
Project Study Information

IRAS Information

IRAS Form

Reference: 99/AA/1234

IRAS Version: 5.9.1

Short title for project:

PANTHER

Key people and organisations

Chief investigator:

Danny McAuley

Project deputy:

Janis Best-Lane

Project funder:

NIHR

Project scope

CTIMP questions

Provide the project EudraCT ID. The required format is ####-####-##

Will any research sites in this study be NHS organisations?

Yes

Does the study involve use of any ionising radiation?

No

Will you be taking new OR existing human tissue samples (or other human biological samples)?

Yes

Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

Yes

Do you plan to include any participants who are children?

No

Do you plan to request research delivery network support? Selecting "yes", does not automatically submit an application for support from the research delivery network. For details on how to apply for support for your study, visit the NIHR website.

Yes

Do you plan to include any participants who are prisoners or young offenders?

No

Proposed Study End Date

31/05/2029

A. Administrative Details

1. In which countries of the UK will the research sites be located? (Tick all that apply)

- ☒ England
- ☒ Scotland
- ☒ Wales
- ☒ Northern Ireland

2. In which country of the UK will the lead NHS R&D office be located?

England 

3. Will any research sites in this study be NHS organisations?

Please note details entered here will be matched to the same question on Project details screen

☒ Yes ☐ No

3a. Are all the research costs and infrastructure costs (funding for the support and facilities needed to carry out the research e.g. NHS support costs) for this study provided by a NIHR Biomedical Research Centre (BRC), NIHR Applied Research Collaboration (ARC), NIHR Patient Safety Translational Research Centre (PSTRC), or an NIHR Medtech and In Vitro Diagnostic Co-operative (MIC) in all study sites?

☐ Yes ☒ No

3b. Have you, or do you intend to, make an application for the study to be considered for NIHR Clinical Research Network (CRN) Support and inclusion in the NIHR Clinical Research Network Portfolio?

☒ Yes ☐ No

4. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

☐ Yes ☒ No

5. Is this a commercially sponsored Phase 1 or Phase 1/2a trial involving healthy volunteers?

☐ Yes ☒ No

6. Full title of the research

Details entered here will be entered into Medicines Information A3

Precision medicine Adaptive Network platform Trial in Hypoxaemic acutE respiratory failuRe

7. Is this application linked to a previous study or another current application?

☐ Yes ☒ No

8. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?

☐ Yes

☒ No

9. Lay Summary of the study

Acute Respiratory Distress Syndrome (ARDS) is a common severe lung condition in the intensive care unit (ICU) that makes it hard to breathe. Inflammation is a natural process that helps our body fight off harmful substances like infections. However, sometimes it can go into overdrive and damage the lungs. About 1 out of every 4 people in the ICU who need a machine to help them breathe (a ventilator) have ARDS. ARDS causes significant death and disability. There are no proven effective medicines to treat it.

We have identified two subgroups of patients with ARDS. We can identify these subgroups by measuring certain substances in the blood. Patients from each subgroup are likely to respond differently to some treatments. We want to be able to identify which patients with ARDS will respond best to a treatment to improve patient care.

We are planning a "platform" clinical trial to test different treatments for ARDS. This type of trial tests several treatments at the same time in a group of people. This means we can find what works and is safe, with the smallest number of patients. We can also test additional treatments during the trial as new information emerges. We hope that this way of testing treatments will help us find effective treatments for ARDS as quickly as possible and save money.

We will start by testing 2 treatments, that are safe and are widely used for other conditions. There is evidence that they may work for ARDS.

We will measure how many patients survive and how long it takes survivors to recover. We plan to conduct this research in multiple countries worldwide.

10. In which aspects of the research process have you actively involved or will you involve patients service users and/ or their carers or members of the public?

- ☒ Design of the research
- ☒ Management of the research
- ☒ Undertaking the research
- ☒ Analysis of results
- ☒ Dissemination of findings
- ☐ None of the above

11. Give details of involvement, or if none please justify the absence of involvement.

Patient and public involvement have been integral in the set up of this study, the writing of the protocol, consent process and the management of the study. PPI members are part of the Trial management group and steering committee.

12. Is the trial a Complex Innovative Design (CID) trial?

☒ Yes

☐ No

12a. If yes, select the trial methodology

Platform trial

B. Research Procedures, Risks and Benefits

1. Non-clinical interventions

(Please complete for each intervention/procedure as follows)

1: Interventions/procedures to be received by each participant as part of the research protocol

2: Number of interventions/procedures which are part of standard care

3: Number of interventions/procedures which are additional to standard care

4: Total number of interventions/procedures

5: Average time taken per intervention/procedure (minutes, hours or days)

6: Details of who will conduct the intervention/procedure and where it will take place

1	2	3	4	5	6
Informed consent to participate in the study	0	1	1	90mins	Delegated and trained site local clinical research team member; doctor and/or PANTHER research nurse
Physical Function Test (SPBB)	0	1	1	10	The site research team will complete this with patient before they are discharged. Conducted by a member of the clinical research team or clinical team that the hospital has deemed qualified to perform the procedure.
Cognitive impairment (MOCA) questionnaire	0	1	1	10	The site research team will complete this with patient before they are discharged.
Hospital Anxiety and Depression Scale (HADS), Objective Social Outcomes Index, Impact of Events Scale, Care and wellbeing needs, Cognitive impairment (MOCA), quality of life questionnaire (EQ-5D-5L)	0	6	6	30	3 and 6 month follow up telephone questionnaire's undertaken by PANTHER study team or site research team.

2. Clinical interventions

(Please complete for each intervention/procedure as follows)

1: Interventions/procedures to be received by each participant as part of the research protocol

2: Number of interventions/procedures which are part of standard care

3: Number of interventions/procedures which are additional to standard care

4: Total number of interventions/procedures

5: Average time taken per intervention/procedure (minutes, hours or days)

6: Details of who will conduct the intervention/procedure and where it will take place

1	2	3	4	5	6
Simvastatin Intervention	0	1	1	5	If randomised into the arm that will be given the intervention. Simvastatin will be administered (usually via tablet) at a dose of 80 mg once daily by the enteral route for up to 28 days whilst the patient is in ICU. Administered by member of the research team or clinical team that the hospital has deemed qualified to perform the procedure.

1	2	3	4	5	6
Baricitinib Intervention	0	1	1	5	If randomised into the arm that will be given the intervention. Baricitinib will be administered (usually via tablet) at a dose of 4mg once daily by the enteral route for up to 10 days. This will be adjusted for patients with renal impairment. Administered by member of the research team or clinical team that the hospital has deemed qualified to perform the procedure.
Blood sample (4mls) is taken for subphenotyping	0	1	1	5	Clinical team member or site study research team member. Collected by member of the clinical research team or clinical team that the hospital has deemed qualified to perform the procedure.
Additional blood samples taken on day 0, day 3 and day 7	0	3	3	5	Clinical team member or site study research team member. Collected by member of the clinical research team or clinical team that the hospital has deemed qualified to perform the procedure.
Tracheal Aspirate	1	0	1	40	Clinical team member or site study research team member. Collected by member of the clinical research team or clinical team that the hospital has deemed qualified to perform the procedure.
Nasal swab (mid-turbinate) taken on day 0	0	1	1	2	Clinical team member or site study research team member. Collected by member of the clinical research team or clinical team that the hospital has deemed qualified to perform the procedure.
Bronchioalveolar Lavage fluid (not all sites)	0	1	1	30-90	Clinical team member or site study research team member. Collected by member of the clinical research team or clinical team that the hospital has deemed qualified to perform the procedure.

3. Will you withhold an intervention, medicine or procedure, which would normally be considered a part of routine care?

☐ Yes

☒ No

4. What are the potential risks and burdens for research participants and how will you minimise them?

ARDS can be life threatening. Evidence suggests that earlier treatment will benefit the patient. Therefore, to ensure there is no delay

to treatment, it is imperative that patients are randomised as soon as they become eligible on ICU. Delays to treatment could affect the scientific validity of the trial, making the results less generalisable to usual practice. Due to their critical illness, most eligible patients for the study will have a reduced level of consciousness and will be unable to give consent at that time. Hence treatment with the study drugs will need to be

started in most cases without prospective consent in place. The specific nature of usual supportive care measures (which includes routinely administered interventions in critical care) are seldom discussed with their families and are presented to patients and their families as a "package deal" when time persists (in contrast to surgical procedures, which are more likely to be discussed in detail). As this is an emergency situation it is not possible to identify eligible patients in advance of them losing the capacity to provide consent. In addition, relatives are likely to be distressed by the patient's illness and admission to critical care at the point the patient is eligible for the trial – and are unlikely to have capacity to make a decision in the short time frame available. The minimisation of further distress has been a priority when deciding on the proposed consent process. The process has been based on qualitative work with family members in similar studies regarding the preferred timing and way of approach for consent. This process has also been used in a number of other similar critical care research studies. After

randomisation, the clinical team will identify the next-of-kin (family / relative / friend) recorded in the patients clinical notes and they will be approached by a member of the clinical research team and asked if they would be happy to provide Personal Legal Consent. The trial will be explained to them, they will be given an information sheet about the trial and they will be asked to give an opinion on the patients' participation in the trial. If a Personal Legal Representative cannot be contacted in an adequate timeframe (approximately 2 hrs) a Professional Legal Representative will be approached. This will be a member of the site clinical team, who is directly involved in the patient's care, based in the hospital and is not part of the research team (i.e. not on the research delegation log). They will be informed about the trial and asked to give an opinion on the patients' participation in the trial. Once patients regain capacity in the hospital, they will be approached by a member of the clinical research team, the trial explained to them, including their participation and that the study was discussed with their Personal or Professional Legal Representative while they lacked capacity. They will then be given the patient information sheet and asked to consent for the continuation of the study. All patients in critical care units are monitored closely and clinical/research staff in this setting are very experienced in assessing mental capacity. Admission of adult patients to ICUs with ARDS will be linked to existing healthcare-related registries and databases in the UK. The following data may be obtained by data linkage with death registries and hospital discharge coding databases in the UK:

- Hospital readmissions, and diagnoses and procedures carried out during readmissions
- Mortality after discharge from the index hospitalization

We will seek consent from patients to collect this data. If the patient does not have capacity consent for this data will be sought from a Personal Legal Representative or a Professional Legal Representative if the former is not available. ICNARC will use patient identifiable data (NHS number, date of birth, post code and sex) which is already collected as part of the CMP national clinical audit to link data with other routinely collected data sets. This allows the research objectives to be achieved in an efficient manner and allows for the best possible follow up of longer term survival for patients. This is not possible without patient identifiable data. The CMP national clinical audit has section 251 approval for use of patient identifiable data for audit.

Confidentiality: Minimal patient identifiable data will be required to enable the trial team to link data to routine data sources.

Use of tissues in future research: a total of 30mls of blood will be collected for future research, all samples will be stored at the Wellcome-Wolfson Institute for Experimental Medicine for analysis in other ethically approved studies.

5. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?

☒ Yes ☐ No

5a. If yes, please give details of procedures in place to deal with these issues.

All interviewers will receive study specific training in these questionnaires. An escalation pathway will be defined in a study manual for participants who are found to be severely/extremely anxious, depressed or requests help. The researcher will determine whether the participant has medical support in place or whether this is required. If the participant is not currently receiving help the researcher will suggest support and that they contact their GP.

6. What arrangements are being made for continued provision of the investigational medicinal product for participants, if appropriate, once the research has finished? If the intention is to not provide IMP to participants when the trial has completed, this must be clearly justified.

Not applicable. The interventions will be provided to the patients for the period that they are in the intensive care unit/hospital. There will be a 3 and 6 month follow up call with patients to determine quality of life and cognitive function via questionnaires.

7. Will you inform the participants' General Practitioner that they are taking part in the trial? (and/or any other healthcare professional responsible for their care).

☒ Yes ☐ No

8. Will you recruit any participants who are involved in current research or have recently been involved in any research prior to recruitment?

Yes

8a. If Yes, please give details and justify their inclusion. If Not Known, what steps will you take to find out?

Co-enrolment of participants in other research studies, including interventional trials, is encouraged. The principle is that co-enrolment should always occur and is only not permitted when there is a clear threat to the validity of either study or it would materially influence the risk to, or be too burdensome to the participants. Decisions regarding co-enrolment with other trials will be made on a trial-by-trial basis. Where PANTHER is also being conducted at the same site as a another study, the decision regarding co-enrolment will lie with the Trial Management Group. Decisions regarding co-enrolment with other trials will be distributed to participating sites as an operational document and will not require or involve amendment of the protocol.

9. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs?

The participant information sheet and consent forms will be translated in to different languages. Local translators, interpreters and support staff can be used to translate information to participants and their family.

10. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)? (Tick as appropriate)

- ☒ Access to medical records by those outside the direct care team
- ☒ Electronic transfer by magnetic or optical media, email or computer networks
- ☐ Sharing of personal data with other organisations
- ☐ Export of personal data outside the EEA
- ☒ Use of personal addresses, postcodes, faxes, emails or telephone numbers
- ☐ Publication of direct quotations from respondents
- ☐ Publication of data that might allow identification of individuals
- ☐ Use of audio/visual recording devices
- ☒ Storage of personal data on any of the following:
- ☒ Manual files (includes paper or film)
- ☒ NHS computers
- ☐ Social Care Service computers
- ☐ Home or other personal computers
- ☐ University computers
- ☐ Private company computers
- ☐ Laptop computers

11. Please describe the physical security arrangements for storage of personal data during the study

All personal identifiable data will be stored on password protected NHS computers and NHS servers. The records will be accessed by the direct healthcare team and members of the local research team who will be registered medical and nursing staff employed by the NHS Trust. Access to this data may be required by auditors and Sponsor representatives for monitoring purposes. This access will be supervised by the healthcare team at site and no personal information will leave the NHS computer. Patient identifiable data (NHS number, date of birth, postcode and sex) will be stored on password protected private computers at ICNARC, this data is already collected as part of the CMP national clinical audit which has section 251 approval for use of patient identifiable data. Data will be linked from the NHS computer to ICNARC CTU, the national clinical audit for critical care and stored securely on password protected computers and protected servers.

12. How will you ensure the confidentiality of personal data?

To minimise the use of personal identifiers, participants will be allocated a unique trial number and this will be used by the PANTHER trial team and in communications with the local research teams at participating sites. The only access to patient identifiable data, needed for telephone follow-up and linking to the Case Mix Programme, national clinical audit will be by ICNARC and the Imperial College Team. ICNARC is registered under the Data Protection Act (Registration number: Z6289325). Confidentiality forms the basics of Imperial's Information Security Policy. All staff employed by Imperial and ICNARC sign a contract, which incorporates a confidentiality clause and the consequences of breaching confidentiality are covered in our Disciplinary Procedure. External researchers, temporary staff and contractors are all required to sign a formal confidentiality agreement with ICNARC. Data security and confidentiality are a fixed agenda item at monthly staff meetings for all staff at ICNARC. The imperial team will access personal data for the purposes of follow up only. This data will only be accessed if there is explicit consent from the patient to do so. The data will be stored in a secure environment on OpenClinica, the trial database for the study. Only those completing follow up will have access to this space. These members of staff will also have completed mandatory data protection training by the college.


13. Who will have access to participants' personal data during the study?

Medical records will only be accessed by the direct healthcare team and members of the local clinical research team who will all be registered medical and nursing staff employed by the NHS Trust. Those outside the direct healthcare team who will require access include auditors, representatives of the sponsor, and regulatory authorities and this would be stated in the patient information sheet and will only access records when consent is in place. Identifiable data, including name and telephone number, will be stored in a secure environment on the trial database system OpenClinica to enable patients to be contacted to complete follow-up questionnaires over the telephone or electronically at three and six months post-randomisation. This will only be collected for patients deemed alive by the hospital prior to the three and six month telephone call/email, in order not to cause additional distress by contacting patients who have passed away in this high-risk cohort. NHS number will also be collected. Randomisation and Clinical data relevant for the trial will be sent to and stored by Imperial College London (Sponsor) securely to enable study analysis, as described in the protocol. Routinely collected data relevant for assessing the trial outcomes (e.g. readmission to critical care and hospital) will be used where possible. Patients will be linked to the Case Mix Programme, the national clinical audit for critical care, through admission number and NHS number obtained through data collection method 1). In addition, access to data held by NHS Digital will be requested, which will include mortality and readmission data through hospital estimates. Only pseudonymised data would be shared with other organisations.

14. Where will the data generated by the study be analysed and by whom?

Hospital sites will enter data on an electronic database, Open Clinica, the data will be extracted from here and analysed by the statisticians at the Imperial Clinical Trials Unit (ICTU). Data collected via the Case Mix Program (CMP) at ICNARC will be generated at ICNARC and transferred to ICTU and analysed by the same statisticians. We also hope to obtain access to the Scottish equivalent of ICNARC to obtain audit information for our Scottish patients:- The Scottish Intensive Care Society Audit Group (SICSAG). NHS digital data will be generated by NHS digital and and transferred to ICTU and analysed by the same statisticians

15. How long will personal data be stored or accessed after the study has ended?

Over 3 years 

16. For how long will you store research data generated by the study?

Minimum of 10 years

17. Please give details of the long term arrangements for storage of research data after the study has ended.

PANTHER will use electronic TMF and ISF. Details of the Archiving facility used by each NHS site (for wet ink documents e.g. original consent forms) and the central management team (for the TMF) will be captured on a retention of records statement. Long term storage will be in line with the Sponsor's archiving SOP.

18. If you will be using identifiable personal data, how will you ensure that anonymity will be maintained when publishing the results?

All analysis will be performed on pseudonymised data, no personal identifiable data will be used in the analysis or the publication in the results.

19. Will individual researchers receive any personal payment over and above normal salary or any other benefits or incentives for taking part in this research?

☐ Yes ☒ No

20. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

☐ Yes ☒ No

21. Please confirm the arrangements for registration of this trial on a public database.

Trial will be registered on a publicly accessible database

C. Transparency

1. How do you intend to report and disseminate the results of the study?

- ☒ Peer reviewed scientific journals
- ☐ Internal report
- ☒ Conference presentation
- ☒ Publication on website
- ☒ Other publication
- ☐ Submission to regulatory authorities
- ☐ Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
- ☐ No plans to report or disseminate the results
- ☐ Other

2. How will you enable sharing of study data with others?

The results of the trial will be made publicly available via institutional websites and also through charity / patient groups(e.g.ICU Steps, Intensive Care Foundation).

Participants will not routinely be given results as this is a trial that is unlikely to offer individual patients or their doctors any information that will be of relevance to their ongoing or future clinical care.

3. How will you enable sharing of tissue samples and associated data with others?

Blood samples will be taken from patients at baseline and day 3 and 7. These will be stored locally at sites initially and will then be transferred to a HTA licenced facility based at Queen's University Belfast . Other studies can apply for ethical approval and tissue bank registration to utilise these samples. Utilising samples for other studies will also be included in the consent form to ensure patients/families are happy for samples to be used in other studies.

4. How and when will you inform participants of the study results?

If there will be no arrangements in place to inform participants please justify this.

Patients have the option to be informed of the results directly, this preference will be obtained from the consent form. The results of the trial will be made publicly available via our trial website, institutional websites and also through charity / patient groups (e.g. ICU Steps, Intensive Care Foundation).

5. Point of Contact for Publication

Chief Investigator

D. Scientific and Statistical Review

1. How has the scientific quality of the trial been assessed?

- ☒ Independent external review
- ☐ Review within a company
- ☒ Review within a multi-centre research group
- ☒ Review within the Chief Investigator's institution or host organisation
- ☐ Other

2. Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:

This research project has undergone internal review with the multiple co-investigators. In addition, the protocol has undergone external peer review as part of the competitive funding process.

3. How have the statistical aspects of the research been reviewed?

- ☒ Review by independent statistician commissioned by funder or sponsor
- ☒ Other review by independent statistician
- ☐ Review by company statistician
- ☐ Review by a statistician within the Chief Investigator's institution
- ☒ Review by a statistician within the research team or multi-centre group
- ☐ Review by educational supervisor
- ☒ Other review by individual with relevant statistical expertise

4. In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

Title	Surname
Prof	Cornelius
Forename/Initials	
Victoria	
Department	Institution
Faculty of Medicine	Imperial College London
Street	City
111 Stadium House, White City Campus	London
Country	Post code
United Kingdom	W12 0BZ
Email	Telephone
v.cornelius@imperial.ac.uk	
Mobile	

5. How was the sample size decided upon?

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.

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)

The sample sizes 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;
- 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

- A power of 86% in hypoinflammatory subphenotype and type I error rate (POR=1) of 17%.
- A power of 71% in the hyperinflammatory subphenotype and type I error rate (POR=1) of 18%.

Type I error rate of 20%

E. Management of the Research

1. Sponsor Organisation status

Academic 

2. Is this study?

- ☐ Single Centre
- ☒ Multi Centre

3. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research?

- ☐ NHS indemnity scheme will apply (NHS sponsors only)
- ☒ Other insurance or indemnity arrangements will apply (give details below)

3a. Other insurance or indemnity arrangements (please Specify)

Imperial College London will provide an indemnity insurance certificate

4. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research?

- ☐ NHS indemnity scheme will apply (NHS sponsors only)
- ☒ Other insurance or indemnity arrangements will apply (give details below)

4a. Other insurance or indemnity arrangements (please Specify)

Imperial college London will provide an indemnity insurance certificate

5. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/ collaborators arising from harm to participants in the conduct of the research?

- ☒ NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)
- ☒ Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

5a. Non-NHS sites (give details of insurance or indemnity arrangements)

Imperial College will provide negligent and non-negligent harm insurance.

6. Has the sponsor(s) made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises?

☒ Yes ☐ No

6a. Please give details of the compensation policy:

Imperial College London will provide an indemnity insurance certificate.

F. Ionising Radiation

1. Does the study involve exposures to radioactive materials?

☐ Yes ☒ No

2. Does the study involve other diagnostic or therapeutic ionising radiation?

☐ Yes ☒ No

3. Has the trial been authorised by a Clinical Radiation Expert (CRE) and a Medical Physics Expert (MPE)?

☐ Yes ☒ No

4. What are the risks associated with ionising radiation exposures within the trial?

N/A

G. Tissue

1. List the human biological material/tissue samples which will be removed and/or stored as part of the research

The following samples will be collected:-

Approximately 30mls of blood will be collected from each patient over a period of 3 days (day 0, day 3 and day 7)

A nasal swab turbinate will be collected on day 0

A tracheal aspirate sample will be collected on day 0, day 3 and day 7

A bronchioalveolar lavage sample will be collected on day 0 and day 3

2. Please explain what licensing arrangements apply to the procurement, processing, distribution or import of the tissues and cells to be used in the research.

Initially the samples will be collected and stored at each participating site. At various time points these samples will be collected, transported and stored by the Queen's University, Belfast which has a HTA licence. Collection, transport and storage of samples will be organised and paid for by the Study. Each research site will complete initial processing and analysis will be managed by the Sponsor.

3. If you are using existing tissue samples where will the samples be obtained from?

- ☐ NHS pathology department(s)/diagnostic archive(s)
- ☐ Other research tissue bank(s) or sample collection(s)

4. Please give details of where the samples will be stored, who will have access and the custodial arrangements.

Samples will initially be stored at each participating site in a -80 Freezer.

At various time points the samples will be transported to the Wellcome-Wolfson Institute for Experimental Medicine at Queen's University Belfast, 97 Lisbon Road, Belfast BT9 7BL.

Access only by the core PANTHER management team

5. If you are obtaining existing tissue samples, will there be consent in place?

Select..

6. What will happen to the samples at the end of the research?

- ☒ Transfer to research tissue bank
- ☐ Storage by research team pending ethical approval for use in another project
- ☐ Storage by research team as part of a new research tissue bank
- ☐ Storage by research team of biological material which is not "relevant material" for the purposes of the Human Tissue Act
- ☐ Disposal in accordance with the Human Tissue Authority's Code of Practice
- ☐ Other
- ☐ Not yet known

7. Please give further details of the proposed arrangements:

Once ethical approval for the PANTHER clinical trial comes to an end, the samples will be registered with the Wellcome-Wolfson Institute for Experimental Medicine at Queen's University Belfast and they will provide Ethical approval. Storage of the samples will remain within PANTHER -80 freezers, but Ethical approval will be provided by the Queen's Belfast University Tissue Bank.

H. Recruitment and Informed Consent Procedure

1. How will potential participants be identified?

Potential participants will be identified by the medical and nursing team on the intensive care unit. They will assess if the patient meets the inclusion criteria and that none of the exclusion criteria are present from the patient's medical history and clinical notes. Patients will be screened at adult, general, critical care units in NHS hospitals by members of the local clinical team (members of the patients direct healthcare team). Patients in critical care units are monitored closely and clinical research staff working in this setting have extensive experience of assessing capacity in their patients. If a patient has capacity they will always be approached to provide informed consent, if the patient does not have capacity, then the Personal Legal Representative (PerLR) will be approached and if not available after two hours a Professional Legal Representative (ProLR) will be sought, if not available after two hours the patient can be randomised and the consent model reattempted until consent is obtained. Once a patient has regained capacity, they will be approached by an authorised member of the site clinical research team for informed deferred consent. This will be done as soon as practically possible (usually within a few days of the patient regaining capacity). A Participant Information Sheet (PIS) will be provided to the patient by an authorised staff member. The PIS will provide information about the purpose of the study, what participation means for the patient, confidentiality and data security, and the future availability of the trial results. A Consent Form will be provided indicating that: the information given, orally and in writing, has been read and understood; participation is voluntary and can be withdrawn at any time without consequence; and that consent is given for access to medical records (including routine data sources) for data collection. The Consent Form will cover consent for use of data already collected for the trial, as well as ongoing data collection and follow-up.

Patients will be given time to read the PIS and have an opportunity to ask any questions they may have about participation in PANTHER. After verifying that the PIS and Consent Form are understood, the person seeking consent will invite the patient to sign the Consent Form and will then add their own name and countersign it. A copy will be given to the patient, a copy placed in the patient's medical notes and the original kept in the Investigator Site File.

Patients will only be approached by authorised staff members who have received training in PANTHER processes and procedures and

have basic understanding of the principles of Good Clinical Practice (GCP). The recruitment process will be done in such a way to mitigate any potential undue influence or coercion. No therapeutic promises will be made.

2. What resources will be used for recruitment?

No resources will be used for recruitment. The clinical information of potential patients will be reviewed by the local NHS staff to assess eligibility.

3. Will identification of potential participants involve access to identifiable information?

☒ Yes ☐ No

3a. If yes, describe what measures will be in place to confirm that access to this information will be lawful.

The clinical information of potential patients will be reviewed by the local NHS staff to assess eligibility. These staff are part of the direct care team.

4. Who will be approaching potential participants and who will be obtaining informed consent?

Only members of the dedicated study clinical research team at site would approach patients to discuss the study and obtain informed consent. Gaining informed consent is a delegated duty and so the team members need to be appropriately trained and on the research delegation log.

5. How, when and where will informed consent be obtained?

PANTHER will use a model of informed deferred consent, as used in a number of recent trials in the UK including REMAP-CAP (ISRCTN67000769), (Fluids in Shock (ISRCTN15244462), AIRWAYS-2 (ISRCTN08256118), PARAMEDIC 2 (SRCTN73485024), VANISH trial (ISRCTN 20769191), 65 trial (ISRCTN10580502) amongst others and has been shown to be acceptable to patients and their family members. Informed consent will be carried out at the hospital site, often at the patients bedside. A Participant Information Sheet (PIS) will be provided to the patient by an authorised staff member. The PIS will provide information about the purpose of the study, what participation means for the patient, confidentiality and data security, and the future availability of the trial results. A Consent Form will be provided indicating that: the information given, orally and in writing, has been read and understood; participation is voluntary and can be withdrawn at any time without consequence; and that consent is given for access to medical records (including routine data sources) for data collection. The Consent Form will cover consent for use of data already collected for the trial, as well as ongoing data collection and follow-up. Patients will be given time to read the PIS and have an opportunity to ask any questions they may have about participation in PANTHER. After verifying that the PIS and Consent Form are understood, the person seeking consent will invite the patient to sign the Consent Form and will then add their own name and countersign it. A copy will be given to the patient, a copy placed in the patient's medical notes and the original kept in the Investigator Site File. These processes have been approved by our lay representatives.

6. How long will potential participants (or their legal representative) be given to decide whether to participate?

ARDS should be treated quickly and delays in administering the appropriate drugs including study drugs may affect patient outcome. Therefore in most cases, the patient will be treated urgently as part of the trial before it is possible to identify and seek consent. The treating doctor will ensure that the patient meets all of the inclusion criteria and none of the exclusion criteria before enrolment. At the first available opportunity, once the clinical condition has stabilised, consent will be sought. Many patients will be unable to consent themselves and so a Personal Legal Representative will be sought and if unavailable a Professional Legal Representative will be approached. They will be given information about the study, including why it was necessary to initiate urgent treatment with the study drugs. They will given adequate time to make a fully informed decision, with the aim of obtaining consent prior to hospital discharge. If the Personal Legal Representative is not able to attend in person, e-consent using the OpenClinica system will be used. The Personal Legal Representative's identity will be verified via a video link or other means, in line with the methods used by the clinical team to update family member / NOK about the clinical management of the participant.

7. How will it be assured that potential participants (or their legal representative) have understood the information and that consent is informed?

The local research teams have extensive experience in dissemination of trial information to patients and their families, and well as determining if participants have understood the information and have capacity. Participants will be given opportunities to ask questions, and can withdraw their consent at any time without giving a reason.

8. What arrangements are in place to obtain informed consent from potential participants (or their legal representative) who do not speak English?

The participant information sheet and consent forms will be translated in to different languages. Local translators and interpreters

can be used at site as per normal local procedures.

9. How will it be ensured that participants can withdraw their consent at any point?

This is stated within the information sheet and consent form and will be reiterated by the clinical research team member obtaining consent.

10. Please provide any further information, in relation to the procedure for recruitment and informed consent for the clinical trial, which has not been provided elsewhere.

Due to rapid changes in these patients, their health could deteriorate very quickly once the eligibility criteria is assessed. Therefore there is a small possibility that the patient may die prior to consent being obtained. In this situation if appropriate a family member (Personal Legal Representative) will be contacted and informed of the patient's inclusion in the trial and consent sought. However there are circumstances where it is not appropriate to discuss the patient's participation in the trial if they have passed away. A professional legal representative will be sought in this case, however if none are available within a suitable timeframe (within 24hrs of the patient passing away) the study will retain the data in the study.

In this circumstance, we will retain the data already collected for this patient and generate a file note to explain this. In our experience with other ICU research (LeoPARDS, BLING III, REMAP-CAP) there are very few instances like this, but there is a slight possibility the patient may pass away and seeking consent after this may not be appropriate. We wish to retain the patient's data so as not to introduce bias in the study as if patients are removed from the analysis because they have passed away could unbalance the trial.

If the patient withdraws their consent after randomisation they will be provided with options. They can either withdraw completely from the trial or from certain elements. Further follow-up visits as part of the clinical trial will cease. However, the participant will be asked if data collection through data linkage of routinely collected data, including long-term follow-up can continue. The options will be captured on the consent form and on the electronic database.

11. Provide a clear indication of what the first act of recruitment will be.

Patients will be screened at adult, general, critical care units in NHS hospitals by members of the local clinical team (members of the patients' direct healthcare team).

12. Clinical Trials Involving Adults Lacking the Capacity to Consent

12a. Provide justification for recruiting incapacitated adults.

The vast majority of participants to a critical care clinical trial will lack capacity as they will be very unwell. We will seek advice and consent about a patient's participation in the collection of research specific data from a Personal Legal Representative or a Professional Legal Representative while the patient lacks capacity.

We believe that this is the only appropriate model for consent in the face of the time pressure of needing to allocate treatment early in the process of critical care referral and stabilisation. Moreover, the process of obtaining consent while active intensive treatment is ongoing and the patient is in a critical state sometimes appears coercive and adds undue stress to an already stressful situation. Due to the severity of illness and its impact on mental capacity of the target population (critically ill patients), it will not be possible to involve PANTHER trial participants early on in the consenting process. Instead, consent will be obtained prior to hospital discharge when their condition allows (e.g. they regain capacity). If the patient does not regain capacity prior to hospital discharge, the decision for use of information in the study will lie with the patients Personal Legal Representative if available. If the Personal Legal Representative does not wish to be involved in the consultation, a Professional Legal Representative will be appointed. If the patient dies, a Professional Legal Representative will be appointed, if none are available the data collected will be retained in the study. These processes have been approved by our lay representatives.

12b. Who will assess and confirm whether a potential participant has the capacity to consent?

Potential participants will be identified by the medical and nursing team on the intensive care unit. They will assess if the patient meets the inclusion criteria and that none of the exclusion criteria are present from the patient's medical history and clinical notes. The clinical information of potential patients will be reviewed by the local NHS staff to assess eligibility. These staff are part of the direct care team

12c. Where capacity to consent will fluctuate or will be borderline, how will potential participants be involved in the

decision to participate in the trial?

The process of obtaining consent while active intensive treatment is ongoing and the patient is in a critical state sometimes appears coercive and adds undue stress to an already stressful situation. Due to the severity of illness and its impact on mental capacity of the target population (critically ill patients), it will not be possible to involve PANTHER trial participants early on in the consenting process. Instead, consent will be obtained prior to hospital discharge when their condition allows (e.g. they regain capacity). If the patient does not regain capacity prior to hospital discharge, the decision for use of information in the study will lie with the patients Personal Legal Representative. If the Personal Legal representative does not wish to be involved in the consultation, a Professional Legal Representative will be appointed. If the patient dies, a Professional Legal Representative will be appointed, if none are available the data collected will be retained in the study.

12d. How will a legal representative be identified?

A Personal Legal representative will be identified via the normal clinical processes of contacting NOK when patients are hospitalised, either via medical notes or the patient themselves.

A Professional Legal Representative will be approached by the clinical research team who is involved in the patient's care, not involved in the study (not listed on the study delegation log) who can provide their independent opinion as to whether the patient is suitable and/or would object to participating in the study.

13. Clinical Trials in Emergency Situations

13a. Will the trial recruit participants in an emergency situation whereby consent from the participant cannot be sought or a legal representative cannot be consulted prior to the participant being recruited into the trial?

☒ Yes ☐ No

13b. Describe why it would not be possible to obtain consent from potential participants or a legal representative prior to recruiting into the clinical trial.

Do to the urgent nature of this critical care study, it may not be possible to obtain consent prior to inclusion in the study. If the patient has capacity we will always seek informed consent before we include them in the study. If the patient does not have capacity and meets the study criteria we will aim to start patient treatment as soon as possible, this may mean neither Personal Legal Representative nor a Professional Legal Representative is available, in this case we will seek consent soon after the study treatment has started.

We will always seek advice and consent about a patient's participation in the collection of research specific data from a Personal Legal Representative or a Professional Legal Representative while the patient lacks capacity. We have included the option of e-consent in this study to allow more options for the Personal Legal Representative to provide their consent if they are not able to visit the hospital during this time. We believe that this is the only appropriate model for consent in the face of the time pressure of needing to allocate treatment early in the process of critical care referral and stabilisation. These processes have been approved by our lay representatives.

13c. What arrangements will be in place to obtain informed consent from the participant or from a legal representative, whichever can be obtained soonest?

As a study we have tried to ensure we have a variety of options available to obtain consent in our study. If the patient does not have capacity prior to inclusion we will seek a Personal Legal Representative consent. If this person is not able to visit the hospital we can offer e-consent through the OpenClinica database. A consent form is sent via email and the personal representative can provide their electronic approval. If a Personal Legal Representative is not available for a patient we will seek Professional Legal Representative. When the patient does regain capacity we will seek informed consent from the patient in every scenario to ensure the patient is aware of their participation and their right to withdraw. If the patient regains capacity but is not able to sign a consent form due to weakness we have an option for an independent witness to sign. If a patient regains capacity but is discharged prior to providing informed consent (e.g. staff capacity) attempts to obtain informed consent from follow up appointments or verbal consent during the follow up call, and this will be documented fully in a study file note.

13d. How will it be ensured that a potential participant has not expressed any previous objection to participate in the clinical trial?

All previous objections to involvement in research / participation would be documented in the patients medical notes and these wishes would be followed. Any objection on the patient behalf by his friends / family would also be followed.

15. Impartial Witness

15a. Is the trial likely to include participants who are unable to sign the consent form and therefore an impartial witness would be required?

☒ Yes ☐ No

15b. Why is it expected that an impartial witness might be required?

If a participant is able to provide consent, but unable to sign / initial the consent form due to reduced arm strength etc, an impartial witness would be able to sign that they witnessed verbal consent into the PANTHER study in the appropriate section of the consent form.

15c. How will an impartial witness be identified?

Clinical team member that is not part of the research team (not on the study delegation log).

15d. How will it be known that the potential participant gives their informed consent?

There will be a section on the participant consent forms for witness consent

16. Cluster Trials

16a. Will the trial involve the recruitment and allocation of an IMP to groups of participants rather than individual participants (cluster trial)?

☐ Yes ☒ No

I. Payment of Compensation

1. Will payment or compensation be offered?

☐ Yes ☒ No

1c. If not, please explain why not

The participants in this study have been admitted to ICU and require emergency treatment, therefore there are no out of pocket expenses for participating in this study. As participating in this study requires no extra time or effort from the patients there is no compensation for time and effort.

2. Describe arrangements for how any payment or compensation will be paid/provided

N/A

3. Are there any conditions attached to the payment or compensation?

☐ Yes ☒ No

A. Trial Identification

A1. National Competent Authority

UK - MHRA

A2. European Clinical Trials Database (EudraCT) number

—

A3. Full title of the trial

Please note details entered here will be inserted into Study Information A6

Precision medicine Adaptive Network platform Trial in Hypoxaemic acutE respiratory failuRe

A3-1. Title of the trial for lay people, in easily understood, i.e. non-technical, language

Precision medicine Adaptive Network platform Trial in Hypoxaemic acutE respiratory failuRe

A3-2. Name or abbreviated title of the trial where available

Please return to [Update project details](#) if you need to amend the short project title entered here.

PANTHER

A4-1. Sponsor's protocol code number:

175151

A4-2. Sponsor's protocol version:

1.0

A4-3. Sponsor's protocol date:

12 December, 2024

A5-1. ISRCTN number

—

A5-2. ClinicalTrials.gov number

—

A5-3. WHO Universal Trial Reference Number (UTRN)

—

A5-4. Other Identifiers:

Name	Identifier
No items	

A6. Is this a resubmission?

☐ Yes

☒ No

A6-1. Indicate the resubmission letter or else select 'First submission'

First Submission

A7. Is the trial part of a Paediatric Investigation Plan?

☐ Yes ☒ No ☐ Not Answered

B. Identification of the sponsor responsible for the request

B. Sponsor Identification

B1. Sponsor

B1-1 Name of organisation

Imperial College London

B1-2 Name of person to contact:

B1-2-1 Given Name

Ruth

B1-2-2 Middle Name

B1-2-3 Family Name

Nicholson

Address

Street Address

5th Floor, Sherfield Building, South Kensington Campus

Town/City

London

Post Code

SW7 2BB

Country

United Kingdom

Telephone Number

Country Dialing Prefix

+44

Local Area Code

0207

Phone Number

5941862

Extension

N/A

Fax Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

E-mail

r.nicholson@imperial.ac.uk

B3. Status of the Sponsor

B3. Status of the Sponsor:

Non-Commercial

B4. Source(s) of Monetary or Material Support for the clinical trial (repeat as necessary)

B4-1. Name of organisation	B4-2. Country
National Institute for Health and Care Research	United Kingdom

B5. Contact point designated by the sponsor for further information on the trial

B5-1 Name of organisation

Imperial College London

B5-2 Functional name of contact point

Janis Best-Lane

Address

Street Address

QEQM Building, St Mary's Hospital, Praed Street

Town/City

London

Post Code

W2 1NY

Country

United Kingdom

Telephone Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

Fax Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

E-mail

panther@imperial.ac.uk

C. Applicant Identification

C1. Request for Authorization to Competent Authority

C1-1, C1-2, C1-3 Who is responsible for the Clinical Authorization Application?

The sponsor

C1-4 Complete the details of the applicant below even if they are provided elsewhere on the form

C1-4-1 Name of organisation

Imperial College London

C1-4-2 Name of person to contact:

C1-4-2-1 Given Name

Ruth

C1-4-2-2 Middle Name

C1-4-2-3 Family Name

Nicholson

Address

Street Address	Town/City
Level 5, Sherfield Building, South Kensington	London
Post Code	Country
SW7 2BB	United Kingdom

Telephone Number		
Country Dialing Prefix	Local Area Code	Phone Number
Extension		

Fax Number		
Country Dialing Prefix	Local Area Code	Phone Number
Extension		

E-mail
rgit.ctimp.team@imperial.ac.uk

C1-5 Request to receive a copy of the CTA data XML

C1-5-1 Do you want a xml file copy of the CTA form data saved on EudraCT?

☒Yes ☐No ☐Not Answered

C1-5-1-1 E-mail

E-mail
panther@imperial.ac.uk

C1-5-1-2 Secure E-mail (EudraLink account)?

☐Yes ☒No ☐Not Answered

C2. Request for Opinion of the Ethics Committee

C2-1, C2-2, C2-3, C2-4 Applicant Identification

The sponsor

C2-5 Complete the details of the applicant below even if they are provided else where on the form

C2-5-1 Organisation
Imperial College London

C2-5-2 Name of contact person

C2-5-2-1 Given Name	C2-5-2-2 Middle Name	C2-5-2-3 Family Name
Keith		Boland

Address

Street Address	Town/City
Level 5, Sherfield Building, South Kensington	London

Post Code

SW7 2BB

Country

United Kingdom

Telephone Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

Fax Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

E-mail

rgit.ctimp.team@imperial.ac.uk

D. Investigational Medicinal Products

D. Investigational Medicinal Products

IMP Name:

PR1

D1/D2. IMP Identification and Status Details

D1-2/D1-3. Investigational medicinal product category:

Test

D2. Status of the IMP

D2-1. Does the IMP to be used in the trial have a marketing authorisation?

☒ Yes ☐ No ☐ Not Answered

D2-1-1-1. Trade Name:

Simvastatin

D2-1-1-1-1. EV Product Code

D2-1-1-2. Name of the MA holder:

Milpharm Limited

D2-1-1-3. MA Number (if MA granted by a Member State)

PL 16363/0600

D2-1-1-4. Is the IMP modified in relation to its MA?

☐ Yes ☒ No ☐ Not Answered

D2-1-2. Which country granted the MA?

United Kingdom

D2-1-2-1. Is this the Member state concerned with this application?

☒ Yes ☐ No ☐ Not Answered

D2-2. IMP to be used in the CT has a marketing authorisation

D2-2. For situations where the IMP to be used in the CT has a Marketing Authorisation in the Member State concerned but the protocol allows that any brand of the IMP with a Marketing Authorisation in that Member State be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start

D2-2-1. In the protocol, is treatment defined only by active substance?

☐Yes ☐No ☒Not Answered

D2-2-2. In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?

☐Yes ☐No ☒Not Answered

D2-2-3. The products to be administered as IMPs are defined as belonging to an ATC group

☐Yes ☐No ☒Not Answered

D2-2-4. Other:

☒Yes ☐No ☐Not Answered

D2-2-4-1. Please specify:

The protocol allows different combinations of marketed products used in local clinical practice. As the IMP is provided from hospital stock and so no particular product is named. For the same reason different drugs from the same class (in terms of pharmacological action) may be used. We are comparing this product with standard care.

D2-3. IMPD submitted / D2-4. IMP previously authorised / D2-5. IMP designated as an Orphan drug / D2-6. Subject of Scientific Advice

D2-3-1, D2-3-2 and D2-3-3: only one may be answered 'Yes' and the others must be answered 'No'

D2-3-1. Full IMPD

☐Yes ☒No ☐Not Answered

D2-3-2. Simplified IMPD

☐Yes ☒No ☐Not Answered

D2-3-3. Summary of product characteristics (SmPC) only

☒Yes ☐No ☐Not Answered

D2-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

☐Yes ☒No ☐Not Answered

D2-5. Has the IMP been designated in this indication as an orphan drug in the Community?

☐Yes ☒No ☐Not Answered

D2-6. Has the IMP been the subject of scientific advice related to this clinical trial?

☐Yes ☒No ☐Not Answered

D3. Description of IMP

D3-1. Product name where applicable

Simvastatin

D3-2. Product code where applicable

D3-3. ATC codes, if officially registered

C10AA01

D3-4. Pharmaceutical Form

Tablet 

D3-4-1. Is this a specific paediatric formulation?

☐Yes ☒No ☐Not Answered

D3-5. Maximum duration of treatment of a subject according to the protocol

Maximum 28 days. simvastatin will be administered once daily until study day 28 or ICU discharge, whichever comes first.

Note: Content will be enabled for D3-6-1 and D3-6-2 only E7-1-1 is selected

D3-6. Dose allowed

D3-6-1. For first trial only

D3-6-1. First dose for first-in-human clinical trial

D3-6-1. Specify per day or total

☐Per day ☐Total ☐Not Answered

D3-6-1. Specify total dose number

D3-6-1. Specify total dose units

Select.. 

D3-6-1. Route of administration (relevant to the first dose)

Select.. 

D3-6-2. For all trials

D3-6-2. Maximum dose allowed

D3-6-2. Specify per day or total

☒Per day ☐Total ☐Not Answered

D3-6-2. Specify total dose number

80

D3-6-2. Specify total dose units

mg milligram(s) 

D3-6-2. Route of administration (relevant to the maximum dose)

Enteral use (Noncurrent) 

D3-7. Routes of administration for this IMP

Selected Routes of administration
Enteral use (Noncurrent)
Oral use

D3-8. Active substances

D3-8. Name of Active Substance (INN or proposed INN if available)

Simvastatin

D3-9-1. CAS Number:

79902-63-9

D3-9-2. Current Sponsor Code:

N/A

D3-9-3. Other Descriptive Name:

N/A

D3-9-4. EudraVigilance Substance Code (if known):

—

D3-9-5. Full Molecular Formula

C₂₅H₃₈O₅

D3-9-6. Chemical/Biological Description of the Active Substance

Simvastatin is a 2,2-dimethylbutanoic acid ester of a hexahydro-1-naphthalenyl group. It is a member of the hexahydronaphthalene class of compounds and is functionally related to lovastatin. Simvastatin is a prodrug of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor. It is a potent inhibitor of this enzyme, which is the rate-limiting enzyme in cholesterol biosynthesis. Simvastatin also increases the breakdown of LDL cholesterol by inducing hepatic LDL receptors.

D3-10. *Strength*

D3-10-1. Concentration Unit:

mg milligram(s)

D3-10-2. Concentration Type:

Equal

D3-10-3. Concentration Number (only use both fields for range):

40

D3-10-3. Concentration Number (only use both fields for range):

—

D3-11. Type of IMP

Does the IMP contain an active substance:

D3-11-1. Of chemical origin?

☒Yes ☐No ☐Not Answered

D3-11-2. Of biological/biotechnological origin? (other than Advanced Therapy IMP (ATIMP))

☐Yes ☒No ☐Not Answered

Is this IMP a:

D3-11-3. Advanced Therapy IMP (ATIMP)?

☐Yes ☒No ☐Not Answered

D3-11-4. Combination product that includes a device, but does not involve an Advanced Therapy

☐Yes ☒No ☐Not Answered

D3-11-5. Radiopharmaceutical medicinal product?

☐Yes ☒No ☐Not Answered

D3-11-6. Immunological medical product (eg vaccine, allergen, immune serum)?

☐Yes ☒No ☐Not Answered

D3-11-7. Plasma derived medicinal product?

☐Yes ☒No ☐Not Answered

D3-11-8. Extractive medicinal product?

☐Yes ☒No ☐Not Answered

D3-11-9. Recombinant medicinal product?

☐Yes ☒No ☐Not Answered

D3-11-10. Medicinal product containing genetically modified organisms?

☐Yes ☒No ☐Not Answered

D3-11-11. Herbal medicinal product?

☐Yes ☒No ☐Not Answered

D3-11-12. Homeopathic medicinal product?

☐Yes ☒No ☐Not Answered

D3-11-13. Another type of medicinal product?

☐Yes ☒No ☐Not Answered

D3-12. Specify the mode of action for the active substance in this medicinal product

Simvastatin is indicated for the treatment of hyperlipidemia to reduce elevated total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), and triglycerides (TG), and to increase high-density lipoprotein cholesterol.

D3-13. Is it an IMP to be used in a first-in-human clinical trial

☐Yes ☒No ☐Not Answered

IMP Name:

PR2

D1/D2. IMP Identification and Status Details

D1-2/D1-3. Investigational medicinal product category:

Test

D2. Status of the IMP

D2-1. Does the IMP to be used in the trial have a marketing authorisation?

☒Yes ☐No ☐Not Answered

D2-1-1-1. Trade Name:

Baricitinib

D2-1-1-1. EV Product Code

D2-1-1-2. Name of the MA holder:

Eli Lilly

D2-1-1-3. MA Number (if MA granted by a Member State)

PLGB 14895/0256

D2-1-1-4. Is the IMP modified in relation to its MA?

☐Yes ☒No ☐Not Answered

D2-1-2. Which country granted the MA?

United Kingdom

D2-1-2-1. Is this the Member state concerned with this application?

☒Yes ☐No ☐Not Answered

D2-2. IMP to be used in the CT has a marketing authorisation

D2-2. For situations where the IMP to be used in the CT has a Marketing Authorisation in the Member State concerned but the protocol allows that any brand of the IMP with a Marketing Authorisation in that Member State be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start

D2-2-1. In the protocol, is treatment defined only by active substance?

☐Yes ☐No ☒Not Answered

D2-2-2. In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?

☐Yes ☐No ☒Not Answered

D2-2-3. The products to be administered as IMPs are defined as belonging to an ATC group

☐Yes ☐No ☒Not Answered

D2-2-4. Other:

☒Yes ☐No ☐Not Answered

D2-2-4-1. Please specify:

The protocol allows different combinations of marketed products used in local clinical practice. As the IMP is provided from hospital stock and so no particular product is named. For the same reason different drugs from the same class (in terms of pharmacological action) may be used. We are comparing this product with standard care.

D2-3. IMPD submitted / D2-4. IMP previously authorised / D2-5. IMP designated as an Orphan drug / D2-6. Subject of Scientific Advice

D2-3-1, D2-3-2 and D2-3-3: only one may be answered 'Yes' and the others must be answered 'No'

D2-3-1. Full IMPD

☐Yes ☒No ☐Not Answered

D2-3-2. Simplified IMPD

☐Yes ☒No ☐Not Answered

D2-3-3. Summary of product characteristics (SmPC) only

☒Yes ☐No ☐Not Answered

D2-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

☐Yes ☒No ☐Not Answered

D2-5. Has the IMP been designated in this indication as an orphan drug in the Community?

☐Yes ☒No ☐Not Answered

D2-6. Has the IMP been the subject of scientific advice related to this clinical trial?

☐Yes ☒No ☐Not Answered

D3. Description of IMP

D3-1. Product name where applicable

Baricitnib

D3-2. Product code where applicable

D3-3. ATC codes, if officially registered

L04AF02

D3-4. Pharmaceutical Form

Coated tablet 

D3-4-1. Is this a specific paediatric formulation?

☐Yes ☒No ☐Not Answered

D3-5. Maximum duration of treatment of a subject according to the protocol
Baricitinib will be administered for 10 days or until hospital discharge, whichever occurs first.

Note: Content will be enabled for D3-6-1 and D3-6-2 only E7-1-1 is selected

D3-6. Dose allowed

D3-6-1. For first trial only

D3-6-1. First dose for first-in-human clinical trial

D3-6-1. Specify per day or total

☐Per day ☐Total ☐Not Answered

D3-6-1. Specify total dose number

D3-6-1. Specify total dose units

Select..

D3-6-1. Route of administration (relevant to the first dose)

Select..

D3-6-2. For all trials

D3-6-2. Maximum dose allowed

D3-6-2. Specify per day or total

☒Per day ☐Total ☐Not Answered

D3-6-2. Specify total dose number

4

D3-6-2. Specify total dose units

mg milligram(s)

D3-6-2. Route of administration (relevant to the maximum dose)

Enteral use (Noncurrent)

D3-7. Routes of administration for this IMP

Selected Routes of administration
Enteral use (Noncurrent)
Oral use

D3-8. Active substances

D3-8. Name of Active Substance (INN or proposed INN if available)

Baricitinib

D3-9-1. CAS Number:

1187594-09-7

D3-9-2. Current Sponsor Code:

N/A

D3-9-3. Other Descriptive Name:

N/A

D3-9-4. EudraVigilance Substance Code (if known):

—

D3-9-5. Full Molecular Formula

C₁₆H₁₇N₇O₂S

D3-9-6. Chemical/Biological Description of the Active Substance

Baricitinib is a (JAK) inhibitor, specifically JAK1 and JAK2. Baricitinib consists of a pyrrolo[3,4-d]pyrimidine ring system, with an imidazole group attached to a phenylurea.

D3-10. *Strength*

D3-10-1. Concentration Unit:

mg milligram(s)

D3-10-2. Concentration Type:

Equal

D3-10-3. Concentration Number (only use both fields for range):

1

D3-10-3. Concentration Number (only use both fields for range):

4

D3-11. Type of IMP

Does the IMP contain an active substance:

D3-11-1. Of chemical origin?

☒Yes ☐No ☐Not Answered

D3-11-2. Of biological/biotechnological origin? (other than Advanced Therapy IMP (ATIMP))

☐Yes ☒No ☐Not Answered

Is this IMP a:

D3-11-3. Advanced Therapy IMP (ATIMP)?

☐Yes ☒No ☐Not Answered

D3-11-4. Combination product that includes a device, but does not involve an Advanced Therapy

☐Yes ☒No ☐Not Answered

D3-11-5. Radiopharmaceutical medicinal product?

☐Yes ☒No ☐Not Answered

D3-11-6. Immunological medical product (eg vaccine, allergen, immune serum)?

☐Yes ☒No ☐Not Answered

D3-11-7. Plasma derived medicinal product?

☐ Yes ☒ No ☐ Not Answered

D3-11-8. Extractive medicinal product?

☐ Yes ☒ No ☐ Not Answered

D3-11-9. Recombinant medicinal product?

☐ Yes ☒ No ☐ Not Answered

D3-11-10. Medicinal product containing genetically modified organisms?

☐ Yes ☒ No ☐ Not Answered

D3-11-11. Herbal medicinal product?

☐ Yes ☒ No ☐ Not Answered

D3-11-12. Homeopathic medicinal product?

☐ Yes ☒ No ☐ Not Answered

D3-11-13. Another type of medicinal product?

☐ Yes ☒ No ☐ Not Answered

D3-12. Specify the mode of action for the active substance in this medicinal product

Baricitinib inhibits the activity of JAK proteins and modulates the signalling pathway of various interleukins, interferons, and growth factors. It was also shown to decrease the proliferation of JAK1/JAK2 expression in mutated cells and induce cell apoptosis.

D3-13. Is it an IMP to be used in a first-in-human clinical trial

☐ Yes ☒ No ☐ Not Answered

D8. Placebo Information

D9. Site(s) where the qualified person certifies batch release

D9-1. IMPs and placebos for which no responsible site needs to be identified

If all the conditions below are met, then tick this box and select below the IMPs and placebos to which this applies ☒

This section is used to identify IMPs and placebos which:

- has a MA in the EU and
- is sourced from the EU market and
- is used in the trial without modification (eg. Not over-encapsulated) and
- the packaging and labelling is carried out for local use only as per article 9.2 of the Directive 2005/28/EC (GCP Directive)

Finished IMP

Description	Associate
PR1-Tablet	<input checked="" type="checkbox"/>
PR2-Coated tablet	<input checked="" type="checkbox"/>

Placebo

Pharmaceutical Form	Route of Administration	Associate
No items		

D9-2. Add Responsible Site

D9-2. Who is responsible in the Community for the certification of the finished IMPs?

D9-2-1/D9-2-2. As a manufacturer, importer or both?

Both ▼

D9-2-3. Site Organisation Name

Aurobindo Pharma - Milpharm Ltd

D9-2-4. Address

Street Address

Odyssey Business Park, Ares Block, West End Road, South Ruislip

Town/City

London

Post Code

HA4 6QD

Country

United Kingdom

D9-2-5. Manufacturer authorisation number

PL 16363/0599

D9-2-5-1. If no authorisation, give the reasons

—

D9-2. Site where the qualified person certifies batch release

Finished IMP

Description	Associate
PR1-Tablet	<input checked="" type="checkbox"/>
PR2-Coated tablet	<input type="checkbox"/>

Placebo

Pharmaceutical Form	Route of Administration	Associate
No items		

D9-2. Who is responsible in the Community for the certification of the finished IMPs?

D9-2-1/D9-2-2. As a manufacturer, importer or both?

Both ▼

D9-2-3. Site Organisation Name

Eli Lilly Company Limited

D9-2-4. Address

Street Address

Lilly House, Basing View

Town/City

Basingstoke

Post Code

RG21 4FA

Country

United Kingdom

D9-2-5. Manufacturer authorisation number

PLGB 14895/0256

D9-2-5-1. If no authorisation, give the reasons

—

D9-2. Site where the qualified person certifies batch release

Finished IMP

Description	Associate
PR1-Tablet	<input type="checkbox"/>
PR2-Coated tablet	<input checked="" type="checkbox"/>

Placebo

Pharmaceutical Form	Route of Administration	Associate
No items		

E. General Information on the Trial

E. Design of the Trial

Medical condition or disease under investigation

E1-1. Specify the medical condition(s) to be investigated:

Critically illnesses including acute respiratory disease syndrome and pandemic infection.

E1-1-1. Medical condition in easily understood language

Critically illnesses including acute respiratory disease syndrome and pandemic infection.

E1-1-2. Identify The Therapeutic Area

Diseases [C] - Respiratory Tract Diseases [C08]

E1-2. MedDRA information

MedDRA Search

Version	Term	Level	Classification Code	SOC	
22.1	Critical illness	PT	10077264	General disorders and administration site conditions	
22.1	Critical illness	LLT	10077264	General disorders and administration site conditions	
22.1	Respiratory, thoracic and mediastinal disorders	SOC	10038738	Respiratory, thoracic and mediastinal disorders	
22.1	Respiratory failure	PT	10038695	Respiratory, thoracic and mediastinal disorders	

E1-3. Is any of the conditions being studied a rare disease?

☐Yes ☒No ☐Not Answered

E2. Objective of the trial

E2-1. Main objective of the trial

To increase the development of new therapies for people with critical illness by creating an international platform trial to test the success of treatments in patients with ARDS and pandemic infection.

E2-2. Secondary objectives of the trial

1. To develop a framework for identifying, developing and testing additional subgroups and therapies in the ongoing platform trial.
2. To play a leading role in international collaboration in research.
3. To provide opportunities for early career investigators to build clinical trial experience.
4. To help collaborate with commercial partners to test promising new treatments for ARDS
5. To be more sustainable through academic and commercial funding opportunities.
6. To collect samples and data on other precision medicine factors
7. To be able to quickly change focus in the event of a new pandemic related to respiratory failure, providing tools to be prepared for a pandemic if needed.

E2-3. Is there a sub-study?

☐Yes ☒No ☐Not Answered

E3. Please list the principal inclusion criteria (list the most important, max 5000 characters)

1) Critically ill patients in hospital and at least 1 of the following:-

a) ARDS

b) A pandemic associated syndrome*

*this will be triggered if a 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 $\geq 30\text{L/min}$ 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,
- $\text{PaO}_2/\text{FiO}_2$ ratio $< 40\text{ kPa}$ from arterial blood gases, or $\text{SpO}_2/\text{FiO}_2 < 315$ from pulse oximetry where $\text{SpO}_2 < 97$.

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

E4. Please list the principal exclusion criteria (list the most important, max 5000 characters)

- (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
- (e) Aged <18 years

E5-1. Primary end point(s) (max 5000 characters)

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.

E5-1-1. Timepoint(s) of evaluation of this end point (max 800 characters)

28 days

E5-2. Secondary end point(s) (max 5000 characters)

- (1) Progression to invasive mechanical ventilation, extracorporeal membrane oxygenation or death among those not receiving that support at baseline
- (2) 28-day vasopressor-free days
- (3) 28-day respiratory support-free days
- (4) Receiving new renal replacement therapy
- (5) ICU length of stay
- (6) Hospital length of stay
- (7) All-cause mortality at 28 and 90 days
- (8) Safety outcomes:-
 - Elevated Creatine Kinase more than 10 times the upper limit of normal
 - Alanine Transaminase or Aspartate Transaminase or both more than 8 times the upper limit of normal
 - Serious infection defined as positive blood cultures requiring treatment and positive pulmonary aspergillosis requiring treatment
 - Venous thromboembolism
 - Stroke
 - Myocardial infarction
 - Ischaemic bowel
 - Gastrointestinal perforation
 - Clinically important gastrointestinal (GI) bleeding confirmed on upper endoscopy
- (9) Serious adverse events
- (10) Physical function (SPPB) at hospital discharge (up to 1 week prior to discharge)
- (11) Cognitive impairment (MoCA) at hospital discharge (up to 1 week prior to discharge)

We are also collecting the following tertiary outcome measures:-

- 1) 14-day delirium and coma free days*
- 2) Incidence of ICU acquired weakness (MMST and hand grip strength dynamometry and maximal inspiratory) at day 7 and ICU discharge*
- 3) Health-related quality of life, (EQ-5D-5L), Hospital Anxiety and Depression Scale (HADS), Social and Wellbeing (SF-36), Impact of Events Scale (6 item), care and wellbeing needs and cognitive impairment (MoCA) at 90 days and 180 days*

* not all sites are expected to collect these endpoints

E5-2-1. Timepoint(s) of evaluation of this end point (max 800 characters)

90 days from randomisation is the final endpoint

E6. Scope of the trial

E6-1. Diagnosis

☐Yes ☒No ☐Not Answered

E6-2. Prophylaxis

☐Yes ☒No ☐Not Answered

E6-3. Therapy

☒Yes ☐No ☐Not Answered

E6-4. Safety

☐Yes ☒No ☐Not Answered

E6-5. Efficacy

☒Yes ☐No ☐Not Answered

E6-6. Pharmacokinetic

☐Yes ☒No ☐Not Answered

E6-7. Pharmacodynamic

☐Yes ☒No ☐Not Answered

E6-8. Bioequivalence

☐Yes ☒No ☐Not Answered

E6-9. Dose Response

☐Yes ☒No ☐Not Answered

E6-10. Pharmacogenetic

☐Yes ☒No ☐Not Answered

E6-11. Pharmacogenomic

☐Yes ☒No ☐Not Answered

E6-12. Pharmacoeconomic

☐Yes ☒No ☐Not Answered

E6-13. Others

☐Yes ☒No ☐Not Answered

E7. Trial type and phase

E7-1. Human pharmacology (Phase I)

☐Yes ☒No ☐Not Answered

E7-2. Therapeutic exploratory (Phase II)

☒Yes ☐No ☐Not Answered

E7-3. Therapeutic confirmatory (Phase III)

☐Yes ☒No ☐Not Answered

E7-4. Therapeutic use (Phase IV)

☐Yes ☒No ☐Not Answered

E8. Design of the Trial

E8-1. Controlled?

☒Yes ☐No ☐Not Answered

Specify:

E8-1-1. Randomised

☒Yes ☐No ☐Not Answered

E8-1-2. Open

☒Yes ☐No ☐Not Answered

E8-1-3. Single blind

☐Yes ☒No ☐Not Answered

E8-1-4. Double blind

☐ Yes ☒ No ☐ Not Answered

E8-1-5. Parallel group

☒ Yes ☐ No ☐ Not Answered

E8-1-6. Cross over

☐ Yes ☒ No ☐ Not Answered

E8-1-7. Other

☒ Yes ☐ No ☐ Not Answered

E8-1-7-1. Specify the design of the trial

Adaptive Platform Trial

E8-2. If controlled, specify the comparator:

E8-2-1. Other medicinal product(s)

☒ Yes ☐ No ☐ Not Answered

E8-2-2. Placebo

☐ Yes ☒ No ☐ Not Answered

E8-2-3. Other

☐ Yes ☒ No ☐ Not Answered

E8-2-4. Number of treatment arms in the trial

3

E8-3. Single site in the Member State concerned (see also section G)

☐ Yes ☒ No ☐ Not Answered

E8-4. Multiple sites in the Member State concerned (see also section G)

☒ Yes ☐ No ☐ Not Answered

E8-4-1. Number of sites anticipated in Member State concerned

E8-5. Multiple Member States

☐ Yes ☒ No ☐ Not Answered

E8-6. Trial involving sites outside the EEA

E8-6-1. Trial being conducted both within and outside the EEA

☐ Yes ☒ No ☐ Not Answered

E8-6-2. Trial conducted completely outside of the EEA

☐ Yes ☒ No ☐ Not Answered

E8-7. Trial having an independent data monitoring committee?

☒ Yes ☐ No ☐ Not Answered

E8-8. Definition of the end of trial and justification in the case where it is not the last visit of the last subject undergoing the trial.

If it is the last visit of the last subject, please enter "LVLS". If it is not LVLS provide the definition.

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

1. There is insufficient funding to support further recruitment to the platform as a whole and no reasonable prospect of additional support being obtained.
2. 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.

E8-9. Initial estimate of the duration of the trial (years, months, days)

E8-9-1. In the MS concerned

Years	Months	Days
4	0	0

E8-10. Proposed date of start of recruitment

E8-10-1. In the Member State concerned

01 June, 2025

E8-10-2. In any country

01 June, 2025

F. Population Of Trial Subjects

F1. Age Range

F1-1. Are the trial subjects under 18?

☐Yes ☒No ☐Not Answered

F1-2. Adult (18-64 years)

☒Yes ☐No ☐Not Answered

F1-2-1. Number of subjects for this age range:

1081

F1-3. Elderly (greater than 65 years)

☒Yes ☐No ☐Not Answered

F1-3-1. Number of subjects for this age range:

1082

F2. Gender

F2-1. Female

☒Yes ☐No ☐Not Answered

F2-2. Male

☒Yes ☐No ☐Not Answered

F3. Group of trial subjects

F3-1. Healthy volunteers

☐Yes ☒No ☐Not Answered

F3-2. Patients

☒Yes ☐No ☐Not Answered

F3-3. Specific vulnerable populations

☐Yes ☒No ☐Not Answered

F4. Planned number of subjects to be included

F4-1. In the member state

F5. Plans for treatment or care after a subject has ended his/her participation in the trial.

If it is different from the expected normal treatment, please specify:

Study treatment will not be provided after participant has completed the study.

G. Investigator Details

G1. National coordinating investigator (for a multicentre trial) or principal investigator (for a single centre trial)

National Coordinating Investigator

G1-1. Given Name

Daniel

G1-2. Middle Name

G1-3. Family Name

McAuley

G1-4. Qualification (MD...)

MBBS, MD

G1-5. Institution Name

Imperial College London

G1-5. Institution Department Name

Surgery and Cancer

Address

Street Address

QEQM, St Mary's Hospital, Praed Street

Town/City

London

Post Code

W2 1NY

Country

United Kingdom

G1-5-5. Please indicate if site is:

NHS

Telephone Number

Country Dialing Prefix

+44

Local Area Code

28

Phone Number

90 976385

Extension

Fax Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

E-mail

d.f.mcauley@qub.ac.uk

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

Anthony

G2-2. Middle Name

G2-3. Family Name

Gordon

G2-4. Qualification (MD...)

MBBS, MD, FFICM, FMedSci

G2-5. Institution Name

St Mary's Hospital

G2-5. Institution Department Name

Surgery & Cancer

Address

Street Address

Praed Street

Town/City

London

Post Code

W2 1NY

Country

United Kingdom

G2-5-5. Please indicate if site is:

NHS

Telephone Number

Country Dialing Prefix

+44

Local Area Code

20

Phone Number

33126328

Extension

Fax Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

E-mail

anthony.gordon@imperial.ac.uk

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

David

G2-2. Middle Name

G2-3. Family Name

Antcliffe

G2-4. Qualification (MD...)

MD

G2-5. Institution Name

Charing Cross Hospital

G2-5. Institution Department Name

Address

Street Address

Town/City

Country

Post Code

United Kingdom

G2-5-5. Please indicate if site is:

NHS

Telephone Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

Fax Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

E-mail

d.antcliffe@imperial.ac.uk

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

Stephen

G2-2. Middle Name

G2-3. Family Name

Brett

G2-4. Qualification (MD...)

MD

G2-5. Institution Name

Hammersmith Hospital

G2-5. Institution Department Name

Address

Street Address

Town/City

Country

Post Code

United Kingdom

G2-5-5. Please indicate if site is:

NHS

Telephone Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

Fax Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

E-mail

stephen.brett@imperial.ac.uk

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

Dhruv

G2-2. Middle Name

G2-3. Family Name

G2-4. Qualification (MD...)

G2-5. Institution Name

Parekh

MD

Queen Elizabeth Hospital Birmingham

G2-5. Institution Department Name

Address

Street Address

Town/City

Country

Post Code

United Kingdom

G2-5-5. Please indicate if site is:

NHS

Telephone Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

Fax Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

E-mail

D.Parekh@bham.ac.uk

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

Valerie

G2-2. Middle Name

G2-3. Family Name

Page

G2-4. Qualification (MD...)

MD

G2-5. Institution Name

Watford General Hospital

G2-5. Institution Department Name

Address

Street Address

Town/City

Country

Post Code

United Kingdom

G2-5-5. Please indicate if site is:

NHS

Telephone Number

Country Dialing Prefix Local Area Code Phone Number
Extension

Fax Number

Country Dialing Prefix Local Area Code Phone Number
Extension

E-mail

valerie.page2@nhs.net

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

Ingeborg

G2-2. Middle Name

G2-3. Family Name

Welters

G2-4. Qualification (MD...)

MD

G2-5. Institution Name

Royal Liverpool Hospital

G2-5. Institution Department Name

Address

Street Address

Town/City

Country

Post Code

United Kingdom

G2-5-5. Please indicate if site is:

NHS

Telephone Number

Country Dialing Prefix Local Area Code Phone Number
Extension

Fax Number

Country Dialing Prefix Local Area Code Phone Number
Extension

E-mail

I.Welters@liverpool.ac.uk

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

Kathryn

G2-2. Middle Name

G2-3. Family Name

Puxty

G2-4. Qualification (MD...)

MD

G2-5. Institution Name

Glasgow Royal Infirmary

G2-5. Institution Department Name

Address

Street Address

Town/City

Country

Post Code

United Kingdom

G2-5-5. Please indicate if site is:

NHS

Telephone Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

Fax Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

E-mail

Kathryn.Puxty@ggc.scot.nhs.uk

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

Anthony

G2-2. Middle Name

G2-3. Family Name

Rostron

G2-4. Qualification (MD...)

MD

G2-5. Institution Name

Sunderland Royal Hospital

G2-5. Institution Department Name

Address

Street Address

Town/City

Country

Post Code

United Kingdom

G2-5-5. Please indicate if site is:

NHS

Telephone Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

Fax Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

E-mail

Anthony.Rostron@newcastle.ac.uk

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

Elankumaran

G2-2. Middle Name

G2-3. Family Name

Paramasivam

G2-4. Qualification (MD...)

MD

G2-5. Institution Name

St James University Hospital

G2-5. Institution Department Name

Address

Street Address

Town/City

Leeds

Post Code

Country

United Kingdom

G2-5-5. Please indicate if site is:

NHS

Telephone Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

Fax Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

E-mail

eparamasivam@nhs.net

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

Tom

G2-2. Middle Name

G2-3. Family Name

Billyard

G2-4. Qualification (MD...)

MD

G2-5. Institution Name

University Hospital Coventry

G2-5. Institution Department Name

Address

Street Address

Town/City

Coventry

Post Code

Country

United Kingdom

G2-5-5. Please indicate if site is:

NHS

Telephone Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

Fax Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

E-mail

Thomas.Billyard@uhcw.nhs.uk

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

Richard

G2-2. Middle Name

G2-3. Family Name

Innes

G2-4. Qualification (MD...)

MD

G2-5. Institution Name

Musgrove Park Hospital

G2-5. Institution Department Name

Address

Street Address

Town/City

Taunton

Post Code

Country

United Kingdom

G2-5-5. Please indicate if site is:

NHS

Telephone Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

Fax Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

E-mail

Richard.Innes@somersetft.nhs.uk

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

Elankumaran

G2-2. Middle Name

G2-3. Family Name

Paramasivam

G2-4. Qualification (MD...)

G2-5. Institution Name

Leeds General Infirmary

G2-5. Institution Department Name

Address

Street Address

Town/City

Leeds

Post Code

Country

United Kingdom

G2-5-5. Please indicate if site is:

NHS

Telephone Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

Fax Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

E-mail

eparamasivam@nhs.net

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

Danny

G2-2. Middle Name

G2-3. Family Name

McAuley

G2-4. Qualification (MD...)

MBBS, MD

G2-5. Institution Name

Royal Victoria Hospital

G2-5. Institution Department Name

Address

Street Address

Town/City

Belfast

Post Code

Country

United Kingdom

G2-5-5. Please indicate if site is:

NHS

Telephone Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

Fax Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

E-mail

d.f.mcauley@qub.ac.uk

G3. Central technical facilities

G4. Trial Networks

G5. Sponsor's Subcontractor Facilities

H. Ethics Committee/National Competent Authority

H. National Competent Authority

H2-1. National Competent Authority name

UK - MHRA

H2.2. Address

Street Address

Town/City

Country

Post Code

—

H2-3. Date of submission

—

H3. Authorisation/Opinion

H3-1/H3-2/H3-3. What is the status of the National Competent Authority's authorisation

Select.. ▾

H. Ethics Committee

H2-1. Ethics Committee name

Not yet known

H2.2. Address

Street Address

Town/City

Country

Post Code

—

H2-3. Date of submission

—

H3. Authorisation/Opinion

H3-1/H3-2/H3-3. What is the status of the Ethics Committee's opinion?

Select.. ▾

Ethics Question Set

Project scope

CTIMP questions

Provide the project EudraCT ID. The required format is ####-#####-##

Will any research sites in this study be NHS organisations? Yes

Does the study involve use of any ionising radiation? No

Will you be taking new OR existing human tissue samples (or other human biological samples)? Yes

Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves? Yes

Do you plan to include any participants who are children? No

Do you plan to request research delivery network support? Selecting "yes", does not automatically submit an application for support from the research delivery network. For details on how to apply for support for your study, visit the NIHR website. Yes

Do you plan to include any participants who are prisoners or young offenders? No

Proposed Study End Date 31/05/2029

A. Administrative Details

6. Full title of the research

Details entered here will be entered into Medicines Information A3

Precision medicine Adaptive Network platform Trial in Hypoxaemic acutE respiratory failuRe

8. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?

☐ Yes

☒ No

9. Lay Summary of the study

Acute Respiratory Distress Syndrome (ARDS) is a common severe lung condition in the intensive care unit (ICU) that makes it hard to breathe. Inflammation is a natural process that helps our body fight off harmful substances like infections. However, sometimes it can go into overdrive and damage the lungs. About 1 out of every 4 people in the ICU who need a machine to help them breathe (a ventilator) have ARDS. ARDS causes significant death and disability. There are no proven effective medicines to treat it.

We have identified two subgroups of patients with ARDS. We can identify these subgroups by measuring certain substances in the blood. Patients from each subgroup are likely to respond differently to some treatments. We want to be able to identify which patients with ARDS will respond best to a treatment to improve patient care.

We are planning a “platform” clinical trial to test different treatments for ARDS. This type of trial tests several treatments at the same time in a group of people. This means we can find what works and is safe, with the smallest number of patients. We can also test additional treatments during the trial as new information emerges. We hope that this way of testing treatments will help us find effective treatments for ARDS as quickly as possible and save money.

We will start by testing 2 treatments, that are safe and are widely used for other conditions. There is evidence that they may work for ARDS.

We will measure how many patients survive and how long it takes survivors to recover. We plan to conduct this research in multiple countries worldwide.

10. In which aspects of the research process have you actively involved or will you involve patients service users and/or their carers or members of the public?

- ☒ Design of the research
- ☒ Management of the research
- ☒ Undertaking the research
- ☒ Analysis of results
- ☒ Dissemination of findings
- ☐ None of the above

11. Give details of involvement, or if none please justify the absence of involvement.

Patient and public involvement have been integral in the set up of this study, the writing of the protocol, consent process and the management of the study. PPI members are part of the Trial management group and steering committee.

12. Is the trial a Complex Innovative Design (CID) trial?

☒ Yes

☐ No

12a. If yes, select the trial methodology

Platform trial

B. Research Procedures, Risks and Benefits

1. Non-clinical interventions

(Please complete for each intervention/procedure as follows)

1: Interventions/procedures to be received by each participant as part of the research protocol

2: Number of interventions/procedures which are part of standard care

3: Number of interventions/procedures which are additional to standard care

4: Total number of interventions/procedures

5: Average time taken per intervention/procedure (minutes, hours or days)

6: Details of who will conduct the intervention/procedure and where it will take place

1	2	3	4	5	6
Informed consent to participate in the study	0	1	1	90mins	Delegated and trained site local clinical research team member; doctor and/or PANTHER research nurse
Physical Function Test (SPBB)	0	1	1	10	The site research team will complete this with patient before they are discharged. Conducted by a member of the clinical research team or clinical team that the hospital has deemed qualified to perform the procedure.
Cognitive impairment (MOCA) questionnaire	0	1	1	10	The site research team will complete this with patient before they are discharged.
Hospital Anxiety and Depression Scale (HADS), Objective Social Outcomes Index, Impact of Events Scale, Care and wellbeing needs, Cognitive impairment (MOCA), quality of life questionnaire (EQ-5D-5L)	0	6	6	30	3 and 6 month follow up telephone questionnaire's undertaken by PANTHER study team or site research team.

2. Clinical interventions

(Please complete for each intervention/procedure as follows)

1: Interventions/procedures to be received by each participant as part of the research protocol

2: Number of interventions/procedures which are part of standard care

3: Number of interventions/procedures which are additional to standard care

4: Total number of interventions/procedures

5: Average time taken per intervention/procedure (minutes, hours or days)

6: Details of who will conduct the intervention/procedure and where it will take place

1	2	3	4	5	6
Simvastatin Intervention	0	1	1	5	If randomised into the arm that will be given the intervention. Simvastatin will be administered (usually via tablet) at a dose of 80 mg once daily by the enteral route for up to 28 days whilst the patient is in ICU. Administered by member of the research team or clinical team that the hospital has deemed qualified to perform the procedure.
Baricitinib Intervention	0	1	1	5	If randomised into the arm that will be given the intervention. Baricitinib will be administered (usually via tablet) at a dose of 4mg once daily by the enteral route for up to 10 days. This will be adjusted for patients with renal impairment. Administered by member of the research team or clinical team that the hospital has deemed qualified to perform the procedure.
Blood sample (4mls) is taken for subphenotyping	0	1	1	5	Clinical team member or site study research team member. Collected by member of the clinical research team or clinical team that the hospital has deemed qualified to perform the procedure.
Additional blood samples taken on day 0, day 3 and day 7	0	3	3	5	Clinical team member or site study research team member. Collected by member of the clinical research team or clinical team that the hospital has deemed qualified to perform the procedure.
Tracheal Aspirate	1	0	1	40	Clinical team member or site study research team member. Collected by member of the clinical research team or clinical team that the hospital has deemed qualified to perform the procedure.
Nasal swab (mid-turbinate) taken on day 0	0	1	1	2	Clinical team member or site study research team member. Collected by member of the clinical research team or clinical team that the hospital has deemed qualified to perform the procedure.

1	2	3	4	5	6
Bronchioalveolar Lavage fluid (not all sites)	0	1	1	30-90	Clinical team member or site study research team member. Collected by member of the clinical research team or clinical team that the hospital has deemed qualified to perform the procedure.

3. Will you withhold an intervention, medicine or procedure, which would normally be considered a part of routine care?

☐ Yes ☒ No

4. What are the potential risks and burdens for research participants and how will you minimise them?

ARDS can be life threatening. Evidence suggests that earlier treatment will benefit the patient. Therefore, to ensure there is no delay to treatment, it is imperative that patients are randomised as soon as they become eligible on ICU. Delays to treatment could affect the scientific validity of the trial, making the results less generalisable to usual practice. Due to their critical illness, most eligible patients for the study will have a reduced level of consciousness and will be unable to give consent at that time. Hence treatment with the study drugs will need to be

started in most cases without prospective consent in place. The specific nature of usual supportive care measures (which includes routinely administered interventions in critical care) are seldom discussed with their families and are presented to patients and their families as a "package deal" when time persists (in contrast to surgical procedures, which are more likely to be discussed in detail). As this is an emergency situation it is not possible to identify eligible patients in advance of them losing the capacity to provide consent. In addition, relatives are likely to be distressed by the patient's illness and admission to critical care at the point the patient is eligible for the trial – and are unlikely to have capacity to make a decision in the short time frame available. The minimisation of further distress has been a priority when deciding on the proposed consent process. The process has been based on qualitative work with family members in similar studies regarding the preferred timing and way of approach for consent. This process has also been used in a number of other similar critical care research studies. After

randomisation, the clinical team will identify the next-of-kin (family / relative / friend) recorded in the patients clinical notes and they will be approached by a member of the clinical research team and asked if they would be happy to provide Personal Legal Consent. The trial will be explained to them, they will be given an information sheet about the trial and they will be asked to give an opinion on the patients' participation in the trial. If a Personal Legal Representative cannot be contacted in an adequate timeframe (approximately 2 hrs) a Professional Legal Representative will be approached. This will be a member of the site clinical team, who is directly involved in the patient's care, based in the hospital and is not part of the research team (i.e. not on the research delegation log). They will be informed about the trial and asked to give an opinion on the patients' participation in the trial. Once patients regain capacity in the hospital, they will be approached by a member of the clinical research team, the trial explained to them, including their participation and that the study was discussed with their Personal or Professional Legal Representative while they lacked capacity. They will then be given the patient information sheet and asked to consent for the continuation of the study. All patients in critical care units are monitored closely and clinical/research staff in this setting are very experienced in assessing mental capacity. Admission of adult patients to ICUs with ARDS will be linked to existing healthcare-related registries and databases in the UK. The following data may be obtained by data linkage with death registries and hospital discharge coding databases in the UK:

- Hospital readmissions, and diagnoses and procedures carried out during readmissions
- Mortality after discharge from the index hospitalization

We will seek consent from patients to collect this data. If the patient does not have capacity consent for this data will be sought from a Personal Legal Representative or a Professional Legal Representative if the former is not available. ICNARC will use patient identifiable data (NHS number, date of birth, post code and sex) which is already collected as part of the CMP national clinical audit to link data with other routinely collected data sets. This allows the research objectives to be achieved in an efficient manner and allows for the best possible follow up of longer term survival for patients. This is not possible without patient identifiable data. The CMP national clinical audit has section 251 approval for use of patient identifiable data for audit.

Confidentiality: Minimal patient identifiable data will be required to enable the trial team to link data to routine data sources.

Use of tissues in future research: a total of 30mls of blood will be collected for future research, all samples will be stored at the Wellcome-Wolfson Institute for Experimental Medicine for analysis in other ethically approved studies.

5. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?

☒ Yes

☐ No

5a. If yes, please give details of procedures in place to deal with these issues.

All interviewers will receive study specific training in these questionnaires. An escalation pathway will be defined in a study manual for participants who are found to be severely/extremely anxious, depressed or requests help. The researcher will determine whether the participant has medical support in place or whether this is required. If the participant is not currently receiving help the researcher will suggest support and that they contact their GP.

6. What arrangements are being made for continued provision of the investigational medicinal product for participants, if appropriate, once the research has finished? If the intention is to not provide IMP to participants when the trial has completed, this must be clearly justified.

Not applicable. The interventions will be provided to the patients for the period that they are in the intensive care unit/hospital. There will be a 3 and 6 month follow up call with patients to determine quality of life and cognitive function via questionnaires.

7. Will you inform the participants' General Practitioner that they are taking part in the trial? (and/or any other healthcare professional responsible for their care).

☒ Yes

☐ No

8. Will you recruit any participants who are involved in current research or have recently been involved in any research prior to recruitment?

Yes

8a. If Yes, please give details and justify their inclusion. If Not Known, what steps will you take to find out?

Co-enrolment of participants in other research studies, including interventional trials, is encouraged. The principle is that co-enrolment should always occur and is only not permitted when there is a clear threat to the validity of either study or it would materially influence the risk to, or be too burdensome to the participants. Decisions regarding co-enrolment with other trials will be made on a trial-by-trial basis. Where PANTHER is also being conducted at the same site as a another study, the decision regarding co-enrolment will lie with the Trial Management Group. Decisions regarding co-enrolment with other trials will be distributed to participating sites as an operational document and will not require or involve amendment of the protocol.

9. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs?

The participant information sheet and consent forms will be translated in to different languages. Local translators, interpreters and support staff can be used to translate information to participants and their family.

C. Transparency

1. How do you intend to report and disseminate the results of the study?

☒ Peer reviewed scientific journals

☐ Internal report

☒ Conference presentation

☒ Publication on website

☒ Other publication

☐ Submission to regulatory authorities

☐ Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators

☐ No plans to report or disseminate the results

☐ Other

2. How will you enable sharing of study data with others?

The results of the trial will be made publicly available via institutional websites and also through charity / patient groups (e.g. ICU Steps, Intensive Care Foundation).

Participants will not routinely be given results as this is a trial that is unlikely to offer individual patients or their doctors any information that will be of relevance to their ongoing or future clinical care.

3. How will you enable sharing of tissue samples and associated data with others?

Blood samples will be taken from patients at baseline and day 3 and 7. These will be stored locally at sites initially and will then be transferred to a HTA licenced facility based at Queen's University Belfast. Other studies can apply for ethical approval and tissue bank registration to utilise these samples. Utilising samples for other studies will also be included in the consent form to ensure patients/families are happy for samples to be used in other studies.

4. How and when will you inform participants of the study results?

If there will be no arrangements in place to inform participants please justify this.

Patients have the option to be informed of the results directly, this preference will be obtained from the consent form. The results of the trial will be made publicly available via our trial website, institutional websites and also through charity / patient groups (e.g. ICU Steps, Intensive Care Foundation).

5. Point of Contact for Publication

Chief Investigator ▼

D. Scientific and Statistical Review

1. How has the scientific quality of the trial been assessed?

- ☒ Independent external review
- ☐ Review within a company
- ☒ Review within a multi-centre research group
- ☒ Review within the Chief Investigator's institution or host organisation
- ☐ Other

2. Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:

This research project has undergone internal review with the multiple co-investigators. In addition, the protocol has undergone external peer review as part of the competitive funding process.

3. How have the statistical aspects of the research been reviewed?

- ☒ Review by independent statistician commissioned by funder or sponsor
- ☒ Other review by independent statistician
- ☐ Review by company statistician
- ☐ Review by a statistician within the Chief Investigator's institution
- ☒ Review by a statistician within the research team or multi-centre group
- ☐ Review by educational supervisor
- ☒ Other review by individual with relevant statistical expertise

4. In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

Title

Prof

Cornelius

Forename/Initials

Victoria

Department

Faculty of Medicine

Institution

Imperial College London

Street

111 Stadium House, White City Campus

City

London

Country

United Kingdom

Post code

W12 0BZ

Email

v.cornelius@imperial.ac.uk

Telephone

Mobile

5. How was the sample size decided upon?

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.

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)

The sample sizes 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;
- 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

- A power of 86% in hypoinflammatory subphenotype and type I error rate (POR=1) of 17%.
- A power of 71% in the hyperinflammatory subphenotype and type I error rate (POR=1) of 18%.

Type I error rate of 20%

F. Ionising Radiation

1. Does the study involve exposures to radioactive materials?

☐ Yes

☒ No

2. Does the study involve other diagnostic or therapeutic ionising radiation?

☐ Yes

☒ No

3. Has the trial been authorised by a Clinical Radiation Expert (CRE) and a Medical Physics Expert (MPE)?

☐ Yes ☒ No

4. What are the risks associated with ionising radiation exposures within the trial?

N/A

G. Tissue

1. List the human biological material/tissue samples which will be removed and/or stored as part of the research

The following samples will be collected:-

Approximately 30mls of blood will be collected from each patient over a period of 3 days (day 0, day 3 and day 7)

A nasal swab turbinate will be collected on day 0

A tracheal aspirate sample will be collected on day 0, day 3 and day 7

A bronchioalveolar lavage sample will be collected on day 0 and day 3

5. If you are obtaining existing tissue samples, will there be consent in place?

Select.. 

6. What will happen to the samples at the end of the research?

- ☒ Transfer to research tissue bank
- ☐ Storage by research team pending ethical approval for use in another project
- ☐ Storage by research team as part of a new research tissue bank
- ☐ Storage by research team of biological material which is not "relevant material" for the purposes of the Human Tissue Act
- ☐ Disposal in accordance with the Human Tissue Authority's Code of Practice
- ☐ Other
- ☐ Not yet known

H. Recruitment and Informed Consent Procedure

1. How will potential participants be identified?

Potential participants will be identified by the medical and nursing team on the intensive care unit. They will assess if the patient meets the inclusion criteria and that none of the exclusion criteria are present from the patient's medical history and clinical notes. Patients will be screened at adult, general, critical care units in NHS hospitals by members of the local clinical team (members of the patients direct healthcare team). Patients in critical care units are monitored closely and clinical research staff working in this setting have extensive experience of assessing capacity in their patients. If a patient has capacity they will always be approached to provide informed consent, if the patient does not have capacity, then the Personal Legal Representative (PerLR) will be approached and if not available after two hours a Professional Legal Representative (ProLR) will be sought, if not available after two hours the patient can be randomised and the consent model reattempted until consent is obtained. Once a patient has regained capacity, they will be approached by an authorised member of the site clinical research team for informed deferred consent. This will be done as soon as practically possible (usually within a few days of the patient regaining capacity). A Participant Information Sheet (PIS) will be provided to the patient by an authorised staff member. The PIS will provide information about the purpose of the study, what participation means for the patient, confidentiality and data security, and the future availability of the trial results. A Consent Form will be provided indicating that: the information given, orally and in writing, has been read and understood; participation is voluntary and can be withdrawn at any time without consequence; and that consent is given for access to medical records (including routine data sources) for data collection. The Consent Form will cover consent for use of data already collected for the trial, as well as ongoing data collection and follow-up.

Patients will be given time to read the PIS and have an opportunity to ask any questions they may have about participation in PANTHER. After verifying that the PIS and Consent Form are understood, the person seeking consent will invite the patient to sign the Consent Form and will then add their own name and countersign it. A copy will be given to the patient, a copy placed in the patient's medical notes and the original kept in the Investigator Site File.

Patients will only be approached by authorised staff members who have received training in PANTHER processes and procedures and have basic understanding of the principles of Good Clinical Practice (GCP). The recruitment process will be done in such a way to mitigate any potential undue influence or coercion. No therapeutic promises will be made.

2. What resources will be used for recruitment?

No resources will be used for recruitment. The clinical information of potential patients will be reviewed by the local NHS staff to assess eligibility.

3. Will identification of potential participants involve access to identifiable information?

☒ Yes ☐ No

3a. If yes, describe what measures will be in place to confirm that access to this information will be lawful.

The clinical information of potential patients will be reviewed by the local NHS staff to assess eligibility. These staff are part of the direct care team.

4. Who will be approaching potential participants and who will be obtaining informed consent?

Only members of the dedicated study clinical research team at site would approach patients to discuss the study and obtain informed consent. Gaining informed consent is a delegated duty and so the team members need to be appropriately trained and on the research delegation log.

5. How, when and where will informed consent be obtained?

PANTHER will use a model of informed deferred consent, as used in a number of recent trials in the UK including REMAP-CAP (ISRCTN67000769), (Fluids in Shock (ISRCTN15244462), AIRWAYS-2 (ISRCTN08256118), PARAMEDIC 2 (SRCTN73485024), VANISH trial (ISRCTN 20769191), 65 trial (ISRCTN10580502) amongst others and has been shown to be acceptable to patients and their family members. Informed consent will be carried out at the hospital site, often at the patients bedside. A Participant Information Sheet (PIS) will be provided to the patient by an authorised staff member. The PIS will provide information about the purpose of the study, what participation means for the patient, confidentiality and data security, and the future availability of the trial results. A Consent Form will be provided indicating that: the information given, orally and in writing, has been read and understood; participation is voluntary and can be withdrawn at any time without consequence; and that consent is given for access to medical records (including routine data sources) for data collection. The Consent Form will cover consent for use of data already collected for the trial, as well as ongoing data collection and follow-up. Patients will be given time to read the PIS and have an opportunity to ask any questions they may have about participation in PANTHER. After verifying that the PIS and Consent Form are understood, the person seeking consent will invite the patient to sign the Consent Form and will then add their own name and countersign it. A copy will be given to the patient, a copy placed in the patient's medical notes and the original kept in the Investigator Site File. These processes have been approved by our lay representatives.

6. How long will potential participants (or their legal representative) be given to decide whether to participate?

ARDS should be treated quickly and delays in administering the appropriate drugs including study drugs may affect patient outcome. Therefore in most cases, the patient will be treated urgently as part of the trial before it is possible to identify and seek consent. The treating doctor will ensure that the patient meets all of the inclusion criteria and none of the exclusion criteria before enrolment. At the first available opportunity, once the clinical condition has stabilised, consent will be sought. Many patients will be unable to consent themselves and so a Personal Legal Representative will be sought and if unavailable a Professional Legal Representative will be approached. They will be given information about the study, including why it was necessary to initiate urgent treatment with the study drugs. They will given adequate time to make a fully informed decision, with the aim of obtaining consent prior to hospital discharge. If the Personal Legal Representative is not able to attend in person, e-consent using the OpenClinica system will be used. The Personal Legal Representative's identity will be verified via a video link or other means, in line with the methods used by the clinical team to update family member / NOK about the clinical management of the participant.

7. How will it be assured that potential participants (or their legal representative) have understood the information and that consent is informed?

The local research teams have extensive experience in dissemination of trial information to patients and their families, and well as determining if participants have understood the information and have capacity. Participants will be given opportunities to ask

questions, and can withdraw their consent at any time without giving a reason.

8. What arrangements are in place to obtain informed consent from potential participants (or their legal representative) who do not speak English?

The participant information sheet and consent forms will be translated in to different languages. Local translators and interpreters can be used at site as per normal local procedures.

9. How will it be ensured that participants can withdraw their consent at any point?

This is stated within the information sheet and consent form and will be reiterated by the clinical research team member obtaining consent.

10. Please provide any further information, in relation to the procedure for recruitment and informed consent for the clinical trial, which has not been provided elsewhere.

Due to rapid changes in these patients, their health could deteriorate very quickly once the eligibility criteria is assessed. Therefore there is a small possibility that the patient may die prior to consent being obtained. In this situation if appropriate a family member (Personal Legal Representative) will be contacted and informed of the patient's inclusion in the trial and consent sought. However there are circumstances where it is not appropriate to discuss the patient's participation in the trial if they have passed away. A professional legal representative will be sought in this case, however if none are available within a suitable timeframe (within 24hrs of the patient passing away) the study will retain the data in the study.

In this circumstance, we will retain the data already collected for this patient and generate a file note to explain this. In our experience with other ICU research (LeoPARDS, BLING III, REMAP-CAP) there are very few instances like this, but there is a slight possibility the patient may pass away and seeking consent after this may not be appropriate. We wish to retain the patient's data so as not to introduce bias in the study as if patients are removed from the analysis because they have passed away could unbalance the trial.

If the patient withdraws their consent after randomisation they will be provided with options. They can either withdraw completely from the trial or from certain elements. Further follow-up visits as part of the clinical trial will cease. However, the participant will be asked if data collection through data linkage of routinely collected data, including long-term follow-up can continue. The options will be captured on the consent form and on the electronic database.

11. Provide a clear indication of what the first act of recruitment will be.

Patients will be screened at adult, general, critical care units in NHS hospitals by members of the local clinical team (members of the patients' direct healthcare team).

12. Clinical Trials Involving Adults Lacking the Capacity to Consent

12a. Provide justification for recruiting incapacitated adults.

The vast majority of participants to a critical care clinical trial will lack capacity as they will be very unwell. We will seek advice and consent about a patient's participation in the collection of research specific data from a Personal Legal Representative or a Professional Legal Representative while the patient lacks capacity.

We believe that this is the only appropriate model for consent in the face of the time pressure of needing to allocate treatment early in the process of critical care referral and stabilisation. Moreover, the process of obtaining consent while active intensive treatment is ongoing and the patient is in a critical state sometimes appears coercive and adds undue stress to an already stressful situation. Due to the severity of illness and its impact on mental capacity of the target population (critically ill patients), it will not be possible to involve PANTHER trial participants early on in the consenting process. Instead, consent will be obtained prior to hospital discharge when their condition allows (e.g. they regain capacity). If the patient does not regain capacity prior to hospital discharge, the decision for use of information in the study will lie with the patients Personal Legal Representative if available. If the Personal Legal Representative does not wish to be involved in the consultation, a Professional Legal Representative will be appointed. If the patient dies, a Professional Legal Representative will be appointed, if none are available the data collected will be retained in the study. These processes have been approved by our lay representatives.

12b. Who will assess and confirm whether a potential participant has the capacity to consent?

Potential participants will be identified by the medical and nursing team on the intensive care unit. They will assess if the patient

meets the inclusion criteria and that none of the exclusion criteria are present from the patient's medical history and clinical notes. The clinical information of potential patients will be reviewed by the local NHS staff to assess eligibility. These staff are part of the direct care team

12c. Where capacity to consent will fluctuate or will be borderline, how will potential participants be involved in the decision to participate in the trial?

The process of obtaining consent while active intensive treatment is ongoing and the patient is in a critical state sometimes appears coercive and adds undue stress to an already stressful situation. Due to the severity of illness and its impact on mental capacity of the target population (critically ill patients), it will not be possible to involve PANTHER trial participants early on in the consenting process. Instead, consent will be obtained prior to hospital discharge when their condition allows (e.g. they regain capacity). If the patient does not regain capacity prior to hospital discharge, the decision for use of information in the study will lie with the patients Personal Legal Representative. If the Personal Legal representative does not wish to be involved in the consultation, a Professional Legal Representative will be appointed. If the patient dies, a Professional Legal Representative will be appointed, if none are available the data collected will be retained in the study.

12d. How will a legal representative be identified?

A Personal Legal representative will be identified via the normal clinical processes of contacting NOK when patients are hospitalised, either via medical notes or the patient themselves.

A Professional Legal Representative will be approached by the clinical research team who is involved in the patient's care, not involved in the study (not listed on the study delegation log) who can provide their independent opinion as to whether the patient is suitable and/or would object to participating in the study.

13. Clinical Trials in Emergency Situations

13a. Will the trial recruit participants in an emergency situation whereby consent from the participant cannot be sought or a legal representative cannot be consulted prior to the participant being recruited into the trial?

☒ Yes ☐ No

13b. Describe why it would not be possible to obtain consent from potential participants or a legal representative prior to recruiting into the clinical trial.

Do to the urgent nature of this critical care study, it may not be possible to obtain consent prior to inclusion in the study. If the patient has capacity we will always seek informed consent before we include them in the study. If the patient does not have capacity and meets the study criteria we will aim to start patient treatment as soon as possible, this may mean neither Personal Legal Representative nor a Professional Legal Representative is available, in this case we will seek consent soon after the study treatment has started.

We will always seek advice and consent about a patient's participation in the collection of research specific data from a Personal Legal Representative or a Professional Legal Representative while the patient lacks capacity. We have included the option of e-consent in this study to allow more options for the Personal Legal Representative to provide their consent if they are not able to visit the hospital during this time. We believe that this is the only appropriate model for consent in the face of the time pressure of needing to allocate treatment early in the process of critical care referral and stabilisation. These processes have been approved by our lay representatives.

13c. What arrangements will be in place to obtain informed consent from the participant or from a legal representative, whichever can be obtained soonest?

As a study we have tried to ensure we have a variety of options available to obtain consent in our study. If the patient does not have capacity prior to inclusion we will seek a Personal Legal Representative consent. If this person is not able to visit the hospital we can offer e-consent through the OpenClinica database. A consent form is sent via email and the personal representative can provide their electronic approval. If a Personal Legal Representative is not available for a patient we will seek Professional Legal Representative. When the patient does regain capacity we will seek informed consent from the patient in every scenario to ensure the patient is aware of their participation and their right to withdraw. If the patient regains capacity but is not able to sign a consent form due to weakness we have an option for an independent witness to sign. If a patient regains capacity but is discharged prior to providing informed consent (e.g. staff capacity) attempts to obtain informed consent from follow up appointments or verbal consent during the follow up call, and this will be documented fully in a study file note.

13d. How will it be ensured that a potential participant has not expressed any previous objection to participate in the clinical trial?

All previous objections to involvement in research / participation would be documented in the patients medical notes and these wishes would be followed. Any objection on the patient behalf by his friends / family would also be followed.

15. Impartial Witness

15a. Is the trial likely to include participants who are unable to sign the consent form and therefore an impartial witness would be required?

☒Yes ☐No

15b. Why is it expected that an impartial witness might be required?

If a participant is able to provide consent, but unable to sign / initial the consent form due to reduced arm strength etc, an impartial witness would be able to sign that they witnessed verbal consent into the PANTHER study in the appropriate section of the consent form.

15c. How will an impartial witness be identified?

Clinical team member that is not part of the research team (not on the study delegation log).

15d. How will it be known that the potential participant gives their informed consent?

There will be a section on the participant consent forms for witness consent

16. Cluster Trials

16a. Will the trial involve the recruitment and allocation of an IMP to groups of participants rather than individual participants (cluster trial)?

☐Yes ☒No

I. Payment of Compensation

1. Will payment or compensation be offered?

☐Yes ☒No

1c. If not, please explain why not

The participants in this study have been admitted to ICU and require emergency treatment, therefore there are no out of pocket expenses for participating in this study. As participating in this study requires no extra time or effort from the patients there is no compensation for time and effort.

2. Describe arrangements for how any payment or compensation will be paid/provided

N/A

3. Are there any conditions attached to the payment or compensation?

☐Yes ☒No

A. Trial Identification

A3. Full title of the trial

Please note details entered here will be inserted into Study Information A6

Precision medicine Adaptive Network platform Trial in Hypoxaemic acutE respiratory failuRe

A3-2. Name or abbreviated title of the trial where available

Please return to [Update project details](#) if you need to amend the short project title entered here.

PANTHER

A4-1. Sponsor's protocol code number:

175151

A4-2. Sponsor's protocol version:

1.0

A4-3. Sponsor's protocol date:

12 December, 2024

A5-1. ISRCTN number

—

A5-2. ClinicalTrials.gov number

—

A5-3. WHO Universal Trial Reference Number (UTRN)

—

A5-4. Other Identifiers:

Name	Identifier
No items	

B. Identification of the sponsor responsible for the request

B1-1 Name of organisation

Imperial College London

B1-2 Name of person to contact:

B1-2-1 Given Name

Ruth

B1-2-2 Middle Name

B1-2-3 Family Name

Nicholson

Address

Street Address

5th Floor, Sherfield Building, South Kensington Campus

Town/City

London

Post Code

SW7 2BB

Country

United Kingdom

Telephone Number

Country Dialing Prefix	Local Area Code	Phone Number	Extension
+44	0207	5941862	N/A

Fax Number

Country Dialing Prefix	Local Area Code	Phone Number
------------------------	-----------------	--------------

Extension

E-mail

r.nicholson@imperial.ac.uk

E. General Information on the Trial

E2. Objective of the trial

E2-1. Main objective of the trial

To increase the development of new therapies for people with critical illness by creating an international platform trial to test the success of treatments in patients with ARDS and pandemic infection.

E2-2. Secondary objectives of the trial

1. To develop a framework for identifying, developing and testing additional subgroups and therapies in the ongoing platform trial.
2. To play a leading role in international collaboration in research.
3. To provide opportunities for early career investigators to build clinical trial experience.
4. To help collaborate with commercial partners to test promising new treatments for ARDS
5. To be more sustainable through academic and commercial funding opportunities.
6. To collect samples and data on other precision medicine factors
7. To be able to quickly change focus in the event of a new pandemic related to respiratory failure, providing tools to be prepared for a pandemic if needed.

E7. Trial type and phase

E7-1. Human pharmacology (Phase I)

☐ Yes ☒ No ☐ Not Answered

E7-2. Therapeutic exploratory (Phase II)

☒ Yes ☐ No ☐ Not Answered

E7-3. Therapeutic confirmatory (Phase III)

☐ Yes ☒ No ☐ Not Answered

E7-4. Therapeutic use (Phase IV)

☐ Yes ☒ No ☐ Not Answered

E8-9. Initial estimate of the duration of the trial (years, months, days)

E8-9-1. In the MS concerned

Years

4

Months

0

Days

0

F. Population Of Trial Subjects

F1. Age Range

F1-1. Are the trial subjects under 18?

☐ Yes ☒ No ☐ Not Answered

F1-2. Adult (18-64 years)

☒ Yes ☐ No ☐ Not Answered

F1-2-1. Number of subjects for this age range:

1081

F1-3. Elderly (greater than 65 years)

☒ Yes ☐ No ☐ Not Answered

F1-3-1. Number of subjects for this age range:

1082

F2. Gender

F2-1. Female

☒ Yes ☐ No ☐ Not Answered

F2-2. Male

☒ Yes ☐ No ☐ Not Answered

F3. Group of trial subjects

F3-1. Healthy volunteers

☐ Yes ☒ No ☐ Not Answered

F3-2. Patients

☒ Yes ☐ No ☐ Not Answered

F3-3. Specific vulnerable populations

☐ Yes ☒ No ☐ Not Answered

F4. Planned number of subjects to be included

F4-1. In the member state

1563

F5. Plans for treatment or care after a subject has ended his/her participation in the trial.

If it is different from the expected normal treatment, please specify:

Study treatment will not be provided after participant has completed the study.

G. Investigator Details

G1. National coordinating investigator (for a multicentre trial) or principal investigator (for a single centre trial)

National Coordinating Investigator

G1-1. Given Name

Daniel

G1-2. Middle Name

G1-3. Family Name

McAuley

G1-4. Qualification (MD...)

MBBS, MD

G1-5. Institution Name

Imperial College London

G1-5. Institution Department Name

Surgery and Cancer

Address

Street Address

QEQM, St Mary's Hospital, Praed Street

Town/City

London

Post Code

W2 1NY

Country

United Kingdom

G1-5-5. Please indicate if site is:

NHS

Telephone Number

Country Dialing Prefix

+44

Local Area Code

28

Phone Number

90 976385

Extension

Fax Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

E-mail

d.f.mcauley@qub.ac.uk

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

Anthony

G2-2. Middle Name

G2-3. Family Name

Gordon

G2-4. Qualification (MD...)

MBBS, MD, FFICM, FMedSci

G2-5. Institution Name

St Mary's Hospital

G2-5. Institution Department Name

Surgery & Cancer

Address

Street Address

Praed Street

Town/City

London

Post Code

W2 1NY

Country

United Kingdom

G2-5-5. Please indicate if site is:

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Local Area Code

20

Phone Number

33126328

Extension

Fax Number

Country Dialing Prefix

Extension

Local Area Code

Phone Number

E-mail

anthony.gordon@imperial.ac.uk

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

David

G2-2. Middle Name

G2-3. Family Name

Antcliffe

G2-4. Qualification (MD...)

MD

G2-5. Institution Name

Charing Cross Hospital

G2-5. Institution Department Name

Address

Street Address

Town/City

Country

Post Code

United Kingdom

G2-5-5. Please indicate if site is:

NHS

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Local Area Code

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Fax Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

E-mail

d.antcliffe@imperial.ac.uk

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

Stephen

G2-2. Middle Name

G2-3. Family Name

Brett

G2-4. Qualification (MD...)

MD

G2-5. Institution Name

Hammersmith Hospital

G2-5. Institution Department Name

Address

Street Address

Town/City

Country

Post Code

United Kingdom

G2-5-5. Please indicate if site is:

NHS

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Phone Number

Extension

E-mail

stephen.brett@imperial.ac.uk

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

Dhruv

G2-2. Middle Name

G2-3. Family Name

Parekh

G2-4. Qualification (MD...)

MD

G2-5. Institution Name

Queen Elizabeth Hospital Birmingham

G2-5. Institution Department Name

Address

Street Address

Town/City

Country

Post Code

United Kingdom

G2-5-5. Please indicate if site is:

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E-mail

D.Parekh@bham.ac.uk

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

Valerie

G2-2. Middle Name

G2-3. Family Name

Page

G2-4. Qualification (MD...)

MD

G2-5. Institution Name

Watford General Hospital

G2-5. Institution Department Name

Address

Street Address

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valerie.page2@nhs.net

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

Ingeborg

G2-2. Middle Name

G2-3. Family Name

Welters

G2-4. Qualification (MD...)

MD

G2-5. Institution Name

Royal Liverpool Hospital

G2-5. Institution Department Name

Address

Street Address

Town/City

Country

Post Code

United Kingdom

G2-5-5. Please indicate if site is:

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I.Welters@liverpool.ac.uk

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

Kathryn

G2-2. Middle Name

G2-3. Family Name

Puxty

G2-4. Qualification (MD...)

MD

G2-5. Institution Name

Glasgow Royal Infirmary

G2-5. Institution Department Name

Address

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E-mail

Kathryn.Puxty@ggc.scot.nhs.uk

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

Anthony

G2-2. Middle Name

G2-3. Family Name

G2-4. Qualification (MD...)

G2-5. Institution Name

Rostron

MD

Sunderland Royal Hospital

G2-5. Institution Department Name

Address

Street Address

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Post Code

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G2-5-5. Please indicate if site is:

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Anthony.Rostron@newcastle.ac.uk

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

Elankumaran

G2-2. Middle Name

G2-3. Family Name

Paramasivam

G2-4. Qualification (MD...)

MD

G2-5. Institution Name

St James University Hospital

G2-5. Institution Department Name

Address

Street Address

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Leeds

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United Kingdom

G2-5-5. Please indicate if site is:

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E-mail

eparamasivam@nhs.net

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

Tom

G2-2. Middle Name

G2-3. Family Name

Billyard

G2-4. Qualification (MD...)

MD

G2-5. Institution Name

University Hospital Coventry

G2-5. Institution Department Name

Address

Street Address

Town/City

Coventry

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Country

United Kingdom

G2-5-5. Please indicate if site is:

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E-mail

Thomas.Billyard@uhcw.nhs.uk

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

Richard

G2-2. Middle Name

G2-3. Family Name

Innes

G2-4. Qualification (MD...)

MD

G2-5. Institution Name

Musgrove Park Hospital

G2-5. Institution Department Name

Address

Street Address

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Taunton

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Country

United Kingdom

G2-5-5. Please indicate if site is:

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E-mail

Richard.Innes@somersetft.nhs.uk

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

Elankumaran

G2-2. Middle Name

G2-3. Family Name

Paramasivam

G2-4. Qualification (MD...)

G2-5. Institution Name

Leeds General Infirmary

G2-5. Institution Department Name

Address

Street Address

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Leeds

Post Code

Country

United Kingdom

G2-5-5. Please indicate if site is:

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eparamasivam@nhs.net

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

Danny

G2-2. Middle Name

G2-3. Family Name

McAuley

G2-4. Qualification (MD...)

MBBS, MD

G2-5. Institution Name

Royal Victoria Hospital

G2-5. Institution Department Name

Address

Street Address

Town/City

Belfast

Post Code

Country

United Kingdom

G2-5-5. Please indicate if site is:

NHS

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E-mail

d.f.mcauley@qub.ac.uk

Medicines Information

A. Trial Identification

A1. National Competent Authority

UK - MHRA

A2. European Clinical Trials Database (EudraCT) number

—

A3. Full title of the trial

Please note details entered here will be inserted into Study Information A6

Precision medicine Adaptive Network platform Trial in Hypoxaemic acutE respiratory failuRe

A3-1. Title of the trial for lay people, in easily understood, i.e. non-technical, language

Precision medicine Adaptive Network platform Trial in Hypoxaemic acutE respiratory failuRe

A3-2. Name or abbreviated title of the trial where available

Please return to [Update project details](#) if you need to amend the short project title entered here.

PANTHER

A4-1. Sponsor's protocol code number:

175151

A4-2. Sponsor's protocol version:

1.0

A4-3. Sponsor's protocol date:

12 December, 2024

A5-1. ISRCTN number

—

A5-2. ClinicalTrials.gov number

—

A5-3. WHO Universal Trial Reference Number (UTRN)

—

A5-4. Other Identifiers:

Name	Identifier
No items	

A6. Is this a resubmission?

☐ Yes

☒ No

A6-1. Indicate the resubmission letter or else select 'First submission'

First Submission 

A7. Is the trial part of a Paediatric Investigation Plan?

☐ Yes ☒ No ☐ Not Answered

B. Identification of the sponsor responsible for the request

B. Sponsor Identification

B1. Sponsor

B1-1 Name of organisation

Imperial College London

B1-2 Name of person to contact:

B1-2-1 Given Name

Ruth

B1-2-2 Middle Name

B1-2-3 Family Name

Nicholson

Address

Street Address

5th Floor, Sherfield Building, South Kensington Campus

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Telephone Number

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Local Area Code

0207

Phone Number

5941862

Extension

N/A

Fax Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

E-mail

r.nicholson@imperial.ac.uk

B3. Status of the Sponsor

B3. Status of the Sponsor:

Non-Commercial

B4. Source(s) of Monetary or Material Support for the clinical trial (repeat as necessary)

B4-1. Name of organisation	B4-2. Country
National Institute for Health and Care Research	United Kingdom

B5. Contact point designated by the sponsor for further information on the trial

B5-1 Name of organisation

Imperial College London

B5-2 Functional name of contact point

Janis Best-Lane

Address

Street Address

QEQM Building, St Mary's Hospital, Praed Street

Town/City

London

Post Code

W2 1NY

Country

United Kingdom

Telephone Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

Fax Number

Country Dialing Prefix

Local Area Code

Phone Number

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E-mail

panther@imperial.ac.uk

C. Applicant Identification

C1. Request for Authorization to Competent Authority

C1-1, C1-2, C1-3 Who is responsible for the Clinical Authorization Application?

C1-4 Complete the details of the applicant below even if they are provided elsewhere on the form

C1-4-1 Name of organisation

Imperial College London

C1-4-2 Name of person to contact:

C1-4-2-1 Given Name

Ruth

C1-4-2-2 Middle Name

C1-4-2-3 Family Name

Nicholson

Address

Street Address

Level 5, Sherfield Building, South Kensington

Town/City

London

Post Code

SW7 2BB

Country

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Telephone Number

Country Dialing Prefix

Local Area Code

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Fax Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

E-mail

rgit.ctimp.team@imperial.ac.uk

C1-5 Request to receive a copy of the CTA data XML

C1-5-1 Do you want a xml file copy of the CTA form data saved on EudraCT?

☒Yes ☐No ☐Not Answered

C1-5-1-1 E-mail

E-mail

panther@imperial.ac.uk

C1-5-1-2 Secure E-mail (EudraLink account)?

☐Yes ☒No ☐Not Answered

C2. Request for Opinion of the Ethics Committee

C2-1, C2-2, C2-3, C2-4 Applicant Identification

The sponsor

C2-5 Complete the details of the applicant below even if they are provided else where on the form

C2-5-1 Organisation

Imperial College London

C2-5-2 Name of contact person

C2-5-2-1 Given Name

Keith

C2-5-2-2 Middle Name

C2-5-2-3 Family Name

Boland

Address

Street Address

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Level 5, Sherfield Building, South Kensington

London

Post Code

Country

SW7 2BB

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Phone Number

Extension

Fax Number

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Local Area Code

Phone Number

Extension

E-mail

rgit.ctimp.team@imperial.ac.uk

D. Investigational Medicinal Products

D. Investigational Medicinal Products

IMP Name:

PR1

D1/D2. IMP Identification and Status Details

D1-2/D1-3. Investigational medicinal product category:

Test

D2. Status of the IMP

D2-1. Does the IMP to be used in the trial have a marketing authorisation?

☒ Yes ☐ No ☐ Not Answered

D2-1-1-1. Trade Name:

Simvastatin

D2-1-1-1. EV Product Code

D2-1-1-2. Name of the MA holder:

Milpharm Limited

D2-1-1-3. MA Number (if MA granted by a Member State)

PL 16363/0600

D2-1-1-4. Is the IMP modified in relation to its MA?

☐ Yes ☒ No ☐ Not Answered

D2-1-2. Which country granted the MA?

United Kingdom

D2-1-2-1. Is this the Member state concerned with this application?

☒Yes ☐No ☐Not Answered

D2-2. IMP to be used in the CT has a marketing authorisation

D2-2. For situations where the IMP to be used in the CT has a Marketing Authorisation in the Member State concerned but the protocol allows that any brand of the IMP with a Marketing Authorisation in that Member State be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start

D2-2-1. In the protocol, is treatment defined only by active substance?

☐Yes ☐No ☒Not Answered

D2-2-2. In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?

☐Yes ☐No ☒Not Answered

D2-2-3. The products to be administered as IMPs are defined as belonging to an ATC group

☐Yes ☐No ☒Not Answered

D2-2-4. Other:

☒Yes ☐No ☐Not Answered

D2-2-4-1. Please specify:

The protocol allows different combinations of marketed products used in local clinical practice. As the IMP is provided from hospital stock and so no particular product is named. For the same reason different drugs from the same class (in terms of pharmacological action) may be used. We are comparing this product with standard care.

D2-3. IMPD submitted / D2-4. IMP previously authorised / D2-5. IMP designated as an Orphan drug / D2-6. Subject of Scientific Advice

D2-3-1, D2-3-2 and D2-3-3: only one may be answered 'Yes' and the others must be answered 'No'

D2-3-1. Full IMPD

☐Yes ☒No ☐Not Answered

D2-3-2. Simplified IMPD

☐Yes ☒No ☐Not Answered

D2-3-3. Summary of product characteristics (SmPC) only

☒Yes ☐No ☐Not Answered

D2-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

☐Yes ☒No ☐Not Answered

D2-5. Has the IMP been designated in this indication as an orphan drug in the Community?

☐Yes ☒No ☐Not Answered

D2-6. Has the IMP been the subject of scientific advice related to this clinical trial?

☐Yes ☒No ☐Not Answered

D3. Description of IMP

D3-1. Product name where applicable

Simvastatin

D3-2. Product code where applicable

D3-3. ATC codes, if officially registered

C10AA01

D3-4. Pharmaceutical Form

Tablet 

D3-4-1. Is this a specific paediatric formulation?

☐Yes ☒No ☐Not Answered

D3-5. Maximum duration of treatment of a subject according to the protocol

Maximum 28 days. simvastatin will be administered once daily until study day 28 or ICU discharge, whichever comes first.

Note: Content will be enabled for D3-6-1 and D3-6-2 only E7-1-1 is selected

D3-6. Dose allowed

D3-6-1. For first trial only

D3-6-1. First dose for first-in-human clinical trial

D3-6-1. Specify per day or total

☐Per day ☐Total ☐Not Answered

D3-6-1. Specify total dose number

D3-6-1. Specify total dose units

Select.. 

D3-6-1. Route of administration (relevant to the first dose)

Select.. 

D3-6-2. For all trials

D3-6-2. Maximum dose allowed

D3-6-2. Specify per day or total

☒Per day ☐Total ☐Not Answered

D3-6-2. Specify total dose number

80

D3-6-2. Specify total dose units

mg milligram(s) 

D3-6-2. Route of administration (relevant to the maximum dose)

Enteral use (Noncurrent) 

D3-7. Routes of administration for this IMP

Selected Routes of administration
Enteral use (Noncurrent)
Oral use

D3-8. Active substances

D3-8. Name of Active Substance (INN or proposed INN if available)

Simvastatin

D3-9-1. CAS Number:

79902-63-9

D3-9-2. Current Sponsor Code:

N/A

D3-9-3. Other Descriptive Name:

N/A

D3-9-4. EudraVigilance Substance Code (if known):

—

D3-9-5. Full Molecular Formula

C₂₅H₃₈O₅

D3-9-6. Chemical/Biological Description of the Active Substance

Simvastatin is a 2,2-dimethylbutanoic acid ester of a hexahydro-1-naphthalenyl group. It is a member of the hexahydronaphthalene class of compounds and is functionally related to lovastatin. Simvastatin is a prodrug of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor. It is a potent inhibitor of this enzyme, which is the rate-limiting enzyme in cholesterol biosynthesis. Simvastatin also increases the breakdown of LDL cholesterol by inducing hepatic LDL receptors.

D3-10. *Strength*

D3-10-1. Concentration Unit:

mg milligram(s)

D3-10-2. Concentration Type:

Equal

D3-10-3. Concentration Number (only use both fields for range):

40

D3-10-3. Concentration Number (only use both fields for range):

—

D3-11. Type of IMP

Does the IMP contain an active substance:

D3-11-1. Of chemical origin?

☒Yes ☐No ☐Not Answered

D3-11-2. Of biological/biotechnological origin? (other than Advanced Therapy IMP (ATIMP))

☐Yes ☒No ☐Not Answered

Is this IMP a:

D3-11-3. Advanced Therapy IMP (ATIMP)?

☐Yes ☒No ☐Not Answered

D3-11-4. Combination product that includes a device, but does not involve an Advanced Therapy

☐Yes ☒No ☐Not Answered

D3-11-5. Radiopharmaceutical medicinal product?

☐Yes ☒No ☐Not Answered

D3-11-6. Immunological medical product (eg vaccine, allergen, immune serum)?

☐Yes ☒No ☐Not Answered

D3-11-7. Plasma derived medicinal product?

☐Yes ☒No ☐Not Answered

D3-11-8. Extractive medicinal product?

☐Yes ☒No ☐Not Answered

D3-11-9. Recombinant medicinal product?

☐Yes ☒No ☐Not Answered

D3-11-10. Medicinal product containing genetically modified organisms?

☐Yes ☒No ☐Not Answered

D3-11-11. Herbal medicinal product?

☐Yes ☒No ☐Not Answered

D3-11-12. Homeopathic medicinal product?

☐Yes ☒No ☐Not Answered

D3-11-13. Another type of medicinal product?

☐Yes ☒No ☐Not Answered

D3-12. Specify the mode of action for the active substance in this medicinal product

Simvastatin is indicated for the treatment of hyperlipidemia to reduce elevated total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), and triglycerides (TG), and to increase high-density lipoprotein cholesterol.

D3-13. Is it an IMP to be used in a first-in-human clinical trial

☐Yes ☒No ☐Not Answered

IMP Name:

PR2

D1/D2. IMP Identification and Status Details

D1-2/D1-3. Investigational medicinal product category:

Test

D2. Status of the IMP

D2-1. Does the IMP to be used in the trial have a marketing authorisation?

☒Yes ☐No ☐Not Answered

D2-1-1-1. Trade Name:

Baricitinib

D2-1-1-1. EV Product Code

D2-1-1-2. Name of the MA holder:

Eli Lilly

D2-1-1-3. MA Number (if MA granted by a Member State)

PLGB 14895/0256

D2-1-1-4. Is the IMP modified in relation to its MA?

☐Yes ☒No ☐Not Answered

D2-1-2. Which country granted the MA?

United Kingdom

D2-1-2-1. Is this the Member state concerned with this application?

☒Yes ☐No ☐Not Answered

D2-2. IMP to be used in the CT has a marketing authorisation

D2-2. For situations where the IMP to be used in the CT has a Marketing Authorisation in the Member State concerned but the protocol allows that any brand of the IMP with a Marketing Authorisation in that Member State be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start

D2-2-1. In the protocol, is treatment defined only by active substance?

☐Yes ☐No ☒Not Answered

D2-2-2. In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?

☐Yes ☐No ☒Not Answered

D2-2-3. The products to be administered as IMPs are defined as belonging to an ATC group

☐Yes ☐No ☒Not Answered

D2-2-4. Other:

☒Yes ☐No ☐Not Answered

D2-2-4-1. Please specify:

The protocol allows different combinations of marketed products used in local clinical practice. As the IMP is provided from hospital stock and so no particular product is named. For the same reason different drugs from the same class (in terms of pharmacological action) may be used. We are comparing this product with standard care.

D2-3. IMPD submitted / D2-4. IMP previously authorised / D2-5. IMP designated as an Orphan drug / D2-6. Subject of Scientific Advice

D2-3-1, D2-3-2 and D2-3-3: only one may be answered 'Yes' and the others must be answered 'No'

D2-3-1. Full IMPD

☐Yes ☒No ☐Not Answered

D2-3-2. Simplified IMPD

☐Yes ☒No ☐Not Answered

D2-3-3. Summary of product characteristics (SmPC) only

☒Yes ☐No ☐Not Answered

D2-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

☐Yes ☒No ☐Not Answered

D2-5. Has the IMP been designated in this indication as an orphan drug in the Community?

☐Yes ☒No ☐Not Answered

D2-6. Has the IMP been the subject of scientific advice related to this clinical trial?

☐Yes ☒No ☐Not Answered

D3. Description of IMP

D3-1. Product name where applicable

Baricitnib

D3-2. Product code where applicable

D3-3. ATC codes, if officially registered

L04AF02

D3-4. Pharmaceutical Form

Coated tablet 

D3-4-1. Is this a specific paediatric formulation?

☐Yes ☒No ☐Not Answered

D3-5. Maximum duration of treatment of a subject according to the protocol

Baricitinib will be administered for 10 days or until hospital discharge, whichever occurs first.

Note: Content will be enabled for D3-6-1 and D3-6-2 only E7-1-1 is selected

D3-6. Dose allowed

D3-6-1. For first trial only

D3-6-1. First dose for first-in-human clinical trial

D3-6-1. Specify per day or total

☐Per day ☐Total ☐Not Answered

D3-6-1. Specify total dose number

D3-6-1. Specify total dose units

Select.. 

D3-6-1. Route of administration (relevant to the first dose)

Select.. 

D3-6-2. For all trials

D3-6-2. Maximum dose allowed

D3-6-2. Specify per day or total

☒Per day ☐Total ☐Not Answered

D3-6-2. Specify total dose number

4

D3-6-2. Specify total dose units

mg milligram(s) 

D3-6-2. Route of administration (relevant to the maximum dose)

Enteral use (Noncurrent) 

D3-7. Routes of administration for this IMP

Selected Routes of administration
Enteral use (Noncurrent)
Oral use

D3-8. Active substances

D3-8. Name of Active Substance (INN or proposed INN if available)

Baricitinib

D3-9-1. CAS Number:

1187594-09-7

D3-9-2. Current Sponsor Code:

N/A

D3-9-3. Other Descriptive Name:

N/A

D3-9-4. EudraVigilance Substance Code (if known):

—

D3-9-5. Full Molecular Formula

C₁₆H₁₇N₇O₂S

D3-9-6. Chemical/Biological Description of the Active Substance

Baricitinib is a (JAK) inhibitor, specifically JAK1 and JAK2. Baricitinib consists of a pyrrolo[3,4-d]pyrimidine ring system, with an imidazole group attached to a phenylurea.

D3-10. *Strength*

D3-10-1. Concentration Unit:

mg milligram(s)

D3-10-2. Concentration Type:

Equal

D3-10-3. Concentration Number (only use both fields for range):

1

D3-10-3. Concentration Number (only use both fields for range):

4

D3-11. Type of IMP

Does the IMP contain an active substance:

D3-11-1. Of chemical origin?

☒ Yes ☐ No ☐ Not Answered

D3-11-2. Of biological/biotechnological origin? (other than Advanced Therapy IMP (ATIMP))

☐ Yes ☒ No ☐ Not Answered

Is this IMP a:

D3-11-3. Advanced Therapy IMP (ATIMP)?

☐ Yes ☒ No ☐ Not Answered

D3-11-4. Combination product that includes a device, but does not involve an Advanced Therapy

☐ Yes ☒ No ☐ Not Answered

D3-11-5. Radiopharmaceutical medicinal product?

☐Yes ☒No ☐Not Answered

D3-11-6. Immunological medical product (eg vaccine, allergen, immune serum)?

☐Yes ☒No ☐Not Answered

D3-11-7. Plasma derived medicinal product?

☐Yes ☒No ☐Not Answered

D3-11-8. Extractive medicinal product?

☐Yes ☒No ☐Not Answered

D3-11-9. Recombinant medicinal product?

☐Yes ☒No ☐Not Answered

D3-11-10. Medicinal product containing genetically modified organisms?

☐Yes ☒No ☐Not Answered

D3-11-11. Herbal medicinal product?

☐Yes ☒No ☐Not Answered

D3-11-12. Homeopathic medicinal product?

☐Yes ☒No ☐Not Answered

D3-11-13. Another type of medicinal product?

☐Yes ☒No ☐Not Answered

D3-12. Specify the mode of action for the active substance in this medicinal product

Baricitinib inhibits the activity of JAK proteins and modulates the signalling pathway of various interleukins, interferons, and growth factors. It was also shown to decrease the proliferation of JAK1/JAK2 expression in mutated cells and induce cell apoptosis.

D3-13. Is it an IMP to be used in a first-in-human clinical trial

☐Yes ☒No ☐Not Answered

D8. Placebo Information

D9. Site(s) where the qualified person certifies batch release

D9-1. IMPs and placebos for which no responsible site needs to be identified

If all the conditions below are met, then tick this box and select below the IMPs and placebos to which this applies ☒

This section is used to identify IMPs and placebos which:

- has a MA in the EU and
- is sourced from the EU market and
- is used in the trial without modification (eg. Not over-encapsulated) and

- the packaging and labelling is carried out for local use only as per article 9.2 of the Directive 2005/28/EC (GCP Directive)

Finished IMP

Description	Associate
PR1-Tablet	<input checked="" type="checkbox"/>
PR2-Coated tablet	<input checked="" type="checkbox"/>

Placebo

Pharmaceutical Form	Route of Administration	Associate
No items		

D9-2. Add Responsible Site

D9-2. Who is responsible in the Community for the certification of the finished IMPs?

D9-2-1/D9-2-2. As a manufacturer, importer or both?

D9-2-3. Site Organisation Name

Aurobindo Pharma - Milpharm Ltd

D9-2-4. Address

Street Address

Odyssey Business Park, Ares Block, West End Road, South Ruislip

Town/City

London

Post Code

HA4 6QD

Country

United Kingdom

D9-2-5. Manufacturer authorisation number

PL 16363/0599

D9-2-5-1. If no authorisation, give the reasons

—

D9-2. Site where the qualified person certifies batch release

Finished IMP

Description	Associate
PR1-Tablet	<input checked="" type="checkbox"/>
PR2-Coated tablet	<input type="checkbox"/>

Placebo

Pharmaceutical Form	Route of Administration	Associate
No items		

D9-2. Who is responsible in the Community for the certification of the finished IMPs?

D9-2-1/D9-2-2. As a manufacturer, importer or both?

Both

D9-2-3. Site Organisation Name

Eli Lilly Company Limited

D9-2-4. Address

Street Address

Lilly House, Basing View

Town/City

Basingstoke

Post Code

RG21 4FA

Country

United Kingdom

D9-2-5. Manufacturer authorisation number

PLGB 14895/0256

D9-2-5-1. If no authorisation, give the reasons

—

D9-2. Site where the qualified person certifies batch release

Finished IMP

Description	Associate
PR1-Tablet	<input type="checkbox"/>
PR2-Coated tablet	<input checked="" type="checkbox"/>

Placebo

Pharmaceutical Form	Route of Administration	Associate
No items		

E. General Information on the Trial

E. Design of the Trial

Medical condition or disease under investigation

E1-1. Specify the medical condition(s) to be investigated:

Critically illnesses including acute respiratory disease syndrome and pandemic infection.

E1-1-1. Medical condition in easily understood language

Critically illnesses including acute respiratory disease syndrome and pandemic infection.

E1-1-2. Identify The Therapeutic Area

Diseases [C] - Respiratory Tract Diseases [C08]

E1-2. MedDRA information

MedDRA Search

Version	Term	Level	Classification Code	SOC	
22.1	Critical illness	PT	10077264	General disorders and administration site conditions	
22.1	Critical illness	LLT	10077264	General disorders and administration site conditions	
22.1	Respiratory, thoracic and mediastinal disorders	SOC	10038738	Respiratory, thoracic and mediastinal disorders	
22.1	Respiratory failure	PT	10038695	Respiratory, thoracic and mediastinal disorders	

E1-3. Is any of the conditions being studied a rare disease?

☐Yes ☒No ☐Not Answered

E2. Objective of the trial

E2-1. Main objective of the trial

To increase the development of new therapies for people with critical illness by creating an international platform trial to test the success of treatments in patients with ARDS and pandemic infection.

E2-2. Secondary objectives of the trial

1. To develop a framework for identifying, developing and testing additional subgroups and therapies in the ongoing platform trial.
2. To play a leading role in international collaboration in research.
3. To provide opportunities for early career investigators to build clinical trial experience.
4. To help collaborate with commercial partners to test promising new treatments for ARDS
5. To be more sustainable through academic and commercial funding opportunities.
6. To collect samples and data on other precision medicine factors
7. To be able to quickly change focus in the event of a new pandemic related to respiratory failure, providing tools to be prepared for a pandemic if needed.

E2-3. Is there a sub-study?

☐Yes ☒No ☐Not Answered

E3. Please list the principal inclusion criteria (list the most important, max 5000 characters)

1) Critically ill patients in hospital and at least 1 of the following:-

a) ARDS

b) A pandemic associated syndrome*

*this will be triggered if a 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 $\geq 30\text{L/min}$ 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,
- $\text{PaO}_2/\text{FiO}_2$ ratio $< 40\text{ kPa}$ from arterial blood gases, or $\text{SpO}_2/\text{FiO}_2 < 315$ from pulse oximetry where $\text{SpO}_2 < 97$.

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

E4. Please list the principal exclusion criteria (list the most important, max 5000 characters)

- (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
- (e) Aged <18 years

E5-1. Primary end point(s) (max 5000 characters)

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.

E5-1-1. Timepoint(s) of evaluation of this end point (max 800 characters)

28 days

E5-2. Secondary end point(s) (max 5000 characters)

- (1) Progression to invasive mechanical ventilation, extracorporeal membrane oxygenation or death among those not receiving that support at baseline
- (2) 28-day vasopressor-free days
- (3) 28-day respiratory support-free days
- (4) Receiving new renal replacement therapy
- (5) ICU length of stay
- (6) Hospital length of stay
- (7) All-cause mortality at 28 and 90 days
- (8) Safety outcomes:-
 - Elevated Creatine Kinase more than 10 times the upper limit of normal
 - Alanine Transaminase or Aspartate Transaminase or both more than 8 times the upper limit of normal
 - Serious infection defined as positive blood cultures requiring treatment and positive pulmonary aspergillosis requiring treatment
 - Venous thromboembolism
 - Stroke
 - Myocardial infarction
 - Ischaemic bowel
 - Gastrointestinal perforation
 - Clinically important gastrointestinal (GI) bleeding confirmed on upper endoscopy
- (9) Serious adverse events
- (10) Physical function (SPPB) at hospital discharge (up to 1 week prior to discharge)
- (11) Cognitive impairment (MoCA) at hospital discharge (up to 1 week prior to discharge)

We are also collecting the following tertiary outcome measures:-

- 1) 14-day delirium and coma free days*
- 2) Incidence of ICU acquired weakness (MMST and hand grip strength dynamometry and maximal inspiratory) at day 7 and ICU discharge*
- 3) Health-related quality of life, (EQ-5D-5L), Hospital Anxiety and Depression Scale (HADS), Social and Wellbeing (SF-36), Impact of Events Scale (6 item), care and wellbeing needs and cognitive impairment (MoCA) at 90 days and 180 days*

* not all sites are expected to collect these endpoints

E5-2-1. Timepoint(s) of evaluation of this end point (max 800 characters)

90 days from randomisation is the final endpoint

E6. Scope of the trial

E6-1. Diagnosis

☐Yes ☒No ☐Not Answered

E6-2. Prophylaxis

☐Yes ☒No ☐Not Answered

E6-3. Therapy

☒Yes ☐No ☐Not Answered

E6-4. Safety

☐Yes ☒No ☐Not Answered

E6-5. Efficacy

☒Yes ☐No ☐Not Answered

E6-6. Pharmacokinetic

☐Yes ☒No ☐Not Answered

E6-7. Pharmacodynamic

☐Yes ☒No ☐Not Answered

E6-8. Bioequivalence

☐Yes ☒No ☐Not Answered

E6-9. Dose Response

☐Yes ☒No ☐Not Answered

E6-10. Pharmacogenetic

☐Yes ☒No ☐Not Answered

E6-11. Pharmacogenomic

☐Yes ☒No ☐Not Answered

E6-12. Pharmacoeconomic

☐Yes ☒No ☐Not Answered

E6-13. Others

☐Yes ☒No ☐Not Answered

E7. Trial type and phase

E7-1. Human pharmacology (Phase I)

☐Yes ☒No ☐Not Answered

E7-2. Therapeutic exploratory (Phase II)

☒Yes ☐No ☐Not Answered

E7-3. Therapeutic confirmatory (Phase III)

☐Yes ☒No ☐Not Answered

E7-4. Therapeutic use (Phase IV)

☐Yes ☒No ☐Not Answered

E8. Design of the Trial

E8-1. Controlled?

☒Yes ☐No ☐Not Answered

Specify:

E8-1-1. Randomised

☒Yes ☐No ☐Not Answered

E8-1-2. Open

☒Yes ☐No ☐Not Answered

E8-1-3. Single blind

☐Yes ☒No ☐Not Answered

E8-1-4. Double blind

☐Yes ☒No ☐Not Answered

E8-1-5. Parallel group

☒Yes ☐No ☐Not Answered

E8-1-6. Cross over

☐Yes ☒No ☐Not Answered

E8-1-7. Other

☒Yes ☐No ☐Not Answered

E8-1-7-1. Specify the design of the trial

Adaptive Platform Trial

E8-2. If controlled, specify the comparator:

E8-2-1. Other medicinal product(s)

☒Yes ☐No ☐Not Answered

E8-2-2. Placebo

☐Yes ☒No ☐Not Answered

E8-2-3. Other

☐Yes ☒No ☐Not Answered

E8-2-4. Number of treatment arms in the trial

3

E8-3. Single site in the Member State concerned (see also section G)

☐Yes ☒No ☐Not Answered

E8-4. Multiple sites in the Member State concerned (see also section G)

☒Yes ☐No ☐Not Answered

E8-4-1. Number of sites anticipated in Member State concerned

E8-5. Multiple Member States

☐ Yes ☒ No ☐ Not Answered

E8-6. Trial involving sites outside the EEA

E8-6-1. Trial being conducted both within and outside the EEA

☐ Yes ☒ No ☐ Not Answered

E8-6-2. Trial conducted completely outside of the EEA

☐ Yes ☒ No ☐ Not Answered

E8-7. Trial having an independent data monitoring committee?

☒ Yes ☐ No ☐ Not Answered

E8-8. Definition of the end of trial and justification in the case where it is not the last visit of the last subject undergoing the trial.

If it is the last visit of the last subject, please enter "LVLS". If it is not LVLS provide the definition.

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

1. There is insufficient funding to support further recruitment to the platform as a whole and no reasonable prospect of additional support being obtained.
2. 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.

E8-9. Initial estimate of the duration of the trial (years, months, days)

E8-9-1. In the MS concerned

Years	Months	Days
4	0	0

E8-10. Proposed date of start of recruitment

E8-10-1. In the Member State concerned

01 June, 2025

E8-10-2. In any country

01 June, 2025

F. Population Of Trial Subjects

F1. Age Range

F1-1. Are the trial subjects under 18?

☐Yes ☒No ☐Not Answered

F1-2. Adult (18-64 years)

☒Yes ☐No ☐Not Answered

F1-2-1. Number of subjects for this age range:

1081

F1-3. Elderly (greater than 65 years)

☒Yes ☐No ☐Not Answered

F1-3-1. Number of subjects for this age range:

1082

F2. Gender

F2-1. Female

☒Yes ☐No ☐Not Answered

F2-2. Male

☒Yes ☐No ☐Not Answered

F3. Group of trial subjects

F3-1. Healthy volunteers

☐Yes ☒No ☐Not Answered

F3-2. Patients

☒Yes ☐No ☐Not Answered

F3-3. Specific vulnerable populations

☐Yes ☒No ☐Not Answered

F4. Planned number of subjects to be included

F4-1. In the member state

F5. Plans for treatment or care after a subject has ended his/her participation in the trial.

If it is different from the expected normal treatment, please specify:

Study treatment will not be provided after participant has completed the study.

G. Investigator Details

G1. National coordinating investigator (for a multicentre trial) or principal investigator (for a single centre trial)

National Coordinating Investigator

G1-1. Given Name

Daniel

G1-2. Middle Name

G1-3. Family Name

McAuley

G1-4. Qualification (MD...)

MBBS, MD

G1-5. Institution Name

Imperial College London

G1-5. Institution Department Name

Surgery and Cancer

Address

Street Address

QEQM, St Mary's Hospital, Praed Street

Town/City

London

Post Code

W2 1NY

Country

United Kingdom

G1-5-5. Please indicate if site is:

NHS

Telephone Number

Country Dialing Prefix

+44

Local Area Code

28

Phone Number

90 976385

Extension

Fax Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

E-mail

d.f.mcauley@qub.ac.uk

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

Anthony

G2-2. Middle Name

G2-3. Family Name

Gordon

G2-4. Qualification (MD...)

MBBS, MD, FFICM, FMedSci

G2-5. Institution Name

St Mary's Hospital

G2-5. Institution Department Name

Surgery & Cancer

Address

Street Address

Praed Street

Town/City

London

Post Code

W2 1NY

Country

United Kingdom

G2-5-5. Please indicate if site is:

NHS

Telephone Number

Country Dialing Prefix

+44

Local Area Code

20

Phone Number

33126328

Extension

Fax Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

E-mail

anthony.gordon@imperial.ac.uk

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

David

G2-2. Middle Name

G2-3. Family Name

Antcliffe

G2-4. Qualification (MD...)

MD

G2-5. Institution Name

Charing Cross Hospital

G2-5. Institution Department Name

Address

Street Address

Town/City

Country

Post Code

United Kingdom

G2-5-5. Please indicate if site is:

NHS

Telephone Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

Fax Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

E-mail

d.antcliffe@imperial.ac.uk

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

Stephen

G2-2. Middle Name

G2-3. Family Name

Brett

G2-4. Qualification (MD...)

MD

G2-5. Institution Name

Hammersmith Hospital

G2-5. Institution Department Name

Address

Street Address

Town/City

Country

Post Code

United Kingdom

G2-5-5. Please indicate if site is:

NHS

Telephone Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

Fax Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

E-mail

stephen.brett@imperial.ac.uk

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

Dhruv

G2-2. Middle Name

G2-3. Family Name

G2-4. Qualification (MD...)

G2-5. Institution Name

Parekh

MD

Queen Elizabeth Hospital Birmingham

G2-5. Institution Department Name

Address

Street Address

Town/City

Country

Post Code

United Kingdom

G2-5-5. Please indicate if site is:

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Telephone Number

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Local Area Code

Phone Number

Extension

Fax Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

E-mail

D.Parekh@bham.ac.uk

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

Valerie

G2-2. Middle Name

G2-3. Family Name

Page

G2-4. Qualification (MD...)

MD

G2-5. Institution Name

Watford General Hospital

G2-5. Institution Department Name

Address

Street Address

Town/City

Country

Post Code

United Kingdom

G2-5-5. Please indicate if site is:

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Extension

Fax Number

Country Dialing Prefix Local Area Code Phone Number
Extension

E-mail

valerie.page2@nhs.net

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

Ingeborg

G2-2. Middle Name

G2-3. Family Name

Welters

G2-4. Qualification (MD...)

MD

G2-5. Institution Name

Royal Liverpool Hospital

G2-5. Institution Department Name

Address

Street Address

Town/City

Country

Post Code

United Kingdom

G2-5-5. Please indicate if site is:

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Telephone Number

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Extension

Fax Number

Country Dialing Prefix Local Area Code Phone Number
Extension

E-mail

I.Welters@liverpool.ac.uk

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

Kathryn

G2-2. Middle Name

G2-3. Family Name

Puxty

G2-4. Qualification (MD...)

MD

G2-5. Institution Name

Glasgow Royal Infirmary

G2-5. Institution Department Name

Address

Street Address

Town/City

Country

Post Code

United Kingdom

G2-5-5. Please indicate if site is:

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Fax Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

E-mail

Kathryn.Puxty@ggc.scot.nhs.uk

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

Anthony

G2-2. Middle Name

G2-3. Family Name

Rostron

G2-4. Qualification (MD...)

MD

G2-5. Institution Name

Sunderland Royal Hospital

G2-5. Institution Department Name

Address

Street Address

Town/City

Country

Post Code

United Kingdom

G2-5-5. Please indicate if site is:

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Phone Number

Extension

Fax Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

E-mail

Anthony.Rostron@newcastle.ac.uk

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

Elankumaran

G2-2. Middle Name

G2-3. Family Name

Paramasivam

G2-4. Qualification (MD...)

MD

G2-5. Institution Name

St James University Hospital

G2-5. Institution Department Name

Address

Street Address

Town/City

Leeds

Post Code

Country

United Kingdom

G2-5-5. Please indicate if site is:

NHS

Telephone Number

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Phone Number

Extension

Fax Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

E-mail

eparamasivam@nhs.net

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

Tom

G2-2. Middle Name

G2-3. Family Name

Billyard

G2-4. Qualification (MD...)

MD

G2-5. Institution Name

University Hospital Coventry

G2-5. Institution Department Name

Address

Street Address

Town/City

Coventry

Post Code

Country

United Kingdom

G2-5-5. Please indicate if site is:

NHS

Telephone Number

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Local Area Code

Phone Number

Extension

Fax Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

E-mail

Thomas.Billyard@uhcw.nhs.uk

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

Richard

G2-2. Middle Name

G2-3. Family Name

Innes

G2-4. Qualification (MD...)

MD

G2-5. Institution Name

Musgrove Park Hospital

G2-5. Institution Department Name

Address

Street Address

Town/City

Taunton

Post Code

Country

United Kingdom

G2-5-5. Please indicate if site is:

NHS

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Phone Number

Extension

Fax Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

E-mail

Richard.Innes@somersetft.nhs.uk

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

Elankumaran

G2-2. Middle Name

G2-3. Family Name

Paramasivam

G2-4. Qualification (MD...)

G2-5. Institution Name

Leeds General Infirmary

G2-5. Institution Department Name

Address

Street Address

Town/City

Leeds

Post Code

Country

United Kingdom

G2-5-5. Please indicate if site is:

NHS

Telephone Number

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Local Area Code

Phone Number

Extension

Fax Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

E-mail

eparamasivam@nhs.net

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

Danny

G2-2. Middle Name

G2-3. Family Name

McAuley

G2-4. Qualification (MD...)

MBBS, MD

G2-5. Institution Name

Royal Victoria Hospital

G2-5. Institution Department Name

Address

Street Address

Town/City

Belfast

Post Code

Country

United Kingdom

G2-5-5. Please indicate if site is:

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Fax Number

Country Dialing Prefix

Local Area Code

Phone Number

Extension

E-mail

d.f.mcauley@qub.ac.uk

G3. Central technical facilities

G4. Trial Networks

G5. Sponsor's Subcontractor Facilities

H. Ethics Committee/National Competent Authority

H. National Competent Authority

H2-1. National Competent Authority name

UK - MHRA

H2.2. Address

Street Address

Town/City

Country

Post Code

—

H2-3. Date of submission

—

H3. Authorisation/Opinion

H3-1/H3-2/H3-3. What is the status of the National Competent Authority's authorisation

Select.. ▾

H. Ethics Committee

H2-1. Ethics Committee name

Not yet known

H2.2. Address

Street Address

Town/City

Country

Post Code

—

H2-3. Date of submission

—

H3. Authorisation/Opinion

H3-1/H3-2/H3-3. What is the status of the Ethics Committee's opinion?

Select.. ▾

