MASTER PROTOCOL

Full Study Title: Precision medicine Adaptive Network platform Trial in Hypoxaemic acutE respiratory failuRe

Study Acronym: PANTHER

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The study will have multiple funders across different regions. All funders will be displayed on the study website.

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This protocol describes the PANTHER trial and provides information about procedures for enrolling participants to the trial. The protocol should not be used as a guide for the treatment of other participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study, but centres enrolling participants for the first time are advised to contact the Trial Coordination centre to confirm they have the most recent version. Problems relating to this trial should be referred, in the first instance, to the Trial Coordination centre.

This trial will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. It will be conducted in compliance with the protocol, the Data Protection Act 2018 and other regulatory requirements as appropriate.

ABBREVIATIONS

AE	Adverse Event
ARDS	Acute Respiratory Distress Syndrome
CI	Chief Investigator
CRF	Case Report Form
DMC	Data Monitoring Committee
EC	Ethics Committee
eCRF	Electronic Case Report Form
EQ-5D-5L	Health-related quality of life questionnaire
HADS	Hospital Anxiety and Depression Scale
ICTU	Imperial Clinical Trials Unit
IMP	Investigational Medicinal Product
ISA	Intervention Specific Appendix
ITMG	International Trial Management Group
ITSC	International Trial Steering Committee
LAR	Legally Authorised Representative
MoCA	Montreal Cognitive Assessment
MMST	Manual Muscle Strength Testing
POR	Proportional Odds Ratio
QA	Quality Assurance
RSI	Reference Safety Information
RSA	Region Specific Appendix
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SF-36	Social and Wellbeing questionnaire
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SPPB	Short Physical Performance Battery function test
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction

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TRIAL SUMMARY

TITLE: Precision medicine Adaptive Network platform Trial in Hypoxaemic acutE respiratory failuRe (PANTHER)

OBJECTIVES
To accelerate the development of pharmacological therapies for critical illness by establishing an international phase 2 precision medicine adaptive platform trial to test the efficacy of prioritised pharmacological interventions in critically ill patients, including acute respiratory distress syndrome (ARDS) and pandemic infection, with different subphenotypes.

PHASE: 2

DESIGN
A multicentre, allocation concealed, randomised, open-label Bayesian adaptive multi-arm platform trial with pre-defined triggers for efficacy and futility stopping (as compared to usual care). The trial will stratify participants by biological markers into different subphenotypes. Initial stratification will be into hyperinflammatory and hypoinflammatory subphenotypes in ARDS based on plasma biomarker profiles. Regular adaptive analyses will enable efficient identification of treatment effects within each subphenotype, stopping interventions where there is evidence of efficacy or futility, and bringing in new interventions and new subphenotypes.

SAMPLE SIZE
As a platform trial the sample size is not fixed. Pre-defined statistical triggers for efficacy and futility determine the stopping of interventions and the replacement by new interventions. The initial maximum number to be recruited globally per intervention for hypoinflammatory patients is 504 and for hyperinflammatory patients it is 529. Usual care is not limited by a maximum sample size and will recruit for the duration of the trial.

INCLUSION/EXCLUSION CRITERIA
Inclusion criteria

1) Critically ill patients in hospital and at least 1 of the following: -
    a) Acute respiratory distress syndrome (ARDS)*
    b) A pandemic associated syndrome (this will be triggered if a new pandemic is declared)

*ARDS as defined by
(i) a known acute clinical insult or new or worsening respiratory dysfunction, and
(ii) receiving respiratory support via invasive mechanical ventilation or non-invasive ventilation including continuous positive airway pressure, or high-flow nasal oxygen ≥30L/min and
(iii) Within the same 24-hour time period:

- bilateral opacities on chest imaging not fully explained by effusions, lobar/lung collapse/atelectasis, or nodules, and
- respiratory failure not fully explained by cardiac failure, fluid overload, pulmonary embolism, acute airways disease, or interstitial lung disease and,
- PaO2/FiO2 ratio <40 kPa from arterial blood gases, or SpO2/FiO2 <315 from pulse oximetry where SpO2 <97.

The time of onset of ARDS is when the last criterion in (iii) is met.

Exclusion criteria
Platform level:
(a) >48 hours from diagnosis of ARDS
(b) Planned withdrawal of life-sustaining treatment within the next 24 hours
(c) Previous enrolment in the PANTHER trial in the last 12 months
(d) Declined consent

Additional intervention-specific exclusion criteria will apply which are detailed in each intervention-specific appendix.

TREATMENT/MAIN STUDY PROCEDURES (including treatment duration and follow-up).
Therapeutic interventions will be compared with usual care within each subphenotype (see intervention appendices). We will start the platform with 2 interventions and usual care. Additional therapeutic interventions can enter the trial by replacing the initial interventions when they reach criteria for efficacy, for futility, or the maximum sample size or if the scope of the platform expands.

OUTCOME MEASURES

PRIMARY ENDPOINT
28-day organ support-free days, incorporating mortality as a composite on an ordinal scale. Organ support is defined as needing either respiratory or cardiovascular support.

SECONDARY ENDPOINT(S)
i. 28-day vasopressor-free days
ii. 28-day respiratory support–free days
iii. Receiving new renal replacement therapy
iv. Progression to invasive mechanical ventilation, extracorporeal membrane oxygenation or death among those not receiving that support at baseline
v. ICU length of stay
vi. Hospital length of stay
vii. All-cause mortality at 28 and 90 days,
viii. Safety outcomes (as defined in secondary endpoint section 3.5)
ix. Serious adverse events
x. Physical function (SPPB) at hospital discharge (up to 1 week prior to discharge)
xi. Cognitive function (MoCA) at hospital discharge (up to 1 week prior to discharge)

<u>If it is not possible to collect physical function and cognitive impairment measures prior to hospital discharge, this will not be a protocol deviation.</u>

TERTIARY ENDPOINT(S)*
i. 14-day delirium and coma free days
ii. Incidence of ICU acquired weakness (MMST and hand grip strength dynamometry and maximal inspiratory pressure) at day 7 and ICU discharge
iii. Health-related quality of life, (EQ-5D-5L) at 90 days and 180 days
iv. Hospital Anxiety and Depression Scale (HADS) at 90 days and 180 days
v. Social and Wellbeing (SF-36) at 90 days and 180 days

vi. Impact of Events Scale (6 item) at 90 days and 180 days
vii. Care and wellbeing needs at 90 days and 180 days
viii. Cognitive function (MoCA) at 90 days and 180 days

*Not all sites are expected to collect these endpoints

PHENOTYPING

Initial subphenotypes will be the hyper and hypoinflammatory subphenotypes described in ARDS.

Over time additional / alternative biomarkers to determine subphenotypes may be added.

1. PROTOCOL STRUCTURE

The structure of this protocol differs from that of a conventional trial due to the trial's adaptive nature. These adaptations are specified using a modular protocol structure.

The master protocol contains information about the general conduct of the platform. Detailed information about the interventions, approaches to subphenotyping, statistical methods and regional specific governance are detailed in separate appendices. The structure of the protocol allows for the addition of a pandemic appendix which would describe how the platform could recruit in the setting of a pandemic.

1.1 Master Protocol

This document acts as the master protocol for the entire platform. It contains all information that is generic to the trial irrespective of the regional location in which the trial is conducted and the interventions being tested.

The protocol has the following additional appendices:

1.2 Intervention Specific Appendices

These will be separate appendices providing information specific to each intervention. Each intervention specific appendix will be submitted to Ethics and local Regulatory Authority prior to commencement. Each intervention specific appendix will include:

- Background of the intervention
- Inclusion/exclusion criteria specific to the intervention
- Delivery of the intervention
- Any intervention specific reporting (including safety)

1.3 Region Specific Appendices

PANTHER is an international trial and will be conducted in various geographical locations. As such, region-specific appendices will include all information required to conduct the trial in a specific region. This will enable the addition of new regions or changes to existing ones without the need to amend the master protocol. The region-specific appendix should be submitted for ethics and regulatory review alongside the master protocol and all other relevant appendices. The region-specific appendix will include:

- Definition of the region
- Organisation of trial management of the region
- Ethical and regulatory considerations

1.4 Statistical Analysis Appendix

This will describe in detail the statistical analyses to be conducted during PANTHER as well as the final analyses after any intervention meets a stopping

rule. It will be updated as required when new interventions or subphenotypes are added.

1.5 Statistical Design Appendix

This appendix will describe the design and simulation study to examine the trial operating characteristics. The trial uses a Bayesian analysis framework, and the design is centred around the selection of optimal stopping rules over the range of potential trial results balancing power and type I error alongside sample size. The statistical design appendix will be updated as the trial progresses and changes may be necessary e.g. in response to the addition of new interventions or new subphenotypes such that the outcome rate or subphenotype proportion in the population differs.

1.6 Subphenotype Appendix

This appendix will describe how subphenotypes will be identified and which devices will be used in the process.

2. BACKGROUND

Critical illness is characterised by life-threatening organ dysfunction caused by a dysregulated host response to an acute insult including infection and trauma, which has significant patient burden and is a major healthcare problem. For those that survive, it can be life-changing, with long term physical and psychological consequences.

Critically ill patients are described in both clinical practice and research according to clinical syndromes, such as Acute Respiratory Distress Syndrome (ARDS). ARDS is characterised by non-cardiogenic pulmonary oedema (identified by opacities on chest X-ray). ARDS affects all age groups, has a high mortality of up to 30-50% and causes a long-term reduction in quality of life for survivors (1, 2). ARDS has significant resource implications in terms of ICU and hospital stay. The delivery of critical care to patients with ARDS accounts for a significant proportion of ICU capacity. In addition, survivors often have long-term physical and cognitive impairment requiring support in the community and many survivors are unable to return to work 12 months after hospital discharge (3-5). The high incidence, mortality, long-term consequences and high economic cost mean that ARDS is an extremely important problem.

There are currently no proven pharmacological treatments for ARDS (outside of COVID-19), other than general supportive therapies and treating the underlying insult. There is significant clinical and biological heterogeneity within critical illness syndromes which has contributed to the failure to date to translate pre-clinical research into effective therapies. Using syndromic definitions does not provide information on which subgroups of patients are likely to respond effectively and safely to a given pharmacological treatment.

A new paradigm in critical care suggests that de-emphasising clinical syndromic definitions and focusing on subphenotypes more closely linked to the host biological response is the key to identifying effective therapeutics (6), which remains a significant area of unmet need. Considerable recent progress has been made towards identifying biological

subphenotypes in patients with ARDS, which appear to respond differently to specific interventions in secondary analysis of completed randomised controlled trials (7–9).

Developing effective pharmacological therapies for ARDS will improve patient outcomes in an area of significant unmet need as well as reducing costs. Survivors of ARDS experience reduced health-related quality of life, with substantial health care and societal costs. Resolution of lung injury is a predictor of less long-term disability in ICU survivors (4). Therefore, effective pharmacological therapies that hasten the resolution of ARDS may also enhance quality of life for ARDS survivors.

In summary, ARDS is a life-threatening condition with high mortality rates and there are no proven pharmacological treatments outside of ARDS caused by COVID-19. Given this landscape of high mortality, biological plausibility, and lack of effective therapies, there is a scientific rationale to repurpose agents with proven safety profiles in critically ill patients outside their licensed indications and prescribing restrictions.

Precautions on use of potential therapies are often derived from chronic use contexts in non-life threatening conditions, not the short-term, high-mortality setting of ARDS. In ARDS, where there is high unmet need, the risk-to-benefit balance likely differs dramatically. The expected benefit (improved survival, reduced duration of organ support) may outweigh potential adverse effects, particularly in the setting where no other therapy exists. In contrast to chronic use where cumulative exposure risks are more relevant, short-duration therapy (or until ICU discharge) in a highly monitored ICU environment substantially mitigates those risks.

As part of routine care laboratory measurements, including liver enzymes, renal function, and full blood count, are regularly measured in patients in ICU. In addition, again as part of routine care, patients in ICU are monitored for signs of infection and antibiotics started where infection is suspected.

Finally where specific laboratory monitoring is required, eg creatine kinase and liver enzymes, these will be measured regularly as defined in the protocol with stopping rules for the IMP based on defined thresholds which have been used safely in the setting of trials of the critically ill. As a result of this clinical routine and protocol defined monitoring in ICU and anticipated risk-to-benefit balance these stopping rules may be more liberal to what has been described in the IMP SmPC for chronic use.

For similar justification, the investigator will use their clinical discretion to follow the guidance for the concomitant use of other drugs detailed in the ‘special warnings and precautions for use’ and ‘interaction with other medicinal products’ provided in the approved version of the IMP SmPC.

Restricting the use of IMPs based on licensing boundaries designed for other populations or long-term settings withholds potential benefit in a condition with high mortality and no proven pharmacological interventions. When paired with appropriate safety monitoring, their repurposing is justified and urgently needed.

This adaptive platform trial which stratifies critically ill patients based on their biological subphenotype, will enable a “precision medicine” approach to accelerate the development of pharmacological therapies for critical care.

2.1 Interventions

Interventions for the platform trial will be selected through a prioritisation process. Initial proposals have come from co-investigators. Over time, external clinical, academic or industry investigators may submit proposals.

Proposals are considered by the PANTHER intervention selection committee based on the existing evidence base, including safety and other pharmacological data, and also feasibility. This committee will then make recommendations to an independent intervention committee who will advise the platform trial management group who will make the final decision about inclusion into the platform. The Trial Steering Committee, Data Monitoring Committee and funder(s) will be informed of the plan to introduce a new intervention prior to the commencement of the intervention.

It is anticipated that new interventions will join the platform at intervals, as others reach criteria for efficacy, for futility, or the maximum sample size. Over time, the evidence supporting interventions is likely to evolve. Therefore, interventions deemed to have insufficient support at the time of assessment may continue to be periodically reconsidered.

Details of each intervention, including rationale, pharmacological information, specific inclusion / exclusion criteria, dose, duration and other intervention specific information are provided in separate intervention appendices.

2.2 Subphenotypes

Multiple approaches to identify subphenotypes of clinical syndromes in critically ill patients have been proposed. These subphenotypes may also determine differential treatment effect. In order to assess treatment response by subphenotype, in this platform subphenotype will be determined prior to randomisation.

Initially the platform will use the hyper and hypoinflammatory subphenotypes previously described in ARDS. More detail about these subphenotypes and how they will be determined in the platform, including devices used, is contained in a separate appendix. It is expected that additional subphenotypes, using different biological samples and devices will be added over time.

3. OBJECTIVES AND ENDPOINTS

3.1 Primary Objective

To accelerate the development of pharmacological therapies for critical illness by establishing an international phase 2 precision medicine adaptive platform trial to test the efficacy of prioritised pharmacological interventions in patients with ARDS and pandemic infection.

3.2 Secondary Objective

To develop an infrastructure for identifying, developing and testing additional subphenotypes and therapies for critical illness in the ongoing platform trial.

3.3 Tertiary Objective

Additional objectives are to establish an ongoing platform trial that:

- plays a leading role in international collaborative research efforts.
- provides a vehicle for early career investigators to build clinical trial capacity.
- can facilitate collaboration with commercial partners to test promising innovative therapies for critical illness.
- is sustainable through a combination of academic and commercial funding opportunities.
- can collect samples and data on other precision medicine factors.
- can rapidly pivot in the event of a new pandemic of a pathogen associated with respiratory failure, providing pandemic preparedness infrastructure.

3.4 Primary Endpoint

Primary endpoint: 28-day organ support-free days, incorporating mortality.

This is a composite ordinal scale outcome. All deaths are scored “-1” on the ordinal scale, i.e., the worst outcome. Then to assess important changes in outcome for surviving participants, the number of days free of organ support up until day 28 is calculated, so that a high score is good as it corresponds to a quicker recovery. Organ support is defined as needing either respiratory or cardiovascular support. Respiratory support is defined as invasive mechanical ventilation or non-invasive ventilation including continuous positive airway pressure or high-flow nasal oxygen with an $FiO_2 \geq 0.4$ and a flow rate ≥30L/min. Cardiovascular support is defined as the continuous infusion of any vasopressor or inotrope medication.

Being free of organ support is defined as the last time receiving support and does not require a specified time period to define success.

3.5 Secondary Endpoints

i. 28-day vasopressor-free days
ii. 28-day respiratory support–free days
Iii. Receiving new renal replacement therapy
iv. Progression to invasive mechanical ventilation, extracorporeal membrane oxygenation or death among those not receiving that support at baseline
v. ICU length of stay
vi. Hospital length of stay
vii All-cause mortality at 28 and 90 days
viii. Safety outcomes:-

- Elevated Creatine Kinase more than 10 times the upper limit of normal
- Alanine Transaminase or Aspartate Transaminase more than 8 times the upper limit of normal
- Severe thrombocytopenia, out of keeping with clinical disease
- Severe neutropenia, out of keeping with clinical disease
- Serious infection defined as a positive blood cultures requiring treatment and pulmonary aspergillosis requiring treatment
- Venous thromboembolism
- Stroke
- Myocardial infarction

- Ischaemic bowel
- Gastrointestinal perforation
- Clinically important gastrointestinal (GI) bleeding. Defined as overt bleeding on GI endoscopy, developing as a complication in the ICU and accompanied by 1 or more of the following features within 24 hours:-
    - Spontaneous drop of systolic, mean arterial pressure or diastolic blood pressure of 20mmHg or more
    - Start of vasopressor or a 20% increase in vasopressor dose
    - Decrease in haemoglobin of at least 2 g/dl
    - Transfusion of 2 unites of packed RBC or more

ix. Serious adverse events
x. Physical function (SPPB) at hospital discharge (up to 1 week prior to discharge)
xi. Cognitive function (MoCA) at hospital discharge (up to 1 week prior to discharge)

If it is not possible to collect physical function and cognitive impairment measures prior to hospital discharge, this will not be a protocol deviation.

3.6 Tertiary Endpoints*

i. 14-day delirium and coma free days
ii. Incidence of ICU acquired weakness (MMST and hand grip strength dynamometry and maximal inspiratory pressure) at day 7 and ICU discharge
iii. Health-related quality of life, (EQ-5D-5L) at 90 days and 180 days
iv. Hospital Anxiety and Depression Scale (HADS) at 90 days and 180 days
v. Social and Wellbeing (SF-36) at 90 days and 180 days
vi. Impact of Events Scale (6 item) at 90 days and 180 days
vii. Care and wellbeing needs at 90 days and 180 days
viii. Cognitive function (MoCA) at 90 days and 180 days

*Not all sites are expected to collect these endpoints

4. STUDY DESIGN

Participants will be recruited from multiple sites internationally. The PANTHER platform will use a Bayesian Adaptive Multi-Arm Trial design, which can be viewed as an extension of a Multi-Arm Multi-Stage (MAMS) design.

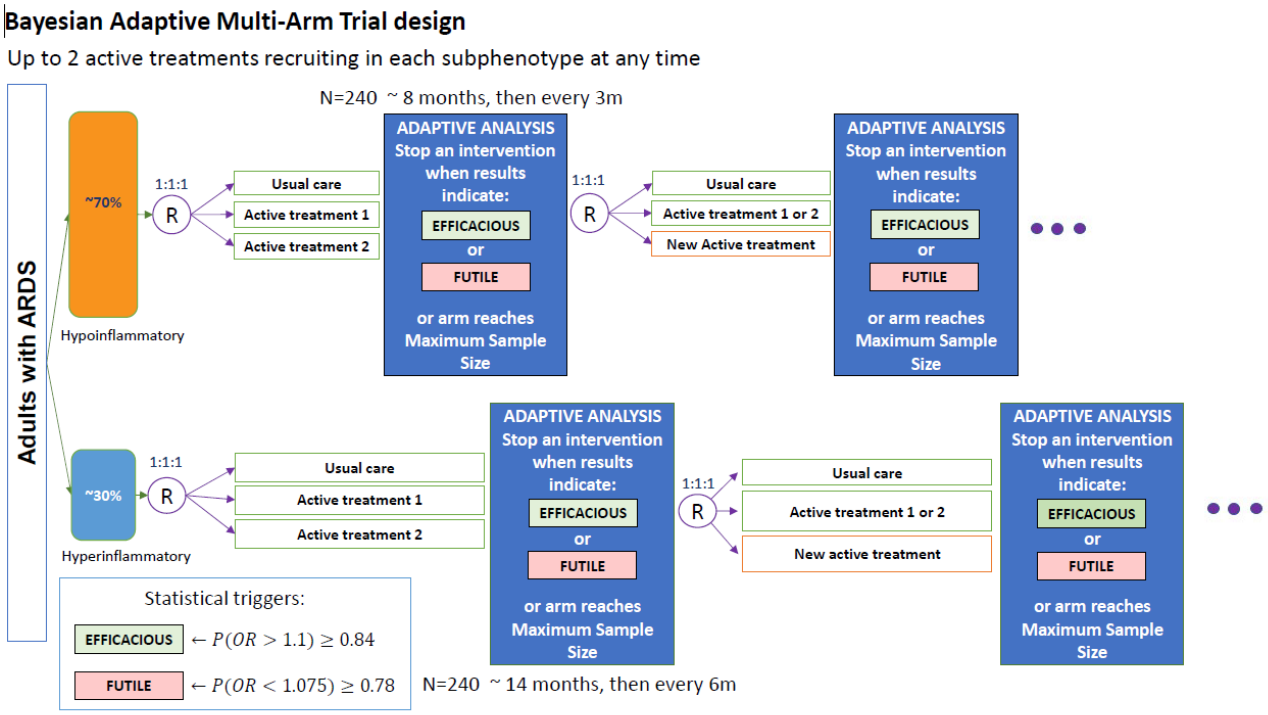
The platform will recruit patients in hospital and who are critically ill with different clinical syndromes. Initially the target population will be patients with ARDS. Over time other clinical syndromes may be added; in particular, the platform will prepare to include patients with pandemic infection. Patients will be stratified into different subphenotype strata prior to randomisation. Initially, the strata will be the hyper and hypoinflammatory subphenotypes described in ARDS. The regular adaptive analyses will enable us to efficiently identify differential treatment responses across subphenotypes by examining treatment effect within subphenotype strata and stopping interventions in each subphenotype where there is evidence of futility or efficacy. The design allows additional new interventions and subphenotypes to be added over time.

Design and planning for the addition of new interventions and subphenotypes will continue as the platform trial is ongoing.

4.1 Design

A multicentre, allocation concealed, randomised, open-label Bayesian adaptive multi-arm platform trial with pre-defined triggers for efficacy and futility stopping (as compared to usual care). Randomisation will be balanced with equal ratios between usual care and each intervention participants are eligible for, i.e. a 1:1 ratio (usual care versus intervention (where eligible) by subphenotype). There is no fixed sample size, but we have capped the sample size for the initial treatments and subphenotype. We will recruit a maximum of 529 per active intervention in the hyperinflammatory subphenotype, and 504 per active intervention in the hypoinflammatory subphenotype. See the statistical design appendix for more information for how this sample size was derived.

Figure 1: Indicative study flow chart demonstrating study design by initial precision medicine subphenotype



5. PARTICIPANT ENTRY

5.1 Study setting and population

The population to be included into the platform will be critically ill patients in hospital (46).

Platform level inclusion criteria

1. Critically ill patients in hospital and at least 1 of the following: -
    a) Acute respiratory distress syndrome (ARDS)*
    b) A pandemic associated syndrome (this will be triggered if a new pandemic is declared)

*ARDS as defined by:-

(i) a known acute clinical insult or new or worsening respiratory dysfunction, and

(ii) receiving respiratory support via invasive mechanical ventilation or non-invasive ventilation including continuous positive airway pressure, or high-flow nasal oxygen ≥30L/min and

(iii) Within the same 24-hour time period:

- bilateral opacities on chest imaging not fully explained by effusions, lobar/lung collapse/atelectasis, or nodules, and
- respiratory failure not fully explained by cardiac failure, fluid overload, pulmonary embolism, acute airways disease, or interstitial lung disease and
- PaO2/FiO2 ratio <40 kPa from arterial blood gases, or SpO2/FiO2 <315 from pulse oximetry where SpO2 <97.

The time of onset of ARDS is when the last criterion in (iii) is met.

Platform level exclusion criteria

(a) >48 hours from diagnosis of ARDS
(b) Planned withdrawal of life-sustaining treatment within the next 24 hours
(c) Previous enrolment in the PANTHER trial in the last 12 months
(d) Declined consent

Additional intervention-specific inclusion / exclusion criteria

These are given in the intervention specific appendices

6. PROCEDURES AND MEASUREMENTS

6.1 Identification and recruitment of participants

Patients will be identified by local clinical and clinical research staff employed in the recruiting hospitals. Patients screened and who meet inclusion criteria who are not recruited on to the study will be documented, including the reason(s) for not being enrolled on the study.

6.2 Screening and pre-randomisation evaluations

The screening will be conducted by local clinical and clinical research staff employed in the recruiting hospitals using the routinely clinically collected data.

Subphenotyping will be undertaken when the patient meets the criteria for inclusion in the trial and the appropriate consent process has been followed. Measurement of the biomarkers to determine subphenotype will take place in real time, prior to randomisation. Details about the subphenotyping process are included in the subphenotype appendix.

6.3 Randomisation and Blinding

The trial is open-label whereby participants, the clinical team and study team will not be masked to the interventions. To avoid bias during the ongoing PANTHER platform, where possible, modifications will be made. Only the unblinded trial statisticians will have access to emerging aggregate data and results by treatment allocation until interventions are stopped. These statisticians will be responsible for carrying out the adaptive analyses and construction of all statistical reports for regular DMC meetings.

Each participant will be assigned a unique trial ID which is linked to their treatment allocation.

Bias will be minimised by the following:

Detection and performance: The primary outcome and most of the secondary outcomes are objective outcomes that will be unaffected by knowledge of treatment allocation. The unblinded trial statistician undertaking the planned adaptive analyses will not be involved in design decisions of the ongoing platform. Delivery of usual care based on international guidelines will decrease the likelihood of performance bias. No aggregate data by intervention will be available to the study team throughout the trial prior to any statistical trigger being met and final analysis.

Selection bias: Treatment allocation will be concealed prior to randomisation using an automated online system. To ensure clinicians have equipoise, we will evaluate screening logs and examine reasons why patients have not been enrolled into the study.

Attrition bias: The primary outcome along with most other outcome data will be collected during the hospital stay. Data on mortality will be derived electronically from routinely collected health data sources where possible. Experience from previous trials indicates missing outcome data for the primary outcome and mortality to day 90 will be minimal both in the UK and at international sites. Withdrawal rates are typically <5% in critical care trials (10,11). We will seek participants' (or their representatives'), permission to retain data collected up until the time-point that they choose to withdraw. This will maximise primary and secondary outcome data acquisition. Our experience in the UK and internationally is that patients normally agree to proceed on this basis.

Reporting bias: Source data verification (from clinical records and hospital computer records as described in the trial monitoring plan) will be used to minimise the risk of reporting bias. The main clinical outcomes of this study (e.g., death, organ support, duration of stay, and serious adverse events) are recorded contemporaneously on participant clinical records.

Treatment fidelity and contamination due to crossover: As the interventions are prescribed and then administered by nurses as part of routine ICU clinical care there is minimal risk that treatment will not be administered. As the interventions likely to be included are not recommended as part of usual care there is also minimal risk of unplanned crossovers within the interventions. In the event of cross-over occurring at a site, the site will be re-trained and if this occurs repeatedly the site will be closed to recruitment.

Randomisation

Allocation to treatment interventions will be via a minimisation algorithm which enables dynamic allocation based on the distribution of recruited participants, allocating participants to the treatment that mainsubtains balance in participant characteristics. To avoid allocations being completely deterministic, we will include random allocation in between 10-20% of cases to ensure unpredictability of individual allocations. This will result in approximately 5-10% of individuals not being allocated to the treatment that minimises imbalance in participant characteristics between treatments. The minimisation algorithm will be applied within subphenotypes separately. Minimisation will then be by country and intervention eligibility. Allocation will be conducted through an online password protected data system

managed centrally by Imperial Clinical Trials Unit who are the data coordinating centre for the platform trial. The algorithm will be updated when subphenotype, countries or interventions change.

6.4 Visit Schedule

	Baseline (24 hours pre randomisation)	**Day 0** (post randomisation)	**D2**	**D6**	**Up to D28**	**Hosp D/C**	**D90**	**D180**	**D365**
Screening	X								
Informed Consent	Patient / PerLR / ProLR will be obtained initially. Retrospective patient consent will be obtained when the patient has recovered capacity to consent.								
Inclusion / Exclusion criteria	X								
Phenotyping	X								
Randomisation	X								
Research samples	X		X	X					
Intervention administration					X				
Baseline data	X								
Data collection / follow up		X	X	X	X	X	X	X	X
Physical function (SPPB)						X			
MOCA						X	X	X	
Data collection in ICU (up to day 90 max)							X		
Vital status							X		
Data collection in hospital (up to day 90 max)							X		
EQ-5D-5L							X	X	
HADS							X	X	
Social and Wellbeing (SF-36)							X	X	
Impact of Events Scale							X	X	
Care and wellbeing needs							X	X	
Long-term follow-up									X

6.5 Treatment

Treatments within the trial will only be provided while the patients are in the ICU and will be provided and administered by local clinical staff.

Eligible patients will be randomised to usual care or one of the interventions for which they are eligible.

Each subphenotype will have its own control which will be usual care. Usual care will be directed by international treatment guidelines, such as the European Society of Intensive Care Medicine ARDS guidelines. Agreement to comply with these guidelines will be a condition for a site to participate in the trial to ensure standardised best practice usual care. We will collect and report key process measurements of usual care (e.g. compliance with protective lung ventilation and prone ventilation) with feedback and education for sites to achieve compliance with these guidelines if needed.

6.6 Follow-up

Patients will be followed up by the clinical research team daily whilst in ICU.

Once the patients have left ICU and been discharged to the ward, they will be followed up prior to hospital discharge. They will also be followed up by telephone or electronically 90 days, and 180 days after randomisation (+14 days). Survival status will be entered at 365 days. Where follow-up is not possible this will not be a protocol deviation.

6.7 Laboratory Evaluations

These will be intervention specific and described in the relevant intervention specific appendix

6.8 Research samples

Research samples will be collected as described in the sample handling manual. In summary there is a tiered approach to the collection of research samples and will include: -

1) blood samples for phenotyping, plasma, serum and RNA on the day of but prior to randomisation, day 2 and day 6.

2) blood samples for cell isolation on the day of randomisation and day 2.

3) tracheal aspirate samples on the day of randomisation, day 2 and day 6 (if intubated).

4) a nasopharyngeal swab on the day of randomisation and

5) a bronchoalveolar lavage sample in selected sites on the day of randomisation and day 2.

Details of the processing, handling and shipping are provided in the sample handling manual. The samples will be sent to a regional central laboratory for storage and analysis to understand the mechanism of effect of the interventions and heterogeneity of treatment effect as well as use in ethically approved studies.

If resources prevent collection of the research samples this is not a protocol deviation.

6.9 Incidental findings

There will be no clinical testing of samples other than to measure the biomarkers to determine subphenotype. Similarly, there are no additional clinical examinations other than routine clinical examination as part of standard care. Therefore, there will be no incidental findings reported to the patient, their clinical care team or their primary care physician.

7. TREATMENTS

7.1 Interventions

Patients will receive usual care or usual care plus the intervention as allocated by randomisation.
Details about the intervention are included in the relevant intervention specific appendix.

7.2 Concomitant Care

Any treatment decisions not outlined in the PANTHER protocol will be left to the judgement of the treating clinician.

7.3 Investigational Medicinal Product Details

Any IMP which has marketing authorisation in the relevant country and is stocked by the site hospital pharmacy, may be employed in this trial.

Interventions that do not have a marketing authorisation in the relevant country will be provided to sites. Details of this supply will be provided in the relevant intervention appendix.

The Summary of Product Characteristics (SmPC) for each approved IMP (or investigator brochure (IB) for unapproved IMP) is provided as a separate document and is filed in the TMF. This is a representative SmPC/IB. The Reference Safety Information within the relevant SmPC/IB is used for drug safety and other reference in this trial. The SmPC/IB will be reviewed annually for potential updates.

The IMP risk classification (or equivalent) for the trial will be completed in each country. The IMP risk classification may vary by country. Labelling and packaging requirements will depend on this classification. See below for illustration purposes. Note the term ‘classification’ may vary by country, see region specific appendix for clarification.

- Classified as a Type A risk (or equivalent), any potential risk is no higher than that of standard medical care. No specific labelling required.
- Classified as a Type B (or equivalent), somewhat higher than the risk of standard medical care. Full labelling may be required.
- Classified as a Type C (or equivalent), markedly higher than the risk of standard medical care. Full labelling may be required.

7.4 Permanent Discontinuation of Study Treatment and Withdrawal from Study

(i) Permanent discontinuation of study treatment

Participants may discontinue study treatment for the following reasons:

- At the request of the participant or consenting legally authorised representative (LAR)
- Serious Adverse Event related to the study drug
- Allergic reaction to IMP
- Decision from the attending ICU physician that the study drug should be discontinued on safety grounds.
- If advised by the international trial steering committee based on advice from the DMC

(ii) Withdrawal from Study

Withdrawal from the study refers to discontinuation of study treatment and study procedures and can occur for the following reasons:

- Participant decision
- Loss to follow-up

(iii) Procedures for Withdrawal from Study

Patients will be free to withdraw at any time. If the patient (or their personal/professional legal representative) wishes to withdraw from the study during the treatment period, the treating physician will no longer follow the trial protocol and the study drug will be stopped. If the participant withdraws from the study this will be documented in the eCRF and medical records.

The patient will be able to either withdraw completely from the trial or from certain elements. Further follow-up as part of the clinical trial will cease. However, the participant will be asked if data collection through routine locally collected clinical data and data linkage, including long-term follow-up can continue.

Participants will be asked if previously collected, stored blood samples can be used for further analyses or if they would prefer their samples to be destroyed.

In the rare situation where the patient is discharged from hospital prior to obtaining consent, the most appropriate member of the site research team (who is also part of the direct care team) will attempt at least one phone call to the patient to inform them of their involvement in the study, provide information about the study and obtain their verbal consent. Following on from the call, or if there is no response to the call, the patient will be sent a covering letter, personalised by the most appropriate member of the site research team (who is also part of the direct care team) or clinical staff member, and a copy of the PIS and Consent Form (postal versions) by post. The letter will direct the patient to the PIS for detailed information on the study and provide telephone contact details if the patient wishes to discuss the trial with a member of the site research team. It will also explain the option to provide consent electronically by completing the online e-consent form if feasible in the region.

If consent to continue is not obtained despite these attempts, data already collected will not be deleted as these will include important safety information which would be processed as part of a legitimate interest.

8. PHARMACOVIGILANCE

8.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the trial medication, whether or not considered related to the IMP.

8.2 Adverse Reaction (AR)

All untoward and unintended responses to an IMP related to any dose administered. All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions (ARs). The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

8.3 Unexpected Adverse Reaction

An AR, the nature or severity of which is not consistent with the applicable product information as set out in the Reference Safety Information (RSI) (in the investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product).

When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected. Side effects documented in the RSI section of the SmPC/IB which occur in a more severe form than anticipated are also considered to be unexpected.

Expectedness assessment will be performed by the Sponsor or person delegated by the Sponsor to assess expectedness.

8.4 Causality

The assignment of causality for adverse events should be made by the investigator responsible for the care of the participant using the definitions in the table below.

If any doubt about the causality exists the local investigator should inform the study coordination centre who will notify the Chief Investigator. The pharmaceutical companies and/or other clinicians may be asked to advise in some cases.

Unrelated:	No evidence of any causal relationship
Unlikely:	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible:	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial

medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).

Probable: There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

Definite: There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

8.5 Severity of Adverse Events

Mild: Awareness of event but easily tolerated

Moderate: Discomfort enough to cause some interference with usual activity

Severe: Inability to carry out usual activity

8.6 Adverse Event recording

As this is a trial is conducted in critically ill patients with life-threatening critical illness then adverse events are expected to occur regularly in most, if not all, patients regardless of treatment assignment. Events that that are expected in this population i.e. events related to the underlying critical illness will not be reported as adverse events. In addition, unless an adverse event is assessed to meet Serious Adverse Event criteria these adverse events will not be reported in the case report form and simply noted in the patient's local medical record. Any additional reporting will be detailed in the RSA and ISA.

8.7 Abnormal Laboratory Test Results

Similarly due to the nature of the underlying critical illness, abnormal laboratory test results will be expected to occur daily for most, if not all, patients and therefore do not need to be reported as an AE/AR in the CRF. They will be recorded in the patients' medical record. Any clinically important abnormal laboratory tests will be repeated at appropriate intervals until they return either to baseline or to a level deemed acceptable by the local investigator.

8.8 Serious Adverse Events (SAE)

(i) Definition of SAE

An SAE is defined as any event that

- Results in death;
- Is life-threatening*;
- Requires hospitalisation or prolongation of existing inpatient's hospitalisation**;
- Results in persistent or significant disability or incapacity;
- Is a congenital abnormality or birth defect;

* "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.

** "Hospitalisation" means any unexpected admission to a hospital department. It does not usually apply to scheduled admissions that were planned before study inclusion or visits to casualty (without admission).

Medical judgement should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/reactions that are not immediately life-threatening, or do not result in death or hospitalisation but may jeopardise a subject, or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

(ii) Reporting of SAEs

The primary and secondary outcomes have been selected to capture the most commonly occurring safety events in critically ill patients (e.g. mortality, organ failure and support). Therefore, any events that are captured as an outcome in the eCRF do not require reporting as an SAE unless in the opinion of the local PI the event was attributable to a study intervention / IMP or the trial protocol.

Rapid reporting of all SAEs i.e. within 24 hours, occurring during the patient's ICU stay up to a maximum of 28 days must be performed as detailed in the study-specific safety reporting instructions.

Active monitoring of participants after discharge from ICU or after 28 days is not required, but if the investigator becomes aware of safety information that appears to be drug or trial related, involving a participant who participated in the study, even after an individual participant has completed the study, this should be reported to the Sponsor.

All SAEs will be reviewed by the Chief Investigator or a designated medically qualified representative to confirm expectedness and causality.

Reporting of SAEs and review by the CI will be via the trial data collection system (CRF/eCRF).

(iii) Definition of a Serious Adverse Reaction (SAR)

A SAR is defined as a SAE that is judged to be (possibly, probably or definitely) related to any dose of study drug administered to the participant.

(iv) Definition of Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any SAR that is NOT consistent with the applicable product information as set out in the Reference Safety Information (RSI) section of the Investigator Brochure (IB) or Summary of Product Characteristics (SmPC).

(v) Reporting of SUSARs

SUSARs should be notified to the appropriate regulatory authority, the relevant EC and the Sponsor in accordance with regulatory requirements. SUSARs which are fatal or life-threatening will be reported not later than 7 days after alerting the sponsor to the reaction. Any additional relevant information will be sent within 8 days of the report. A SUSAR which is not fatal or life-threatening will be reported within 15 days of first knowledge by the sponsor. The sponsor will inform all investigators about SUSARs occurring on the study.

Follow up of participants who have experienced a SUSAR should continue until recovery is complete or the condition has stabilised.

SUSAR reports will be unblinded prior to submission if required by national regulatory requirements.

SUSARs reported in one region may be required to be reported in another, further details of this will be provided in the RSAs.

8.9 Pregnancy

Where the IMP is not approved in pregnancy, it will be an exclusion criterion for the IMP. Should pregnancy occur, it is not considered an SAE but should be recorded and followed up to ensure a congenital abnormality does not occur. Due to the life-threatening illness at the time of recruitment, pregnancy is not expected to occur.

8.10 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the regulatory authority and the EC of the measures taken and the circumstances giving rise to those measures.

8.11 Additional definitions for safety reporting in medical device trials

In some regions PANTHER safety reporting on the device may be required. Please see your region-specific appendix for further details..

9. STATISTICAL ANALYSES

Sample Size and power considerations

The trial has no fixed sample size due to its adaptive design. Extensive simulations were undertaken to estimate the sample size distribution for the initial subphenotypes and two active interventions to be compared to usual care. We report the **expected mean** and **80th percentile** of the simulated distribution, and the **maximum sample size** we will stop recruitment at if no statistical triggers are met.

A **maximum cap** will be used as a guideline by the DMC within each active treatment intervention and subphenotype to ensure the trial does not continue perpetually when there is a low likelihood of a trial trigger being met. The maximum cap is set at the frequentist sample size without any plan for early stopping and the DMC will evaluate the value of continuing after this sample size has been reached.

Usual care is not limited by a maximum sample size and will recruit for the duration of the trial.

The initial sample sizes are as follows:

Sample size distribution attributes	**Hypoinflammatory** n per intervention	**Hyperinflammatory** n per intervention

Expected mean	120	82
80th percentile	240	156
Maximum cap	504	529

This sample size was calculated based on iterations of different statistical triggers and timing schedules evaluating these against the resulting trial operating characteristic in terms of Type I and Type II error for a realistic range of minimal clinically important differences (MCID). This process resulted in the following optimal design characteristics (triggers and timing of these triggers):

Timing of triggers: Starting at n=80 per intervention and then every 3 months after that in hypoinflammatory. Hyperinflammatory adaptive analysis will be aligned with the hypoinflammatory adaptive analysis, the first taking place after n=80, and then taking place every 6 months in line with the hypoinflammatory analysis.

Statistical Triggers:

• Efficacy will be triggered within intervention and subphenotype if there is at least an 84% probability of the proportional odds ratio exceeding 1.1

• Futility will be triggered if there is at least a 78% probability of the proportional odds ratio falling below 1.075

The sample sizes in the table above are calculated based on the following assumptions:

• a 70: 30 ratio for hypoinflammatory: hyperinflammatory subphenotype;

• primary outcome distributions by subphenotype based on data from the HARP-2 trial (10);

• a minimally clinically important proportional odds ratios of 1.4 in the hypoinflammatory and 1.3 in the hyperinflammatory subphenotype. These were selected to yield a similar absolute reduction in mortality (~5%) over 28 days in each subphenotype

The same assumptions provide the following bounds for power and type I error rates over the initial 4-year funded period. Only upper and lower bounds can be provided (except where these coincide) since the actual operating characteristics will depend on whether the (non-binding) futility trigger is acted upon.

- A power of 92-96% in hypoinflammatory subphenotype and type I error rate (POR=1) of 17-19%.
- A power of 70-71% in the hyperinflammatory subphenotype and type I error rate (POR=1) of 18%.

A type I error rate of around 20% was judged as acceptable trade-off for enabling rapid identification of possibly effective treatments at phase II. Further precision in estimation and strength of evidence for the intervention will be gained at phase III. The total sample sizes presented are the number needed without missing data. Loss-to-follow up needs to be factored into recruitment targets.

The sample size required for any new interventions will depend on the primary outcome distribution and anticipated effect size of the new intervention and may require further simulations.

Full details of the initial and any new sample size simulations are provided in the Statistical Design Appendix

9.1 Planned recruitment rate

Initial recruitment projections are one patient per site per month, starting with 30 sites at 12 months after the planned start date, rising to 70 sites by 21 months to the end of initial 5-year funded period. Additional sites may be added as additional funding becomes available.

9.2 Statistical analysis

This section details the general analysis principles and provides a summary of the analytical approach that PANTHER will follow. The full analyses details will be described in the Statistical Analysis Appendix.

9.3 General principles

All between intervention comparisons will be with usual care using contemporaneous participants who were eligible to be randomized to the intervention in question. No comparisons between two active interventions will be undertaken. All inferential analysis will be undertaken in a Bayesian framework.
The flow of participants through the trial and trial results will be reported according to the CONSORT extension for adaptive designs (12).

9.4 Adaptive analyses

Regular adaptive analyses will be carried out to monitor the accrued data. Participant baseline characteristics will be summarised by treatment group and overall using suitable descriptive statistics. Adaptive analysis will include formal stopping rules on the primary outcome which will be triggered by comparing the estimated treatment effect to predefined efficacy and futility boundaries. Summary and between-intervention statistics for secondary and safety outcomes will be presented by treatment group.

The first adaptive analysis will take place at the end of the calendar month when the cumulative number of participants recruited into the larger (hypoinflammatory) subphenotype reaches 240, i.e. 80 per intervention. Thereafter, adaptive analyses will take place every 3 calendar months unless recruitment varies substantially from the planned recruitment rate, in this case the frequency of the adaptive analysis will be revised. The hypoinflammatory subphenotype will be analysed at every adaptive analysis; the smaller (hyperinflammatory) subphenotype will be included in the regular adaptive analysis when its cumulative recruitment total has reached 240 participants and at alternating analyses thereafter, i.e. every 6 months, unless recruitment varies substantially from the planned recruitment rate.

When a new treatment intervention is added to the hypoinflammatory subphenotype, it will be analysed at the first adaptive analysis when it exceeds 80 recruits and at every analysis thereafter until stopping. When a new treatment intervention is added to the

hyperinflammatory subphenotype, it will be analysed at the first analysis when it exceeds 80 recruits and at alternate analyses thereafter until stopping. The threshold of 80 recruits was chosen to maximise the potential for early stopping (and hence the efficiency of the platform) while also limiting type I error rates, which are higher in smaller samples.

Recruitment to a treatment group within a given subphenotype will be halted when an analysis reveals that an efficacy or futility boundary has been breached, or when the sample size cap is reached or at the discretion of the DMC based on wider review of the trial data. At this point, a final analysis of that treatment within subphenotype with respect to all outcomes will be carried out. After a treatment is stopped a new treatment intervention within that subphenotype may be initiated.

At the first adaptive analysis, confirmation of the validity of the proportional odds assumption will be carried out in each subphenotype. This will be based on the observed distribution of the primary outcome ordinal scale in each treatment intervention compared to usual care. If the proportional odds assumption is not met, then alternative categorisations (i.e. grouping some categories in the ordinal scale together) will be explored. For all adaptive analysis we will examine the consistency of the unadjusted between-group treatment effect across the composite outcome elements (death and organ support free days) for each comparison within each subphenotype.

Very little missing data are expected for the primary outcome; we anticipate minimal loss to follow-up, and eCRFs will be designed so that recording of primary outcome data is mandatory. If the level of missingness does not exceed 5% then the missing data will be assumed to be ignorable, i.e. a complete case analysis will be carried out. If over 5% of outcome data are missing, then the missingness pattern and relationship to other variables will be explored and multiple imputation will be performed.

Statistical stopping triggers

The criteria for stopping recruitment to a treatment group within either subphenotype are based on the probability that the unadjusted odds ratio crosses a predefined value by a predetermined probability threshold. The initial triggers for stopping were identified through extensive simulations to optimise the trial operating characteristics and achieve an appropriate balance between the sample size needed, maximising the power to graduate treatments exceeding the minimal clinically important effect and minimising the chance of graduating treatments with no effect (type I error).

Stopping recruitment to a treatment within either subphenotype will be considered if any of the following conditions are met at any adaptive analysis:

• For efficacy if there is at least an 84% probability of the proportional odds ratio exceeding 1.1.

• For futility if there is at least a 78% probability of the proportional odds ratio falling below 1.075.

These are considered non-binding stopping rules as the DMC will also take into consideration information presented on other outcomes including safety and recruitment data.
If neither of the statistical thresholds are met nor the DMC recommends stopping recruitment to a treatment group at an adaptive analysis, recruitment will stop for futility if the sample size within a treatment group exceeds the frequentist sample size cap for

either subphenotype. This approach prevents perpetual recruitment where there is no or a low likelihood of meeting a trigger. Full simulations details examining the operating characteristics of the proposed design and alternatives for a range of possible threshold values can be found in the statistical design appendices.

9.5 Primary Estimand for Adaptive and Final Analysis

The primary estimand for the primary outcome is specified in the table below. An intercurrent event is an event that occurs after randomisation and may impact the outcome or stop us observing the outcome. Three intercurrent events have been identified: death; non-adherence; and use of other effective medications. We want to estimate the treatment effect regardless of non-adherence and use of other medications (treatment policy approach). The intercurrent event of death is handled by including it in the primary outcome definition (composite strategy).

Estimand attribute	**Primary estimand**
Population	Patients meeting the inclusion criteria and no exclusion criteria
Treatment conditions	(Active treatment + usual care) vs usual care
Outcome variable	An ordinal outcome: composite of organ support-free days up to 28 days and death
Population-level summary measure	Proportional odds ratio comparing each active treatment vs usual care
Intercurrent event: strategies	
	Death: Composite strategy (included in the outcome) **Protocol non-adherence**: Treatment policy strategy **Use of other effective medications**: Treatment policy strategy

9.6 Primary Modelling Approach for Adaptive and Final Analysis

'Adaptive analyses' are those performed regularly to make decisions for changing the trial. 'Final analysis' will performed once an intervention arm has met a statistical trigger and the DMC have confirmed stopping.

The primary efficacy analyses will be based on single Bayesian proportional odds logistic regression models fitted for each subphenotype. The primary **adaptive analysis** will be **unadjusted** and the **final primary efficacy** analyses will be **adjusted** for minimisation covariates and other strong prognostic variables. For adaptive and final analyses the posterior distribution of the proportional odds ratio (POR) associated with each treatment (relative to usual care) will be estimated using Markov Chain Monte Carlo techniques and the mean and 95% credible interval reported, and for the adaptive analyses the probability of exceeding the relevant statistical triggers (see above in Statistical stopping triggers). POR>1 relative to usual care indicates a favourable treatment effect. We will also examine the treatment effect across both subphenotypes by combining the data across

subphenotypes and using the same regression model, reporting the POR and 95% credible interval. Full details of the adaptive and final analyses will be specified in the corresponding SAPs.

The primary analysis will use neutral informative prior distribution on the treatment effect where the variance will be chosen to only make extreme results highly unlikely. Where external trial evidence is available on the effect of an intervention in a particular subphenotype, a sensitivity analysis will include this evidence in the analysis using an informative prior distribution. Unadjusted and adjusted treatment effects will be presented in all reports.

Secondary efficacy endpoints

Secondary efficacy outcomes will be summarised and tabulated and unadjusted treatment effects will be calculated at each adaptive analysis. Full model-based analyses will be performed only at the final analysis for each treatment intervention in each subphenotype (i.e. once recruitment to a treatment group within a subphenotype is stopped).

Estimands for analysis of secondary efficacy endpoints will use the same treatment conditions, the same population, and intercurrent events and strategies to handle these, apart from the outcome *'Progression to invasive mechanical ventilation, extracorporeal membrane oxygenation or death'* which will use the population consisting of those participants not intubated at baseline and the handling of mortality which will alter depending on the nature of the outcome and its interpretation in relation to death, and length of stay which will use the population who survived. The outcome variable and population-level summary measure will vary as appropriate for each endpoint. All secondary estimands will be specified in the SAP.

Treatment effects for final analysis will be estimated using a regression modelling approach in a Bayesian framework with vague priors. Adjustment for baseline values will be used where suitable.
Analysis of ordinal secondary outcomes (days free of vasopressor or respiratory support) will be as per the primary outcome. Analysis of binary outcomes at single time points will use logistic regression. Analysis of continuous outcomes will use linear regression.

Posterior mean contrasts (differences, odds ratios, incidence rate ratios) between treatment groups will be reported together with 95% credible intervals. Model assumptions will be examined using residual analysis including examination of graphical displays such as normal quantile plots.

Serious Adverse events

In addition to the information on safety provided by the adaptive analyses of the primary and secondary outcomes, cumulative data on SAEs will be presented to the Data Monitoring Committee on a regular basis.
As there is monitoring of important safety outcomes through primary and secondary outcomes (eg mortality, organ support), these events will not be recorded as SAEs as described above. All other SAEs will be tabulated by arm and compared between arms through calculation of incident rate ratios (IRR) and 95% credible intervals (CI).

Estimands for SAEs will be based on the same treatment conditions and population as the primary estimand. Three intercurrent events have been identified: death; non-adherence; and use of other effective medications that prevent or affect the occurrence of SAEs. We will specify appropriate analytical approaches to handle these events in the analysis of SAEs in the detailed statistical analysis plan. SAEs will be summarised at the Preferred Term level and System Organ Class level and tabulated by treatment intervention.

Full analysis plan details plus supplementary and secondary estimand definitions with corresponding analysis details are specified in the statistical analysis appendices.

10. REGULATORY, ETHICAL AND LEGAL ISSUES

10.1 Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki.

10.2 Good Clinical Practice

The study will be conducted in accordance with the guidelines laid down by the International Conference on Harmonisation for Good Clinical Practice (ICH GCP E6 guidelines).

10.3 Ethics Committee Approval

(i) Initial Approval

Prior to the shipment of IMP (where applicable)/device and the enrolment of participants, the EC must provide written approval of the conduct of the study at named sites, the protocol and any amendments, the Participant Information Sheet and Consent Form, any other written information that will be provided to the participants, and any advertisements that will be used.

(ii) Approval of Amendments

Proposed amendments to the protocol and aforementioned documents must be submitted to the relevant EC for approval. Amendments requiring EC approval may be implemented only after a copy of the EC's approval letter has been obtained. If, after an adaptive analysis an intervention is deemed harmful or futile, as determined by the DMC, removal of these interventions may be implemented without submitting an amendment to the Sponsor, regulatory authority or EC. An official letter from the Data Monitoring Committee (DMC) will be submitted to the Sponsor, regulatory authority and EC detailing the decision soon as possible after implementation. Any additional interventions will always be submitted to the Sponsor, regulatory authority and EC for approval prior to implementation.

Further details can be found in the region-specific appendices.

(iii) End of Trial Notification

The EC and regulatory authority will be informed about the end of the trial, within the required timelines.

10.4 Regulatory Authority Approval

The study will be performed in compliance with each country's regulatory requirements. Clinical Trial Authorisation from the appropriate Regulatory Authorities must be sought/obtained (as applicable to local country regulations) prior to the start of the study. In addition, the Regulatory Authorities must approve amendments prior to their implementation (as instructed by the Sponsor), receive SUSAR reports and annual safety updates, and be notified of the end of the trial.

10.5 Non-Compliance and Serious Breaches

All protocol deviations and protocol violations will be reported via the eCRF/CRF and reviewed by the Chief Investigator and / or trial manager / delegate and reported to the ICTU Head of QA on a monthly basis. Protocol violations will be reported to the Sponsor.

An assessment of whether the protocol deviation/violation constitutes a serious breach will be made. A serious breach is defined in the RSA.

The Sponsor will be notified within 24 hours of identifying a likely Serious Breach. If a decision is made that the incident constitutes a Serious Breach, this will be reported to the regulatory authorities in accordance with local regulatory requirements.

10.6 Insurance and Indemnity and Sponsor

The Sponsor has civil liability insurance, which covers this study in all participating countries. Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

Imperial College London will act as the main Sponsor for this trial. Delegated responsibilities will be assigned to the sites taking part in the trial. Other delegated responsibilities will be documented as required in regional appendices and the relevant contracts.

10.7 Trial Registration

The study will be registered on the ISRCTN registry.

10.8 Informed Consent

The consent process will be conducted as per local regulatory authority/EC requirements and recommendations. If the patient has capacity, they will always be approached to provide their informed consent. Eligible patients for this trial will be critically ill. As such, they may be sedated for comfort, safety and to facilitate standard life saving ICU procedures, thus where permitted by the local regulatory authorities a deferred/delayed consent model can be used.

The consent process is detailed further in the region-specific appendices.

10.9 Participant Confidentiality

The investigator must ensure that the participant’s confidentiality is maintained. On the CRF or other documents submitted to the Sponsors, participants will be identified by a participant ID number only. Documents that are not submitted to the Sponsor (e.g., signed informed consent form) should be kept in a strictly confidential file by the investigator.

The investigator shall permit direct access to participants' records and source documents for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor, Regulatory Authorities and ECs.

10.10 Data Protection and Participant Confidentiality

The investigators and study site staff will comply with the requirements of local Data Protection laws concerning the collection, storage, processing and disclosure of personal information.

This is detailed further in the region-specific appendices.

10.11 End of Trial

The trial is designed as a platform allowing for the continued evaluation of interventions for critically ill patients. The platform allows for the trial to be potentially perpetual, with multiple interventions that can be evaluated at any one time and over time. Frequent adaptive analyses are conducted to determine whether an intervention being studied should continue or cease due to efficacy or futility.

The trial will continue unless the ITSC agrees that one or more of the following situations apply:

- There is insufficient funding to support further recruitment to the platform as a whole and no reasonable prospect of additional support being obtained.
- New information makes it inappropriate to continue to randomise to any of the current interventions and this also makes it inappropriate to remain open to pursue new interventions for investigation.
-

10.12 Study Documentation and Data Storage

The investigator must retain essential documents until notified by the Sponsor, and for at least 10 years after study completion. Participant files and other source data (including copies of protocols, CRFs, original reports of test results, IMP dispensing logs, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) must be retained. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

11. DATA MANAGEMENT

11.1 Source Data

Source documents include original documents related to the trial, to medical treatment and to the history of the participant, and adequate source documentation must be maintained to

allow reliable verification and validation of the trial data. What constitutes the source data for this trial will be outlined in the Source Data agreement.

11.2 Language

CRFs will be in an appropriate language for the regions in which the study is conducted Generic names for concomitant medications should be recorded in the CRF wherever possible. All written material to be used by participants must use vocabulary that is clearly understood and be in the language appropriate for the study site.

11.3 Database

Trial data will be collected on an electronic case report form (eCRF). Data will be entered via web-based database through electronic data capture (EDC). The database used to capture this information is the OpenClinica database. Data is entered into the database by the site team. The database will raise automatic queries and allow manual queries to also be raised which will be checked and validated by the Trial Manager and Monitor. All data, changes to data and query resolution will be included in an audit trail including dates. Specific instructions on how to enter data including drug naming and deal with queries are detailed in the eCRF completion guide. Automated Randomisation will be carried out using the OpenClinica system in accordance with ICTU specific SOPs.

Adverse events will be captured in the eCRF and all Serious Adverse Events will require sign off by the Principal Investigator at the site.

Exceptions to this will be detailed in the RSA.

11.4 Data Collection

All data for the study will be entered into the eCRF via the OpenClinica database. These data will include demographics, previous medical history, blood results, vital signs, organ support and follow-up information.

Details of procedures for eCRF/CRF completion will be provided in a study manual.

Exceptions to this will be detailed in the RSA.

11.5 Archiving

All trial documentation, including that held at participating sites and the trial coordinating centre, will be archived for a minimum of 10 years following the end of the study.

12. STUDY MANAGEMENT STRUCTURE

The overall co-ordination of the trial will be managed by ICTU and the Chief Investigator. Local co-ordinating centres will be in place in each region to manage the day-to-day running of the trial.

The following groups and trial committees will be established.

12.1 International Trial Steering Committee

An International Trial Steering Committee (ITSC) will be convened including as a minimum an independent Chair, independent clinicians, independent statistician, lay members, the Chief Investigator and the Senior Statistician. The role of the ITSC is to provide overall supervision of trial conduct and progress. Details of membership, responsibilities and frequency of meetings will be defined in a separate Charter.

12.2 International Trial Management Group

A International Trial Management Group (ITMG) will be convened including investigators from each region, other co-investigators and key collaborators, trial statisticians, a lay person and trial managers. The ITMG will be responsible for day-to-day conduct of the trial and operational issues. Details of membership, responsibilities and frequency of meetings will be defined in separate terms of Reference.

12.3 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be convened including at least an independent Chair and two other independent members. It will include suitable experienced clinicians / clinical trialists and statisticians. The role of the DMC is advisory to the ITSC and Sponsor. It will monitor unblinded data emerging in the trial. Details of membership, responsibilities and frequency of meetings will be defined in a separate Charter

12.4 Early Discontinuation of the Study

The formal stopping rules for each study drug in each subphenotype are described in the statistical analyses section. The DMC may recommend early stopping of the trial or any intervention if there is a safety issue. If these instances arise, guidance will be provided to local sites about continuation of interventions and follow-up visits.

12.5 Risk Assessment

A study-specific risk assessment will be performed prior to the start of the study to assign a risk category of ‘low’, ‘medium’ or ‘high’ to the trial. This overall risk assessment will be carried out by the ICTU Head of QA in collaboration with the Study Manager and the result will be used to guide the monitoring plan. The risk assessment will consider all aspects of the study and will be updated as required during the course of the study. A risk assessment will also be generated per intervention and will be reviewed each time an intervention is added.

12.6 Monitoring

The study will be monitored periodically by trial monitors to assess the progress of the study, verify adherence to the protocol, ICH GCP E6 guidelines and other national/international requirements and to review the completeness, accuracy and consistency of the data.

A monitoring plan will be devised based on a study risk analysis and described in detail in the monitoring manual by the project managers. Initiation visits will be conducted for all sites prior to the recruitment of participants. These visits will be conducted either remotely or on site depending on availability of the site and study team.

The trial will involve a combination of central, remote and on-site monitoring. On site visits will be conducted by trained monitors during the recruitment phase of the trial and at close-out as required by the protocol and trial procedures according to the monitoring manual to ensure patient safety, accurate data collection and reporting. Central monitoring will be conducted regularly where data queries and protocol deviations are reviewed and any required further site training is conducted.

Remote monitoring will also be utilised with sites in between on-site visits, to enable the study team to complete knowledge checks and follow up with training for new site members.

12.7 Quality Control and Quality Assurance

Quality Control will be performed according to ICTU internal procedures. The study may be audited by a Quality Assurance representative of the Sponsor and/or ICTU. All necessary data and documents will be made available for inspection.

The study may be participant to inspection and audit by regulatory bodies to ensure adherence to GCP and jurisdictional requirements.

12.8 Peer review

This trial was externally peer reviewed as part of the funding process.

12.9 Public Involvement

Patient and Public Involvement (PPI) has been integral to the development of this proposal. A PPI Advisory Group has been established, who have reviewed this protocol and have provided their strong endorsement. The PPI group highlighted identifying treatments for ARDS as a priority and supported testing multiple treatments simultaneously through a platform trial, and recruiting patients in both subphenotypes, placing value on excluding a potential benefit in each subphenotype. The group were supportive of the initial treatments to be tested in terms of safety and information on their potential efficacy. The PPI group were also supportive of our consent model. There was support for taking research samples to understand how the treatments work and to identify new subgroups in which the treatments might work better. The group highlighted the benefit of involving multiple countries and felt any new treatments would thus have international acceptance.

As development work for this application, an international public survey (n=9726 in 13 countries including all proposed PANTHER collaborating countries) was conducted, which found wide support for a precision medicine, adaptive platform trial, biological sampling, and the consent processes. A systematic review on public views on consent to participate in acute care research was completed. It found high levels of acceptability of the current consent processes in critical care and highlighted avenues to ensure diversity of participants recruited (translations/translators, accommodating lower literacy levels and consideration of diverse cultures).

Going forward the PPI group will provide oversight to ensure the trial maintains a patient focus. The PPI group plans to meet virtually during the trial to facilitate participation. PPI representatives will be included on trial management and oversight groups.

The PPI group will help develop any study materials relevant to participants, their families, or the public.

The study team will also work with the PPI group to develop strategies to improve inclusivity and access underserved groups. The study team will capture, evaluate, and report the impact of PPI activity through maintaining a log of PPI activity and input throughout the trial. A summary of patient and public involvement using the GRIPP2 framework will be reported.

12.10 Publication and Dissemination policy

A series of outputs to maximise the impact of this research has been planned and is detailed in the table below.

Type of output	Strategy to maximise impact
Presentations	Key national and international conferences will be targeted to ensure trial results reach key professional groups. The aim will be to share presentations simultaneously on-line to increase access. It is anticipated that presentations will be delivered by the investigators, and patient and public partners.
Podcasts	Podcasters will be contacted to develop accessible podcasts to help disseminate trial findings to professional and lay audiences.
Infographics	Infographics and animated summaries will be developed for professional and lay audiences in partnership with our PPI group, which will be disseminated through institutional press offices, our trial website, and social media.
Academic publications	The trial protocol and statistical analysis plan, and the main trial findings will be published in open access, peer-reviewed, scientific journals. Results of each intervention in each subphenotype may be published separately or in combination. Where required publications will comply with the publication policies of clinical trials groups that have endorsed or supported the study.
Public engagement events	Information about the study will be presented at Science Festivals and regional events, to explain the importance of the research, how patients and public can be involved, and to share the research findings.

The study team will work with the PPI group to develop a public dissemination plan. The PPI group will assist with making the research findings accessible, co-producing a patient friendly summary of results for dissemination to participants and relatives, patient charities, PPI organisations and the public through the media and social media.

The trial website will be used to provide information about the trial, including lay versions and public-facing documents summarising the results for patients and caregivers. The trial website will have a dedicated ‘Patients and Public’ page. Details of the website will be included in the trial patient information sheet. We will provide regular updates about the trial via the study website, social media (trial-specific Twitter account), and newsletters, and send progress summaries to clinicians and researchers. Key findings will be posted on the trial and institutional websites. Summaries of the results will be provided on the trial website in different languages. We will work with institutional communication offices to prepare press releases as appropriate.

In keeping with best practice for research we will provide a lay summary of results, as well as reporting trial results to participants in a suitable format.

Information concerning the study, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of the Sponsor. The investigator may use this information for the purposes of the study only.

It is understood by the investigator that the Sponsor will use information developed in this clinical study in connection with the development of the IMP/device and, therefore, may disclose it as required to other clinical investigators, commercial entities and to Regulatory Authorities. In order to allow the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to the Sponsor.

Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from the Sponsor.

Therefore, all information obtained as a result of the study will be regarded as confidential, at least until appropriate analysis and review by the investigator(s) are completed.

The results will also be submitted to appropriate trial registries/databases in keeping with applicable regulatory requirements.

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13. REVISION HISTORY

Version	Date	Summary of changes
1.0	03 Mar 2025	First version
2.0	11 Jun 2025	Section 2. Background – further detail added Figure 1. Colours amended Section 8.4 Causality – wording removed at request of MHRA
2.1	30 JUL 2025	6.4 Visit schedule and 6.8 Research sample timeframes amended

SIGNATURE PAGE 1 (Chief Investigator)

The signature below constitutes approval of this protocol by the signatory, on behalf of the Protocol Development Group, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: PANTHER

Protocol Number: 175151

Signed: Danny McAuley Digitally signed by Danny McAuley Date: 2025.09.15 22:51:28 +01'00'

Danny McAuley
Professor

Date: 18.08.2025

SIGNATURE PAGE 2 (SPONSOR)

The signatures below constitute approval of this protocol by the signatory.

Study Title: PANTHER

Protocol Number: 175151

Signed: Ruth Nicholson Digitally signed by Ruth Nicholson Date: 2025.09.22 14:05:01 +0

Name of Sponsor's Representative
Title
Sponsor name

Date: _____

SIGNATURE PAGE 3 (STATISTICIAN)

The signatures below constitute approval of this protocol by the signatory.

Study Title: PANTHER

Protocol Number: 175151

Signed: Victoria Cornelius Digitally signed by Victoria Cornelius Date: 2025.09.16 13:53:22 +01'00' _____

Victoria Cornelius
Professor
Imperial College London

Date: _____

SIGNATURE PAGE 4 (PRINCIPAL INVESTIGATOR)

The signature of the below constitutes agreement of this protocol by the signatory and provides the necessary assurance that this study will be conducted at his/her investigational site according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: PANTHER

Protocol Number: 175151

Protocol Version: 1.0

Address of Institution: _____

_____

_____

Signed: _____

Print Name and Title: _____

Date: _____

APPENDICES