: Discomfort enough to affect/reduce normal activity

Severe: Complete inability to perform daily activities and lead a normal life

13.3 Reference Safety Information

Reference safety information can be found in the SmPC under section 4.8.

13.4 Notification and recording of Adverse Events (AEs) or Reactions (ARs)

All AE and ARs unless listed in section 13.6, are to be documented in the participants' medical notes and the eCRF. Participants will be followed up by the research team until resolved.

13.5 Notification of AEs of Special Interest (AESIs)

Not applicable.

13.6 AEs that do not require reporting

AEs or SAEs that are expected and do not require reporting for this trial are taken from the SmPC. However, AEs and SAEs that are defined as DLT events (Table 1) will be reported.

Similarly, considering that all eligible patients are critically ill and at increased risk of experiencing multiple AEs, the below list defines possibly and definitely expected AEs or SAEs related to organ failure and critical illness which are exempt from regulatory reporting.[11 43]

AEs or SAEs not requiring reporting in this trial:

Prolonged bleeding time, fishy taste, headaches, circulatory effects (e.g. hypo/hypertension), rash, abdominal pain, nausea, vomiting, rise in body temperature or fever, shivering, chills, tiredness, transient increase in liver function tests, metabolic overload symptoms (hepatomegaly with or without icterus, change in reduction in bleeding time, coagulation time, prothrombin time, splenomegaly, headache, stomach pains, fatigue, hyperglycemia), 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 (atrial arrhythmias, right bundle branch block, and ST and T wave changes), elevated troponin level, elevated BNP or NT ProBNP level, high white cell count, pulmonary infiltrate, pleural effusion, cardiomegaly, shock, worsening organ failure, or sepsis.

13.7 Notification and reporting of Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs)

All SAEs, apart from those listed in 13.6 and SUSARs will be recorded in the participants' notes, the eCRF, the sponsor SAE form and reported to the sponsor (administered by the Joint

Research Management Office (JRMO) or agreed representative) and the IMP provider (as per contract with the funder/manufacturer) within 24 hours of the site becoming aware of the event.

Nominated co-investigators (as listed) will be authorised to sign the SAE forms in the absence of the PI at the participating site.

13.8 Sponsor medical assessment

Sponsor has delegated the responsibility for oversight of IMP safety profile and medical assessment of AEs, ARs, SAEs and SUSARs to the CI as medical assessor. The CI must review all SAEs within 72 hours of receipt. This review should encompass seriousness, relatedness, and expectedness. Day 0 for all SUSARs is when the SAE / SUSAR is received by the CI and / or coordinating team and / or Sponsor (whichever is first).

It is noted that the CI cannot downgrade the PI assessment of an event's causality. If there is disagreement between CI and PI assessment, no pressure should be placed on the PI to alter their assessment, but the CI can liaise with the site PI before the CI's final decision. The CI and PI assessment can differ.

13.9 Procedures for reporting blinded SUSARs

Not applicable as there will be no blinding.

13.10 Urgent safety measures

The CI may take urgent safety measures to ensure the safety and protection of the clinical study participants from any immediate hazard to their health and safety, in accordance with Regulation 30 of the Medicines for Human Use (Clinical Trials) regulations. The measures should be taken immediately. In this instance, the approval of the Competent Authority prior to implementing these safety measures is not required.

The CI has an obligation to inform both the MHRA and Research Ethics Committee (REC) in writing **within 3 days** of implementing the Urgent Safety Measure. They must also submit a substantial amendment documenting the changes with 14 days of implementing the urgent safety measure. The JRMO must be sent a copy of the correspondence with regards to this matter as soon as it is sent.

13.11 Pregnancy

There is no evidence on the safety of this medicine during pregnancy or breastfeeding. Therefore, pregnant patients will be excluded from the trial. As per hospital policy, female patients of childbearing potential (16-55) will receive a routine pregnancy test at critical care admission. These results will be considered when screening patients for eligibility to be included in the trial and pregnant patients will be excluded from participation. Any unexpected pregnancies occurring during the administration of the IMP is not considered to be an SAE or an AE and will be reported per Sponsor SOP and followed up to term. The Sponsor should be notified immediately (within 24 hours of site becoming aware of the pregnancy), using the Sponsor pregnancy form. Follow-up information should be submitted as and when it becomes available up to the birth of the infant. Any events to the mother or child that occur during the pregnancy until birth that could be considered to be a SAE must be reported to the Sponsor in line with section 13.7 using the Sponsor SAE reporting from. The Sponsor will arrange for a review of the pregnancy report by an appropriate expert medic (usually a consultant obstetrician). The study team must follow all instructions provided by the Sponsor's expert. The pregnancy reporting procedure will be the same as the SAE reporting route. If a pregnancy is confirmed during the trial IMP administration phase, the IMP will be stopped, if ongoing, as soon as the study team becomes aware of the pregnancy and the participant will be withdrawn from the trial. In this case the participant will be replaced. Pregnancies conceived after the 11 days of IMP administration will not be followed up due to the short half-life of the IMP (54 minutes).

14.0 Annual reporting

14.1 Development Safety Update Report (DSUR)

The DSUR will be written by the CI (following Sponsor procedures) and submitted to the sponsor for review prior to submission to the MHRA. The DSUR is due for submission within 60 days of the end of the reporting period. The reporting period is annually from the date on the "Notice of acceptance letter" from the MHRA. The sponsor's delegated Medical Assessor, usually the CI, will carry out a risk benefit analysis of the IMPs encompassing all events having arisen on the study. REC will be sent a copy of the DSUR.

15.0 Statistical and data analysis

15.1 Sample size calculation

A total of 36 participants will be recruited (randomised 1:3 control:intervention). The number of participants treated on each dose of Omegaven will be determined by the escalation / de-escalation rule specified in the BOIN design shown in **Figure 2** and **Table 1**, which aims to exclude a toxicity rate of ≥ 30%. The minimum number of participants to be treated on a single dose is nine and the maximum is 27. Assuming mortality of approximately 20-30% in critically ill patients, we will replace up to a maximum of three patients in each study phase in case of patient death, or withdrawal. There is no formal assessment of sample size required for a phase I dose escalation trial, however 36 participants (nine control and 27 intervention) will be sufficient to provide pilot data on the exploratory outcomes. A published study with eight patient samples per group enabled examination of the p38 inhibitor and identification of a doubling in proliferation and cytotoxicity as measured by granzyme and perforin expression using nine patients per group would provide almost 80% power to detect a mean difference of 12 in %CD107a CD8+ EMRA T cells (assuming SD=6 and α=0.05) (unpublished data, Henson)[15]. Early phase trials often use less conservative type I error rates as they can be considered screening studies to inform a future definitive trial; with this sample size the trial would have 87.4% power for α=0.1 and 94.4% for α=0.2 using the parameters given above.

15.2 Planned recruitment rate

The estimated planned recruitment rate is two to three patients per month. Since the inclusion criteria is all adult patients predicted stay of 72 hours in critical care, we are aiming to finish the study over a 12–15-month recruitment period. The CI has a track record of leading research studies like ASICS [44] and PROSPER. The study coordinator is responsible for driving recruitment and support and encourage the delivery team to meet the recruitment target.

15.3 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 and MHRA once reviewed by sponsor. The EOT notification must be received by REC and MHRA within 90 days of the end of the trial. If the study is ended prematurely, the CI will notify the Sponsor, REC, and MHRA within 15 days, including the reasons for the premature termination.

15.4 Statistical Analysis

After the completion of the dose-escalation (stopping rule met), the maximum tolerable dose (primary outcome) will be calculated using an isotonic regression considering the DLT events across all doses[35]. This computation is implemented by the "BOIN" app available at http://www.trialdesign.org.[26] The maximum tolerable dose is selected as the dose for which the isotonic estimate of the toxicity rate is $\leq$0.359 and closest to the target toxicity rate (0.30). If there are ties, the higher dose level is selected when the isotonic estimate is lower than the target toxicity rate and the lower dose level is selected when the isotonic estimate is greater than or equal to the target toxicity rate.

Analyses of the exploratory outcomes will estimate dose-response effects of Omegaven, using the data from the control group as a comparator. Analyses of the exploratory clinical and laboratory outcomes will primarily use descriptive statistics. Quantitative data will be summarised by group, using descriptive statistics including mean (standard deviation) or median (interquartile range), as appropriate. Categorical data will be summarised by group, using frequencies and percentages. Further exploratory analysis of the laboratory outcomes will use repeated measures analysis of covariance including data at all follow-up time-points to compare each dose level with concurrently randomised controls, adjusting for baseline values. Differences between groups will be described using point estimates and 95% confidence intervals.

Given that the majority of data collection will occur in hospital, we anticipate a low missing data rate. A full statistical analysis plan will be drawn up prior to analysis, and will include handling of missing data, outliers, protocol violations.

15.5 Summary of baseline data and flow of participants

Reporting of trial results and flow of participants will be in accordance with the CONSORT Dose-finding extension (CONSORT-DEFINE) guidance.[45]

15.6 Analysis of participant populations

Analyses will include all participants who receive at least one dose of Omegaven.

15.7 Primary endpoint analysis

Described in section 15.4.

15.8 Secondary endpoint analysis

N/A.

15.9 Safety analysis

Frequencies and type of AEs will be recorded for each randomised group (control and intervention), and each dose level of Omegaven.

15.10 Subgroup analyses

There is no planned subgroup analysis.

15.11 Adjusted analysis

As described in section 15.4 the exploratory analysis of the laboratory outcomes will adjust for baseline values in the analysis of covariance. There will be no additional adjustments.

15.12 Interim analysis and criteria for the premature termination of the study

There will be no interim analysis. However, there is a safety assessment, before every dose-escalation, which might trigger staying on the same dose, dose de-escalation or termination.

15.13 Procedure(s) to account for missing or spurious data

There will be no imputation of missing data on the exploratory outcomes. The reasons for missing data will be recorded in the CRF, for e.g. withdrawal etc.

15.14 Other statistical considerations

As described in section 9.0 if a patient withdraws, dies, or is excluded by their Intensive Care Consultant with clinical responsibility for patient care or the study team during the 10-day dosing period, they will be replaced. Three such patients, in case of withdrawal or death, will be replaced in each study phase.

16.0 Data handling and record keeping

16.1 Source data and source documents

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. Source data are contained in source documents (original records or certified copies). Only members of the direct care team are entitled to have access to patients' medical records before consenting to the trial. A source data agreement will be in place for the site. 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.

16.2 Case Report Forms (CRFs)

A summary of the data collection points and times can be found in section 8.2 Research staff at each hospital will be responsible for the completion of the electronic case report form for the duration of the study. Site will be provided with a paper data collection tool that matches the electronic Case Report Form (eCRF) however, it is not compulsory to complete this if it has been completed electronically.

The eCRF and randomisation system will be custom designed by Queen Mary University of London using a bespoke clinical trial database system called 'Datameld' and will be hosted on a secure server in accordance to Sponsor requirements. A requirement specifications document will be created detailing these aspects of the database.

16.3 Data capture

Data required for the trial will be collected by the delegated investigators or the research nurses and captured in an eCRF. Source data will be obtained from the sites medical notes including the electronic patient record and in accordance with the source data agreement at each site. Source data will be reviewed as part of the source data verification during site monitoring.

16.4 Transferring and transporting data

All data must be handled in accordance with the Data Protection Act (2018) and General Data Protection Guidelines. No data will be transferred outside of the UK. Identifiable information will not be stored, transported on any portable device (e.g. laptops, memory sticks) unless it is encrypted and will not be sent electronically; if it is not subject to end-to-end encryption. Barts Health Participant Identifiable Data (PID) will not be taken out of Barts Health without participant consent.

16.5 Data Management

A full data management plan will be developed to describe in detail the methods of data management. All participant data collected will be entered onto a secure electronic data entry system. The site Principal Investigator will oversee and be responsible for data collection, quality and recording. Collection of data can be delegated (as per the Delegation Log) by the site Principal Investigator to qualified members of the research team. Data entered onto the secure electronic data entry system will undergo validation checks for completeness, accuracy and consistency of data. The electronic storage will be located on a restricted area of the file server. Submitted data will be stored securely against unauthorised manipulation and accidental loss. Queries on incomplete, inaccurate or inconsistent data will be sent to the local research team at participating sites for resolution. Security of the electronic data entry system is maintained through usernames and individual permissions approved centrally by the HIPPO trial mangers. Central back-up procedures are in place. Storage and handling of confidential trial data and documents will be in accordance with the Data Protection Act (2018) and General Data Protection Regulations. Representatives of the trial management team will require access to patient notes for quality assurance purposes and source data verification, but patients' confidentiality will be respected at all times. 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.

16.6 HIPPO Database

The HIPPO trial will be using a bespoke clinical trial database system called 'Datameld'. The HIPPO trial database manager will design and maintain the trial database in compliance with the Sponsor SOP for Data Management Systems. The database will be hosted on a secure server located within the United Kingdom, with access restricted to authorised personnel. The system is backed up regularly and is available 24/7, including on weekends and bank holidays. Further requirements will be defined in the Requirement and Specification Document (RSD) and stored in the TMF. A database service agreement will be executed for this trial.

17.0 Confidentiality

The CI will be the data custodian for all data generated during the study.

The CI and the study team will ensure that all participants' identities are protected at every stage of the study. To ensure this, at time of screening, each participant will be allocated a unique screening number by the research nurses before the patients undergo any further procedures.

The PI is responsible for protecting the identity of participants at their site. Participants will be referred to only by their unique study identifier whenever data is transferred outside of the site, and in all correspondence between the site and the coordinating centre, co-investigators, sponsor, or anyone associated with the study. Under no circumstances, patient identifiable data or consent forms will leave the site. No participants will be individually identifiable from any publications resulting from the study.

Information regarding study participants will be kept confidential and managed in accordance with the Data Protection Act (2018), the UK Policy Framework for Health and Social Care and Research Ethics Committee approval. All study data will be stored in line with the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments and the Data Protection Act. Study data will be archived in line with the Medicines for Human Use (Clinical Trials) Regulations 2004 and all subsequent amendments, and as defined in the JRMO SOP 20 Archiving.

17.1 De-identification of participants

A screening log will be maintained at site throughout the study, detailing the potential participant's initials and a screening ID to allow their identification by relevant site staff. Once the participant has completed screening procedures and is enrolled onto the study, they will be allocated a unique trial identifier by the coordinating team. All data will be de-identified before it is used. Identifiable data will be de-identified, kept secure, and maintained by the creation and use of a unique identifier for each participant. Encrypted data will be password protected with limited access afforded to the minimum number of individuals necessary for quality control, audit, and analysis.

18.0 Monitoring, Audit, and Inspection

18.1 Monitoring

The JRMO Clinical Trial Monitor has the responsibility of monitoring the trial at Barts Health NHS Trusts. A trial specific Monitoring Plan will be developed by the JRMO and CI, detailing all monitoring procedures including onsite visits based on the Sponsor risk assessment; the Sponsor and CI will agree on the monitoring plan. The Investigation site team will be initiated and monitored in line with JRMO SOP 28 – Monitoring.

18.2 Auditing

The Sponsor retains the right to audit any aspect of the study, study sites, or central facilities. In addition, any part of the study may be inspected by the regulatory bodies, and funders where

applicable. All sites and vendors are asked to inform the Sponsor if notified of any Audit or inspection affecting this study.

19.0 Compliance

The CI will ensure that the protocol and study is conducted in compliance with the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments, current UK Policy Framework for Social and health care research (2017), GCP guidelines, the Human Tissue Act 2004, the World Medical Association Declaration of Helsinki, the Sponsor's and study specific SOPs, and other regulatory requirements. The study will not commence until sponsor permission to activate sites is received. Sites will be individually activated by the CI and team; this will not occur until site approval is granted.

19.1 Non-Compliance

Non-compliances may be captured from a variety of different sources including monitoring visits, eCRFs, communications and updates. The Sponsor will maintain a log of the non-compliances to ascertain if there are any trends developing which need to be escalated. The CI and the trial coordinating team should assess the non-compliances and action a timeframe in which they need to be dealt with. This assessment should include the need to escalate to the Sponsor. Any event with the potential to affect participant safety or data integrity should be reported to the Sponsor within 24 hours of the trial coordinating team becoming aware. Where applicable corrective and preventative actions (CAPA) should be assigned. Each action will be given a different timeframe dependent on the severity. If the actions are not dealt with accordingly, the Sponsor will agree an appropriate action, including an on-site audit. Deviations from the protocol which are found to frequently recur are not acceptable. This will require immediate action and could potentially be classified as a serious breach. Protocol deviations must be documented on the supplementary form in the eCRF.

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used (i.e. it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the study protocol).

Non-compliances may be captured from a variety of different sources including monitoring visits, CRFs, communications and updates. The sponsor will maintain a log of non-compliances to ascertain if there are any trends developing which need to be escalated.

19.2 Notification of Serious Breaches to GCP and/or the protocol

A 'serious breach' is a breach which is likely to affect to a significant degree:

- The safety or physical or mental integrity of the participants of the study; or
- The scientific value of the study

The site PI is responsible for reporting any potential serious breaches to the sponsor (research.safety@qmul.ac.uk) within 24 hours of becoming aware of the event.

The CI is responsible for reporting any potential serious breaches to the JRMO **within 24 hours** of becoming aware of the event. The Sponsor is responsible for determining whether a potential serious breach constitutes a serious breach and will work with the CI to investigate and notify and report to the MHRA and REC (as applicable) within 7 working days of becoming aware of the serious breach.

20.0 Declaration of interests

The CI/PI and all committee members for the overall study management will provide the below details as required by the Sponsor:

- Personal or professional relationships with the IMP manufacturer/company
- Ownership interests that may be related to products, services, or interventions considered for use in the study or that may be significantly affected by the study.
- Commercial ties (e.g., pharmaceutical, behaviour modification, and/or technology companies).
- Non-commercial potential conflicts (e.g., professional collaborations that may impact on academic promotion).
- Full details will be held within the trial master file. Please address enquiries to the CI.
- All study committee members will complete competing interest declarations.

21.0 Peer review

The protocol has been reviewed by the funder Fresenius Kabi as part of the funding application process. Furthermore, the protocol has undergone a scientific peer review by two independent experts in the field (independent of QMUL and Barts Health).

22.0 Public and Patient Involvement (PPI)

Both the Fresenius Kabi grant application and protocol have been reviewed by PPI. The PPI have been involved in the initial design of all trial participant facing literature, design of the trial and to ensure that the trial proposal is understandable to intended participant population. A PPI representative will also be invited to be member of the Trial Steering Committee (TSC).

23.0 Insurance

The insurance that QMUL has in place provides cover for the design and management of the study as well as "No Fault Compensation" for participants, which provides an indemnity to participants for negligent and non-negligent harm.

24.0 Study committees

The CI will take overall responsibility for the delivery of the HIPPO trial and oversee progress against timelines/ milestones.

24.1 Trial Management Group (TMG)

The TMG will consist of the CI, trial managers, 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.

24.2 Trial Steering Committee

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

24.3 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.

25.0 Publication and dissemination policy

25.1 Publication

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 HIPPO Trial Group. The trial steering committee will agree the membership of a writing committee, which will take primary responsibility for final data analysis and writing of the scientific report. 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.

25.2 Dissemination policy

The data generated from the entire trial including any sub-studies will be solely owned by QMUL and upon completion of the trial, the data will be analysed, tabulated and a Final Trial Report prepared. The role of Data Controller will be solely QMUL. The CI will be Data Custodian for the entirety of the trial and QMUL serve as Data Processor.

25.3 Access to the final study dataset

Access to the final dataset will be granted only to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections. A full (detailed list) of who will have access to the Final Trial Dataset will be as per the Data Management Plan and will outline the access, data entry, upload and/or transfer.

26.0 Archiving

During the course of the trial, all records are the responsibility of the CI and will be kept in secure conditions. When the research study is complete, it is a requirement of the Queen Mary University of London and Barts Health Policy that the records are kept for a further 25 years as per sponsor SOP 20 Archiving. Any destruction of essential documents will require authorisation from the Sponsor.

27.0 References

1. Monegro AF, Muppidi V, Regunath H. Hospital-Acquired Infections. StatPearls. Treasure Island (FL)2024.
2. National Institute for Health and Care Excellence. Healthcare-associated infections: prevention and control in primary and community care. London2017.
3. NHS England. Healthcare associated infections Redditch2024 [cited NHS England. Available from: https://www.england.nhs.uk/patient-safety/healthcare-associated-infections/ accessed 28/05/2024.
4. Care Quality Commisssion. NHS trusts: information for providers 2022 [Available from: https://www.cqc.org.uk/guidance-regulation/providers/assessment/single-assessment-framework/safe/infection-prevention-control.
5. Cassini A, Plachouras D, Eckmanns T, et al. Burden of Six Healthcare-Associated Infections on European Population Health: Estimating Incidence-Based Disability-Adjusted Life Years through a Population Prevalence-Based Modelling Study. *PLoS Med* 2016;13(10):e1002150. doi: 10.1371/journal.pmed.1002150 [published Online First: 20161018]
6. Grasselli G, Scaravilli V, Mangioni D, et al. Hospital-Acquired Infections in Critically Ill Patients With COVID-19. *Chest* 2021;160(2):454-65. doi: 10.1016/j.chest.2021.04.002 [published Online First: 20210420]
7. Conway Morris A, Datta D, Shankar-Hari M, et al. Cell-surface signatures of immune dysfunction risk-stratify critically ill patients: INFECT study. *Intensive Care Med* 2018;44(5):627-35. doi: 10.1007/s00134-018-5247-0 [published Online First: 20180607]
8. Ibn Saied W, Mourvillier B, Cohen Y, et al. A Comparison of the Mortality Risk Associated With Ventilator-Acquired Bacterial Pneumonia and Nonventilator ICU-Acquired Bacterial Pneumonia. *Crit Care Med* 2019;47(3):345-52. doi: 10.1097/CCM.0000000000003553
9. Boisrame-Helms J, Toti F, Hasselmann M, et al. Lipid emulsions for parenteral nutrition in critical illness. *Prog Lipid Res* 2015;60:1-16. doi: 10.1016/j.plipres.2015.08.002 [published Online First: 20150928]
10. Singer P, Blaser AR, Berger MM, et al. ESPEN guideline on clinical nutrition in the intensive care unit. *Clin Nutr* 2019;38(1):48-79. doi: 10.1016/j.clnu.2018.08.037
11. Guirgis FW, Black LP, Rosenthal MD, et al. LIPid Intensive Drug therapy for Sepsis Pilot (LIPIDS-P): Phase I/II clinical trial protocol of lipid emulsion therapy for stabilising cholesterol levels in sepsis and septic shock. *BMJ Open* 2019;9(9):e029348. doi: 10.1136/bmjopen-2019-029348 [published Online First: 20190918]
12. Rangel-Huerta OD, Aguilera CM, Mesa MD, et al. Omega-3 long-chain polyunsaturated fatty acids supplementation on inflammatory biomakers: a systematic review of randomised clinical trials. *Br J Nutr* 2012;107 Suppl 2:S159-70. doi: 10.1017/S0007114512001559
13. Lu C, Sharma S, McIntyre L, et al. Omega-3 supplementation in patients with sepsis: a systematic review and meta-analysis of randomized trials. *Ann Intensive Care* 2017;7(1):58. doi: 10.1186/s13613-017-0282-5 [published Online First: 20170605]
14. Grau-Carmona T, Bonet-Saris A, Garcia-de-Lorenzo A, et al. Influence of n-3 polyunsaturated fatty acids enriched lipid emulsions on nosocomial infections and clinical outcomes in critically ill patients: ICU lipids study. *Crit Care Med* 2015;43(1):31-9. doi: 10.1097/CCM.0000000000000612
15. Henson SM, Macaulay R, Riddell NE, et al. Blockade of PD-1 or p38 MAP kinase signaling enhances senescent human CD8(+) T-cell proliferation by distinct pathways. *Eur J Immunol* 2015;45(5):1441-51. doi: 10.1002/eji.201445312 [published Online First: 20150330]
16. Pradelli L, Klek S, Mayer K, et al. Omega-3 fatty acid-containing parenteral nutrition in ICU patients: systematic review with meta-analysis and cost-effectiveness analysis. *Crit Care* 2020;24(1):634. doi: 10.1186/s13054-020-03356-w [published Online First: 20201103]
17. Burkhart CS, Dell-Kuster S, Siegemund M, et al. Effect of n-3 fatty acids on markers of brain injury and incidence of sepsis-associated delirium in septic patients. *Acta Anaesthesiol Scand* 2014;58(6):689-700. doi: 10.1111/aas.12313 [published Online First: 20140324]
18. Grecu I, Mirea L, Grintescu I. Parenteral fish oil supplementation in patients with abdominal sepsis. *Clinical Nutrition* 2003;22:S23. doi: 10.1016/S0261-5614(03)80086-9
19. Hall TC, Bilku DK, Al-Leswas D, et al. A randomized controlled trial investigating the effects of parenteral fish oil on survival outcomes in critically ill patients with sepsis: a pilot study. *JPEN J Parenter Enteral Nutr* 2015;39(3):301-12. doi: 10.1177/0148607113518945 [published Online First: 20140109]
20. Eltweri AM, Thomas AL, Chung WY, et al. The Effect of Supplementary Omegaven® on the Clinical Outcome of Patients With Advanced Esophagogastric Adenocarcinoma Receiving Palliative Epirubicin, Oxaliplatin, and Capecitabine Chemotherapy: A Phase II clinical trial. *Anticancer Res* 2019;39(2):853-61. doi: 10.21873/anticanres.13185
21. Linecker M, Botea F, Aristotele Raptis D, et al. Perioperative omega-3 fatty acids fail to confer protection in liver surgery: Results of a multicentric, double-blind, randomized controlled trial. *J Hepatol* 2020;72(3):498-505. doi: 10.1016/j.jhep.2019.10.004 [published Online First: 20191015]
22. Khor B-S, Liaw S-J, Shih H-C, et al. Randomized, Double Blind, Placebo-Controlled Trial of Fish-oil-based Lipid Emulsion Infusion for Treatment of Critically Ill Patients With Severe Sepsis. *Asian Journal of Surgery* 2011;34(1):1-10. doi: https://doi.org/10.1016/S1015-9584(11)60011-0
23. Sungurtekin H, Degirmenci S, Sungurtekin U, et al. Comparison of the effects of different intravenous fat emulsions in patients with systemic inflammatory response syndrome and sepsis. *Nutr Clin Pract* 2011;26(6):665-71. doi: 10.1177/0884533611418783
24. Council for International Organizations of Medical Sciences Working Group VI. Management of Safety Information from Clinical Trials. Geneva, Switzerland, 2005.

25. Yap C, Rekowski J, Ursino M, et al. Enhancing quality and impact of early phase dose-finding clinical trial protocols: SPIRIT Dose-finding Extension (SPIRIT-DEFINE) guidance. *BMJ* 2023;383:e076386. doi: 10.1136/bmj-2023-076386
26. Zhou Y, Lin R, Kuo YW, et al. BOIN Suite: A Software Platform to Design and Implement Novel Early-Phase Clinical Trials. *JCO Clin Cancer Inform* 2021;5:91-101. doi: 10.1200/CCI.20.00122
27. Yan F, Thall P, Lu K, et al. Phase I–II clinical trial design: a state-of-the-art paradigm for dose finding. *Annals of Oncology* 2018;29(3):694-99.
28. Kurzrock R, Lin CC, Wu TC, et al. Moving Beyond 3+3: The Future of Clinical Trial Design. *Am Soc Clin Oncol Educ Book* 2021;41:e133-e44. doi: 10.1200/EDBK_319783
29. Le Tourneau C, Lee JJ, Siu LL. Dose escalation methods in phase I cancer clinical trials. *J Natl Cancer Inst* 2009;101(10):708-20. doi: 10.1093/jnci/djp079 [published Online First: 20090512]
30. National Institutes of Health. ATP III Guidelines at a glance quich desk reference, 2001.
31. SERVICES USDOHAH. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, 2017.
32. Pande S. Causality or Relatedness Assessment in Adverse Drug Reaction and Its Relevance in Dermatology. *Indian J Dermatol* 2018;63(1):18-21. doi: 10.4103/ijd.IJD_579_17
33. Uppsala Monitoring Centre. The use of the WHO-UMC system for standardised case causality assessment. In: WHO, ed. Uppsala, 2018.
34. East and South East London Pathology Partnership. Haematology and Blood Transfusion Laboratory Handbook: East and South East London Pathology Partnership, 2024.
35. Liu S, Yuan Y. Bayesian optimal interval designs for phase I clinical trials. *Journal of the Royal Statistical Society: Series C: Applied Statistics* 2015:507-23.
36. Bayesian Optimal Interval (BOIN) Design for Phase I Clinical Trials (V3.0.7.0) [program]: Available at: www.trialdesign.org, 2024.
37. Lamontagne F, Richards-Belle A, Thomas K, et al. Effect of Reduced Exposure to Vasopressors on 90-Day Mortality in Older Critically Ill Patients With Vasodilatory Hypotension: A Randomized Clinical Trial. *JAMA* 2020;323(10):938-49. doi: 10.1001/jama.2020.0930
38. Curry N, Davenport R, Lucas J, et al. The CRYOSTAT2 trial: The rationale and study protocol for a multi-Centre, randomised, controlled trial evaluating the effects of early high-dose cryoprecipitate in adult patients with major trauma haemorrhage requiring major haemorrhage protocol activation. *Transfus Med* 2023;33(2):123-31. doi: 10.1111/tme.12932 [published Online First: 20221102]
39. Davenport R. ACIT-2: An observational study investigating the systemic inflammatory, coagulation and genomic response in humans to severe injury and bleeding after major trauma: ISRCTN; 2021 [updated 27/03/2024. Available from: https://www.isrctn.com/ISRCTN12962642 accessed 28/05/2024.
40. Huerta LE, Wanderer JP, Ehrenfeld JM, et al. Validation of a Sequential Organ Failure Assessment Score using Electronic Health Record Data. *J Med Syst* 2018;42(10):199. doi: 10.1007/s10916-018-1060-0 [published Online First: 20180914]
41. Yuan Y, Hess KR, Hilsenbeck SG, et al. Bayesian Optimal Interval Design: A Simple and Well-Performing Design for Phase I Oncology Trials. *Clin Cancer Res* 2016;22(17):4291-301. doi: 10.1158/1078-0432.CCR-16-0592 [published Online First: 20160712]
42. The British Association for Parenteral and Enteral Nutrition. Parenteral Nutrition Monitoring Letchworth, England.: The British Association for Parenteral and Enteral Nutrition; 2024 [Available from: https://www.bapen.org.uk/education/nutrition-support/parenteral-nutrition/parenteral-nutrition-monitoring/ accessed 28/05/2024 2024.
43. Cook D, Lauzier F, Rocha MG, et al. Serious adverse events in academic critical care research. *CMAJ* 2008;178(9):1181-4. doi: 10.1503/cmaj.071366
44. McNelly A, Langan A, Bear DE, et al. A pilot study of alternative substrates in the critically Ill subject using a ketogenic feed. *Nature Communications* 2023;14(1):8345. doi: 10.1038/s41467-023-42659-8
45. Yap C, Solovyeva O, de Bono J, et al. Enhancing reporting quality and impact of early phase dose-finding clinical trials: CONSORT Dose-finding Extension (CONSORT-DEFINE) guidance. *BMJ* 2023;383:e076387. doi: 10.1136/bmj-2023-076387 [published Online First: 20231020]