UK Region Specific Appendix

PANTHER:-

Precision medicine Adaptive Network platform Trial in Hypoxaemic acutE respiratory failuRe

UK Region Specific Appendix Version V1.1 dated 05 AUG 2025

This protocol has regard for the HRA guidance

This UK Region Specific Appendix applies to the following:-

Country	United Kingdom

**Note this appendix covers procedures in the trial specific to the UK.*

ABBREVIATIONS

ARDS	Acute Respiratory Distress Syndrome
CCC	Confirmation of Capacity & Capability
CI	Chief Investigator
CRF	Case Report Form
DSUR	Development Safety Update Report
EC	Ethics Committee
eCRF	Electronic Case Report Form
eISF	Electronic Investigator Site File
eTMF	Electronic Trial Master File
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practitioner
HRA	Health Research Authority
ICTU	Imperial Clinical Trials Unit
ICU	Intensive Care Unit
ICNARC	Intensive care national audit & research centre
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITMG	International Trial Management Group
ITSC	International Trial Steering Committee
MHRA	Medicines and Healthcare products Regulatory Agency
NIHR	National Institute of Health & Care Research
NHS	National Health Service
NOK	Next of Kin
PerLR	Personal Legal Representative
PI	Principal Investigator
ProLR	Professional Legal Representative

REC	Research Ethics Committee
RCC	Regional Coordinating Centre
RSA	Region Specific Appendix
RSI	Reference Safety Information
SAE	Serious Adverse Effect
SmPC	Summary of Product Characteristics
SUSAR	Serious Unexpected Serious Adverse Reaction
TMF	Trial Master File
USM	Urgent Safety Measure

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1 APPENDIX STRUCTURE

The structure of this protocol differs to that of a conventional trial due to the trial's adaptive nature. These adaptations are specified using a modular protocol structure. For further details on the structure of protocol please see section 1 of the master protocol.

The master protocol contains information about the general conduct of the platform irrespective of the regional location in which the study is conducted and the interventions being studied.

The master protocol omits information specific to regions as the locations the trial is being conducted in are expected to change over time. Information specific to a region is contained in the region-specific appendices (RSA). Each region should submit only their region-specific appendix to the relevant ethics committee (EC).

2 UK STUDY ADMINISTRATION STRUCTURE

2.1 COORDINATING CENTRE AND DATA MANAGEMENT

The sponsor for this study is Imperial College London. Imperial College London will maintain overall responsibility for the trial. They have delegated responsibility of the coordinating and data centres in the UK to the Imperial Clinical Trials Unit (ICTU). This document details the responsibilities of ICTU.

2.2 UK REGIONAL COORDINATING CENTRE

The UK region co-ordinating centre (RCC) will be responsible for the following aspects of study management in the UK:

- Liaison with the ITSC and other RCCs in relation to data management, Case-Report Forms (CRFs), and site management
- Management of study budget and liaison with funding bodies
- Development, maintenance, and administration of the study database
- Recruitment and selection of sites
- Data management
- Protocol training of site investigators and research coordinators
- Preparation and arrangement of investigator payments
- Management of regulatory affairs
- Management of study set up including assistance with Institutional Review Board (IRB) & Regulatory authority applications (HRA, REC & MHRA)
- Management of study set up including assistance with site approvals (confirmation of capacity & capability (CCC))
- Initiation, monitoring and close-out visits
- Organization of investigator meetings
- Submission of the Development Safety Update Report (DSUR) to the UK regulatory authorities.
- Submission of SUSARs to the regulatory authorities
- Coordination of data entry and feedback of data queries
- Study communications

- Liaison with ITMG to develop study documents and materials that are standardized as much as possible.
- Management of publications lists for the region

2.3 CONTACT DETAILS

UK Chief Investigator
Prof Danny McAuley
Room 02.057, Wellcome-Wolfson Institute for Experimental Medicine
97 Lisburn Road, Belfast, BT9 7AE
Tel: 02890 976385
Email: d.f.mcauley@qub.ac.uk

2.4 COORDINATING CENTRE

Address:
ICTU
Imperial College London
Stadium House
68 Wood Lane
London
W12 7RH
Tel: General tel 0207 5945906
Email: panther@imperial.ac.uk

Name of contact person
Mrs Mary Cross
Email: panther@imperial.ac.uk

2.5 TRIAL MANAGEMENT

Ms Janis Best-Lane
Ms Elizabeth Fagbodun
Imperial College London
QEQM, St Mary's Hospital
Praed Street
London
W2 1NY

2.6 LABORATORIES

Prof Cecilia O'Kane
Wellcome-Wolfson Institute for Experimental Medicine
97 Lisburn Road, Belfast, BT9 7AE
Tel: 02890 976384
Email: c.okane@qub.ac.uk
Judit Barabas, Research technician

Email: Judit.Barabas@qub.ac.uk

2.7 UK MANAGEMENT COMMITTEE AUTHORISATION

The UK members of the ITMG have read this appendix and recognise that it is the official UK regional appendix for the PANTHER trial. Signed on behalf of the committee

X Danny McAuley

Digitally signed by Danny McAuley
Date: 2025.09.15 22:49:47 +01'00'

Danny McAuley
UK Executive Director

2.8 FUNDING OF REGION

The PANTHER Trial is currently funded by the National Institute of Health & Care Research (NIHR) within the UK.

Funder reference: NIHR158714

New sources of funding will be sought as appropriate for new interventions and for continuation of the study over time.

2.8.1 Site Costs

Any payments due to sites will be detailed in the contract between site and the sponsor.

3 TRIAL BACKGROUND AND RATIONALE

There are no issues expected in relation to the background or rationale of the master protocol. Although all interventions are currently available to sites in the UK, sites can opt out of particular interventions.

4 TRIAL DESIGN

4.1 STUDY SETTING

As detailed in section 5.1 of the master protocol.

4.2 INTERVENTIONS

Interventions offered to sites within the UK will be dependent on the availability and feasibility of the intervention in the UK.

5 TRIAL CONDUCT

5.1 RECRUITMENT

As detailed in section 6.1 of the master protocol.

5.2 PREGNANCY TESTING AND BREASTFEEDING

No further exclusions apply apart from those listed in the master protocol and the intervention specific appendices.

5.3 TREATMENT ALLOCATION

Randomisation will occur online via the OpenClinica database. Data management and transfer will comply with the Data Protection Act 2018 and GDPR.

A change in database systems will not be considered a substantial amendment so long as the randomisation procedures are the same.

Further details in section 6.3 of the master protocol.

5.3.1 Data management

As detailed in the master protocol section 11

5.3.2 Data collection

As detailed in the master protocol section 11.4

Data collected from patients within the study will be linked to existing healthcare-related registries and databases in the UK such as ICNARC. Additional data may be obtained by data linkage with death registries and hospital discharge coding databases in the UK.

5.4 QUALITY ASSURANCE AND MONITORING

5.4.1 Quality assurance

As detailed in section 12.7 of the Master protocol

The study may be subject to inspection and audit by regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd Edition).

5.4.2 Monitoring

A monitoring plan will be devised based on a risk analysis and described in detail in the monitoring manual.

In the UK monitoring will be conducted by a representative of ICTU, Imperial College London.

Medical records, any other relevant source documents and the electronic site investigator files must be accessible to the monitor for these visits during the course of the study and at the completion of the study as required.

5.4.3 Study Management

In the UK the PANTHER trial will utilise an electronic Trial Master File (eTMF). The eTMF system, Florence and will host both the Trial Master File and the Investigator Site Files (ISFs). Each UK site will have access to the eISF for their site, a small paper file of wet signed documents will be retained at site, containing such documents as consent forms.

6 PHARMACOVIGILANCE

6.1 ADVERSE EVENTS (AES)

Adverse Event reporting will be as defined in the master protocol in section 8.

Table 1. Adverse events categorisation.

	IMP
Non-Serious	*Adverse Event (AE)
Serious	Serious Adverse Event (SAE) Serious Adverse Reaction (SAR) Suspected, Unexpected Serious Adverse Reaction (SUSAR)

**not collected in the PANTHER trial*

For definitions of the above event categorisations see section 8 of the master protocol.

6.2 SERIOUS ADVERSE EVENTS (SAES)

The PANTHER trial is considered a CTIMP.

Any SAE must be reported regardless of relatedness within 24 hours to the sponsor (via the OpenClinica database and Trials Unit study management team):

- If the event is deemed related to the IMP this would be considered a SAR.
- If an SAE is deemed related to the IMP and unexpected, this would be considered a SUSAR.

Any events that are captured as an outcome in the eCRF do not require reporting as an SAE unless in the opinion of the local PI the event was attributable to a study intervention / IMP or the trial protocol

6.3 SAE REPORTING

Reporting to the Sponsor

If the AE is assessed as serious by the site PI or designated staff member, this should be reported to the Sponsor immediately or within 24 hours of becoming aware of the event via the OpenClinica database.

Reporting to the MHRA - IMP

SAEs will be reported to the MHRA via the DSUR report. SUSARs will be reported as they occur to the MHRA.

Suspected unexpected serious adverse reaction (SUSARs)

A SUSAR is an adverse event which is suspected to be related to the IMP, and the event is serious and unexpected. The following reporting timelines apply:-

- **If the SUSAR results in death or is life-threatening –** the Sponsor will report to the MHRA as soon as possible and no later than 7 days of the Sponsor has become aware of the event.
- **If the SUSAR does not result in death or is life-threatening –** the Sponsor will report to the MHRA within 7-15 days of the Sponsor has become aware of the event.

Reporting to the REC

The Sponsor will report the SAE to the REC within 15 days of the CI becoming aware, those that in the CI's opinion are:-

- **'related'** – to the study (that is, it resulted from administration of any of the research procedures) and
- **unexpected** (that is, the type of event is not listed in the IB/protocol as an expected occurrence).

This means all SUSARs should be reported to the REC within the timeframes above

Reporting to the device manufacturer

The Sponsor will inform the device manufacturer of device deficiencies as indicated in the agreement with the device manufacturer who will then report to the MHRA to ensure the appropriate corrective actions are taken.

Reporting to the local NHS Trust

Local research governance procedures at each site, e.g., NHS Trust, should be followed.

Reporting to the Investigators

All PIs within the trial at other sites should be informed of any SUSAR by the CI, though not necessarily within the 7/15-day deadline but certainly within 3 months. If the CI is informed of any SUSARs from other trials using this IMP, the CI should inform the PI as above.

6.4 DEVICE DEFICIENCIES

During the PANTHER trial if any device deficiencies are discovered, these should be reported using a Device Deficiency Form. The PI or designated site member should complete the form and send this to the PANTHER trial team immediately or within 24 hours of becoming aware of the deficiency. The form is available on the PANTHER trial website.

6.5 ANNUAL SAFETY REPORTING

A Development Safety Update Report (DSUR) should be submitted to the MHRA within 60 days of the anniversary of the MHRA approval by the Sponsor.

See appendix A for more detail on reporting procedures.

6.6 URGENT SAFETY MEASURE

An urgent safety measure (USM) is defined as an appropriate measure taken to protect a research participant from an immediate hazard to their health and safety. If a USM is required as part of PANTHER a notification will be submitted in IRAS to the REC. If this requires a change to the protocol an amendment will be submitted

7 ETHICS AND REGULATIONS

This is detailed in the master protocol in section 10; however, the following will also apply in the UK:

7.1 HRA

Health Research Authority (HRA) approval will be obtained prior to starting the study in addition to approvals from the competent authority and ethics committee. Each participating site will confirm capacity and capability prior to commencing.

The HRA and all participating sites also need to be notified of all protocol amendments to assess whether the amendment affects the institutional approval for each site.

7.2 MHRA

This study has Clinical Trials Authorisation from the UK Competent Authority; MHRA. Reference: CTA 19174/0458/001-0001

7.3 AMENDMENTS

Amendments to the protocol will be decided by the Chief Investigator and the ITMG and will be submitted to the Imperial College London Research Governance and Integrity Team for review prior to submission. Whether the changes in the protocol are substantial or non-substantial will be guided by the amendment tool as provided by the HRA/REC. An updated version and date of the protocol will be documented in the title and footer of the document, the approval pack (containing the updated protocol) will also be sent to all participating sites.

7.4 CONSENT PROCESS

The consent process is broadly described in the master protocol. However, a detailed description of the consent process in the UK is provided below:

If the patient has capacity, they will always be approached to provide their informed consent. If the patient does not have capacity, a family member or independent doctor (or suitable healthcare professional) will be approached. Due to the emergency nature of the trial, if the patient lacks capacity and a family member or independent healthcare professional is not available, a deferred consent model will be adopted. This is to ensure that treatment can start as soon as possible. Treatment is more likely to be beneficial if given earlier and would reflect how a treatment would be used in clinical practice if shown to be effective. Consent will be sought soon after.

If the patient lacks capacity, then a family member / next of kin (NOK) will be approached to provide their consent on behalf of the patient, (known as a personal legal representative consent). This may be after treatment if the trial has already started due to the emergency nature of critical illness management. If this is the case, consent from the patient or their personal legal representative (PerLR) will be sought as soon as possible. If the PerLR is not able to attend in person, e-consent using the OpenClinica system or telephone consent will be used. The PerLR 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. If a family member/NOK is not available a doctor, pharmacist, prescriber, or other healthcare professional such as a matron or ACCP with a deep understanding of medical treatments who is not part of the study (i.e. not on the trial research delegation log) will be approached to give their professional legal representative (ProLR) consent. This would usually be a senior treating clinician of the patient who is independent of the trial. Once the patient regains capacity, they will be approached to provide their retrospective consent to remain in the study.

We will use a 2-hour window as established in other emergency UK ICU-based trials (ISRCTN18035454) to guide the emergency consent process if the patient lacks capacity.

- If the patient lacks capacity and a family member / next of kin is in attendance or will arrive within 2 hours, then seek PerLR consent.
- If the patient lacks capacity and a family member / next of kin is not available within 2 hours, then seek ProLR consent.
- If the patient lacks capacity and neither a PerLR nor a ProLR are available within 2 hours, then the patient can be included without prior consent.

Participants will be provided with a copy of the signed Participant Information Sheet/Informed Consent Form document. The original Informed Consent Form will be retained with the source documents.

7.5 SERIOUS BREACH OF GCP

A serious breach is defined as:

A breach of the conditions and principles of GCP in connection with a trial or the trial protocol, which is likely to affect to a significant degree:

- The safety or physical or mental integrity of trial participants; or

- The overall scientific value of the trial

7.6 CONTACT WITH PRIMARY CARE PHYSICIAN (GENERAL PRACTITIONER)

Patient GPs will be informed of the patient's enrolment in the study as part of the usual NHS discharge procedure at site. The study will also mandate that site teams a separate, additional letter to the patient's GP with their consent.

7.7 DATA PROTECTION AND PARTICIPANT CONFIDENTIALITY

The investigators and study site staff will comply with the requirements of the Data Protection Act 2018 and the UK GDPR, concerning the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

7.8 DEVELOPMENTAL SAFETY UPDATE REPORTS

Developmental Safety Update Reports (DSUR) will be submitted by the Sponsor, in accordance with local / national regulatory requirements.

7.9 END OF TRIAL

Should the trial end, a Clinical Study Report summarising the study results will be prepared and submitted to the REC within 90 days of the end of trial definition being met. In the event of a premature halt of the trial, the timeframe is 15 days, and the reasons should be clearly explained in the notification.

The results will be submitted to appropriate trial registries/databases in keeping with ISRCTN in accordance with UK regulatory requirements.

7.10 REFERENCE NUMBER

REC: 25/NW/0103

8 IMP REQUIREMENTS

8.1 DISTRIBUTION OF STUDY DRUG

The IMP for the PANTHER trial will either be provided from local hospital stock or provided by the Sponsor/manufacturer. The provision for each IMP will be detailed in the pharmacy manual. The study drug may be commercial stock (licensed and used within indication of SmPC), or clinical trial stock (could be licensed and used outside of indication or unlicensed).

8.2 LABELLING AND PACKAGING

The MHRA IMP risk classification for the trial is Type A risk adapted CTIMP as any potential risk is no higher than that of standard medical care. As new interventions are added to the trial, this will be reviewed. Commercial IMP taken from hospital stock already stored in the hospital will not require a study specific label. Where licensed stock is provided to sites by the Sponsor/manufacturer, clinical trial labelling may be used, this will be detailed in the pharmacy manual.

If unlicensed IMP is used within the trial, specific clinical trial labelling will be required. Clinical trial labelling in this instance will be compliant with EU GMP Annex 13.

8.3 STORAGE AND DISPENSING

Storage conditions for the IMP should be as per Summary of Product Characteristics (SmPC) for that product. If IMP is obtained from commercial hospital stock, storage monitoring requirements are risk adapted, and temperature monitoring will be as per local site practice. No reporting of temperature excursions to the Sponsor is required. As stock is 'off the shelf' local practice for dealing with temperature excursions in drug storage areas should be followed.

If the IMP is provided by the Sponsor and as clinical trial stock then as this is a Type A risk trial the temperature monitoring is risk-adapted, any specific requirements from the manufacturer or Sponsor will be detailed in the pharmacy manual per specific IMP.

8.4 ACCOUNTABILITY

Where IMP is taken from routine hospital stock, accountability will be risk adapted, and there will be no requirement for trial specific accountability. Each site hospital pharmacy should plan to supply drug stock according to their local practices. Sites will be encouraged to include the trial name on the patient prescription for traceability.

Where IMP is provided by the Sponsor/manufacturer and/or provided via clinical trial stock accountability may be mandated, this will be instructed by intervention and detailed in the pharmacy manual.

8.5 RETURNS AND DESTRUCTION

Where IMP is taken from routine hospital stock and only administered to participants while they are inpatients in ICU, there will not be any drug returned to site pharmacies. Site pharmacies should follow their local practice / policies for drug destruction and documentation. No approval from Sponsor is required.

Where IMP is provided by the Sponsor/manufacturer and/or provided via clinical trial stock returns and destruction may be mandated, this will be instructed by intervention and detailed in the pharmacy manual.

8.6 IMP RECALL

In the event of an IMP recall the MHRA will be notified immediately by the IMP manufacturer/supplier and/or the trial Sponsor/delegate (whoever is leading), if not identified by the MHRA themselves. The Sponsor will liaise with sites directly if any batches are required to be recalled from site.

8.7 SAMPLE MANAGEMENT

As detailed in the sample collection and processing guide.

9 DEVICE

In the UK sites will use the Randox device as detailed in section 4.1 of the subphenotype appendix. If other devices become available in the platform, they may be used in the UK when the subphenotype appendix is updated and approved.

10 REVISION HISTORY

Version	Date	Summary of changes
1.0	03 MAR 2025	First version
1.1	05 AUG 2025	Update to Appendix A. Removal of sponsor requirement to report SAEs to the MHRA within 7 days.

11 APPENDIX A