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NIHR | National Institute for Health Research

Precision medicine Adaptive Network platform Trial in Hypoxaemic acutE respiratory failuRe

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SPONSOR: IMPERIAL COLLEGE LONDON

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Agenda

- Background
- Interventions: Simvastatin & Baricitinib
- Consent
- IMP Management
- Sample Collection
- Follow up
- Site Training

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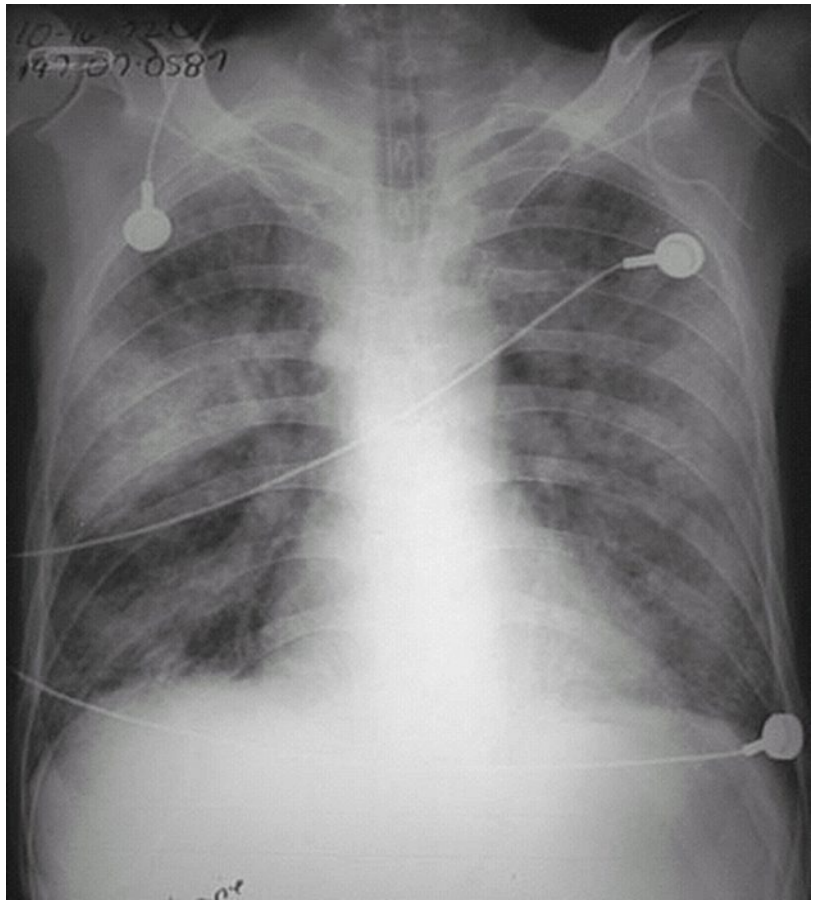
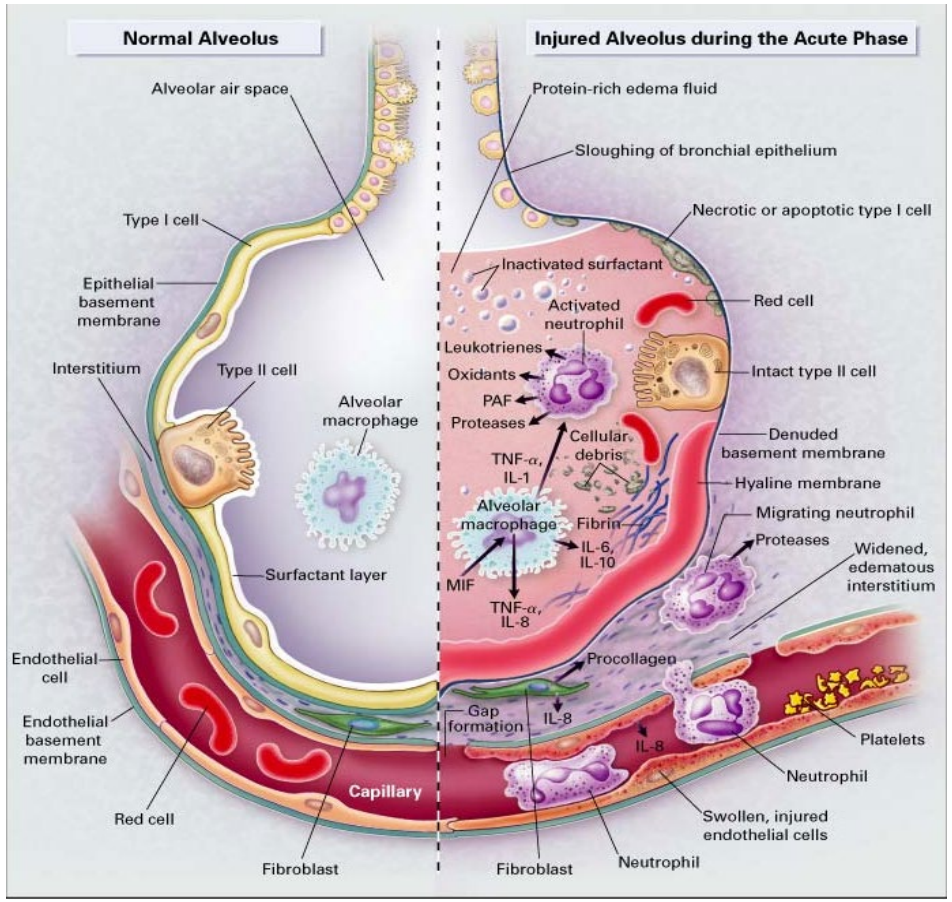
Background





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Research Question

In patients with ARDS with hyperinflammatory and hypoinflammatory phenotypes:

- Does simvastatin or baricitinib improve 28-day organ-support free days?

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Rationale

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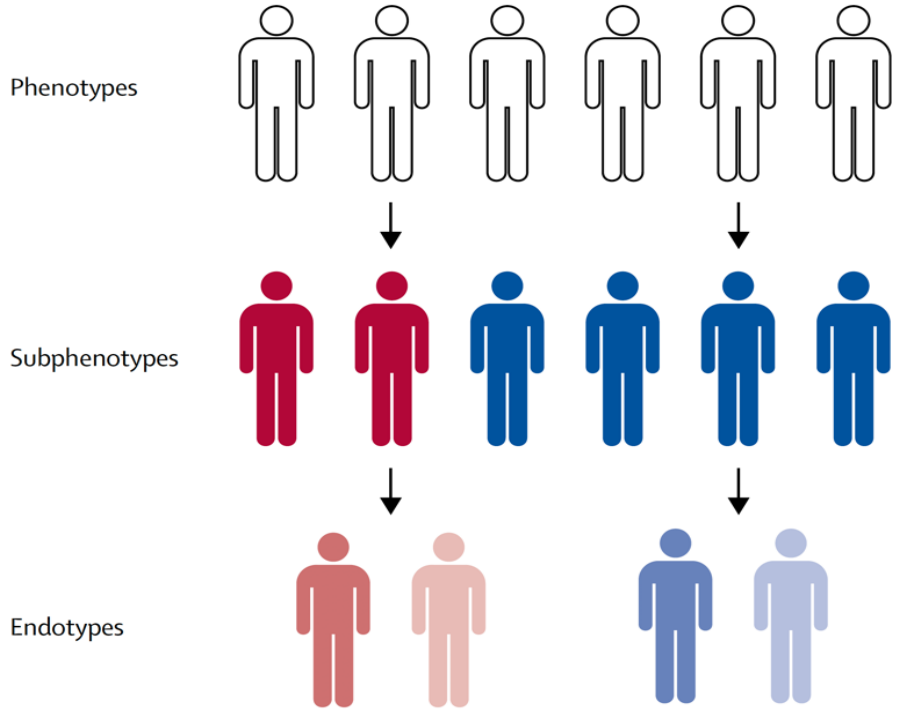
ARDS phenotypes demonstrate differential responses to specific interventions in secondary analyses of completed clinical trials.

Reducing heterogeneity might solve the problem of lack of pharmacological therapies.



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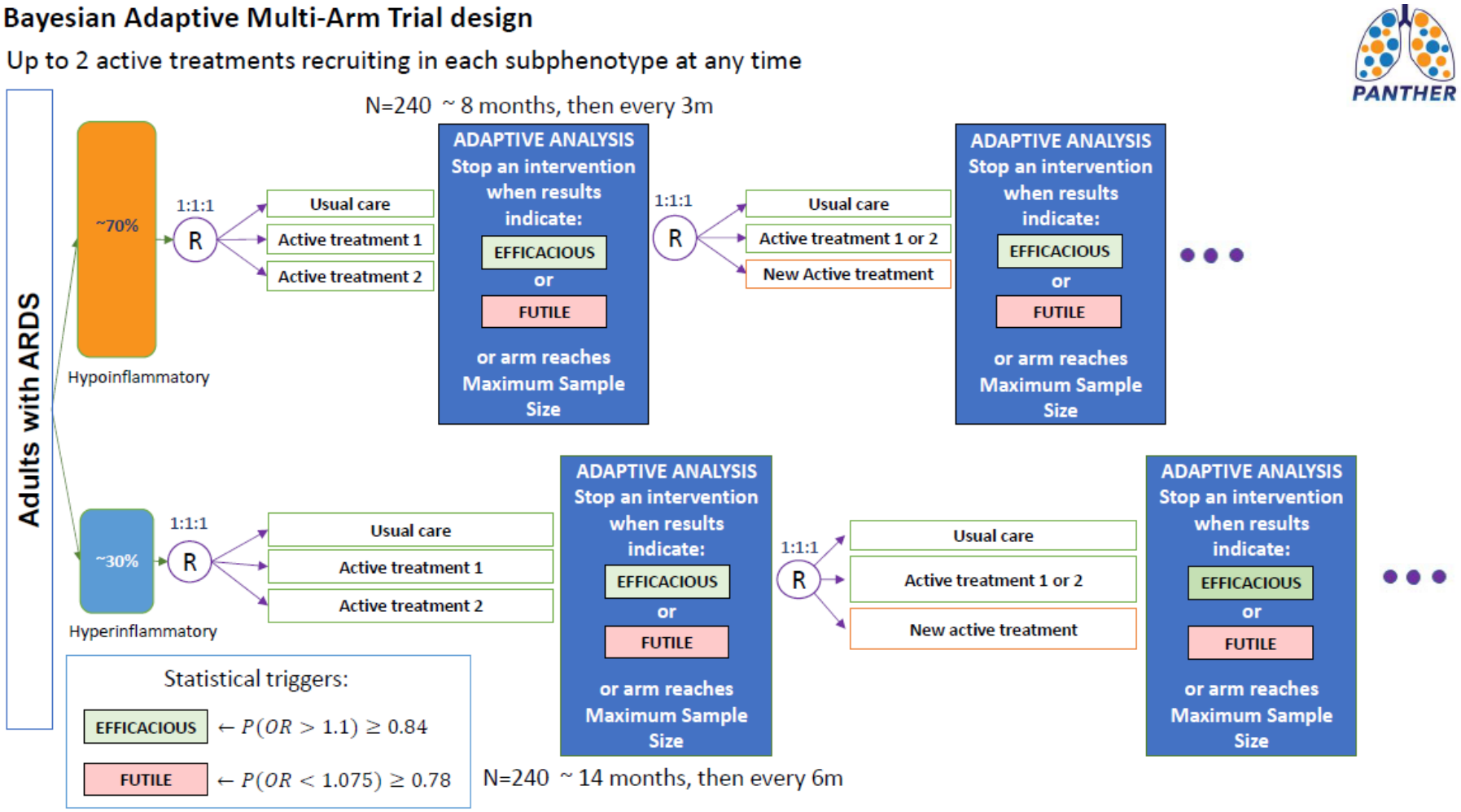
Trial Design – Traditional Vs Adaptive Platform Trial



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The Study

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Adaptive – no fixed sample size

- Sample size projections evaluated by extensive simulation

Planned recruitment rate and retention

- 70 centres worldwide, 1 patient / ICU / month
- 4 years initial recruitment – study designed to be potentially perpetual

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Primary Endpoints

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28-day organ support-free days incorporating mortality

- Ordinal scale - composite of:
  - in-hospital death (-1)
  - number of days alive and not requiring organ support

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Secondary Endpoints

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- 28-day vasopressor-free days
- 28-day respiratory support–free days
- Receiving new renal replacement therapy
- Progression to invasive mechanical ventilation, extracorporeal membrane oxygenation or death among those not receiving that support at baseline
- ICU length of stay
- Hospital length of stay

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Secondary Endpoints Cont.

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All-cause mortality at 28 and 90 days

- Safety Outcomes – please refer to protocol
- Serious adverse events
- Physical function (SPPB) at hospital discharge (up to 1 week prior to discharge) – **unlikely to be collected in UK**
- Cognitive function (MoCA Mini) at hospital discharge (up to 1 week prior to discharge)*

**** If these cannot be completed it will not be a protocol deviation***

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Tertiary Endpoints

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

Not all sites are expected to collect these endpoints

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Trial Design – Modular protocol structure

- Master Protocol
- Intervention Specific Appendices
- Subphenotype Appendix
- Regional Appendix
- Statistical Design Appendix

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Platform Inclusion Criteria

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

a) Acute respiratory distress syndrome (ARDS)*

b) A pandemic associated syndrome (this will be triggered if a new pandemic is declared)

*ARDS as defined by

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

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

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

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

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

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Platform Exclusion Criteria

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

NB - Intervention exclusions will also apply

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Subphenotypes

Subphenotypes of ARDS to be studied:

- Hyperinflammatory
- Hypoinflammatory

PANTHER aims to identify which subphenotype will respond best to a treatment to improve patient care.

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Device – Randox multiSTAT

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- The MultiSTAT device is a fully automated immunoanalyser that enables on-site simultaneous detection of analytes from a single sample of blood.
- It requires a sample of approximately 200µl of blood which is centrifuged and diluted 4-fold prior to analysis.
- The results are generated typically within 60 minutes.
- Please refer to the device manual for further details.

Phenotype classification

- IL-6 and sTNFR1 measured by point of care assay
- Worst Bicarbonate level from a plasma or arterial blood gas in last 24hrs prior to randomisation
- Logistic regression equation

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Current Interventions

Simvastatin

Baricitinib

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Intervention Specific Appendices

Refer to the ISA for:

- Intervention rationale
- Intervention specific eligibility criteria
- Concomitant care
- Potential intervention specific adverse events

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Background - Simvastatin

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- Simvastatin is a statin that has shown potential in modifying pathogenic mechanisms in ARDS.
- While HARP-2 trial found no overall benefit, a secondary analysis indicated improved 28-day survival in patients with ARDS with the hyperinflammatory subphenotype.
- In COVID-19-related ARDS, simvastatin 80mg improved organ support-free days.
- The drug is generally well tolerated, and safe with recommended safety monitoring during the 28-day treatment period.
- These findings support further testing in a phenotype-stratified trial.

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Exclusion Criteria - Simvastatin

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- Age <18 years
- Patient is known to be pregnant
- Creatine kinase >10 times the upper limit of the normal range
- Liver transaminases >8 times the upper limit of the normal range
- Currently receiving ongoing treatment with any of the following: itraconazole, ketoconazole, HIV protease inhibitors, nefazodone, cyclosporine, amiodarone, verapamil, or diltiazem
- Severe renal impairment (eGFR < 30mL/min and not receiving renal replacement therapy)
- Current or recent treatment (within 2 weeks) with statins
- Physician decision that a statin is required for proven indication
- Contraindication to enteral drug administration, e.g., patients with mechanical bowel obstruction. Patients with high gastric aspirates due to an ileus are not excluded
- Known hypersensitivity to simvastatin
- Breast Feeding
- Any other medical condition or treatment that, at the clinical discretion of the investigator, is considered not in the participants best interest to start treatment with the IMP based on the approved version of the IMP SmPC.

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Background - Baricitinib

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- Baricitinib is an oral JAK1/2 inhibitor used for autoimmune diseases and has shown to reduce mortality in COVID-19 patients with ARDS.
- There is evidence supporting potential benefit in both hypoinflammatory and hyperinflammatory subphenotypes.
- Baricitinib was chosen over other immunomodulators due to its broad-anti-inflammatory activity but relatively short duration of effect.
- The recommended dose is 4mg daily for 10 days, with adjustments for renal dysfunction.

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Exclusion Criteria - Baricitinib

PANTHER

- Age <18 years
- Patient is known to be pregnant
- Absolute neutrophil count less than $0.5x10^9/L$
- Liver transaminases >8 times the upper limit of the normal range
- Currently receiving ongoing immunosuppressants (high-dose corticosteroids, T-cell-targeted or B-cell-targeted therapies, interferon, or JAK inhibitors)
- Severe renal impairment (eGFR < 15mL/min) or receiving renal replacement therapy
- Known active tuberculosis infection or, if known, latent TB treated for less than 4 weeks with appropriate anti-tuberculosis therapy per local guidelines
- Known hypersensitivity to baricitinib
- Breast feeding
- Known herpes zoster virus, hepatitis B virus, hepatitis C virus or human immunodeficiency virus (HIV)
- Any other medical condition or treatment that, at the clinical discretion of the investigator, is considered not in the participants best interest to start treatment with the IMP based on the approved version of the IMP SmPC.

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Usual Care

- Each subphenotype will have a control which will be usual care.
- Usual care will be directed by international treatment guidelines, such as the European Society of Intensive Care Medicine ARDS guidelines.
- Agreement to comply with these guidelines will be a condition for a site to participate in the trial to ensure standardised best practice usual care.

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Eligibility Confirmation

- Eligibility must be confirmed by a clinician on the delegation log.
- Here a clinician is defined as any role who has prescribing rights i.e. nurses, practitioners.
- Clinicians **must** confirm their eligibility review by completing an eligibility form.
- The form **must** be filed in the medical records – this is an MHRA requirement.
- Please ensure any lab values are entered on the form, this is also an MHRA requirement.

Site Name	
Patient ID	

PANTHER Eligibility form

Complete this form as part of the screening process for the PANTHER trial – to be completed by a clinician on the delegation log and filed in the medical records and eISF once complete.

Here, clinician is defined as any role who has prescribing rights i.e. nurses, practitioners.

Platform Inclusion Criteria	Please circle which apply	
Critically ill patients in hospital with at least one of the following: - a) Acute respiratory distress syndrome (ARDS)* b) A pandemic associated syndrome (this will be triggered if a new pandemic is declared) *ARDS as defined by:- (i) a known acute clinical insult or new or worsening respiratory dysfunction, and (ii) receiving respiratory support via invasive mechanical	Yes	No

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IMP Management

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Drug	Hospital Stock	Provided by Sponsor	Storage Conditions	Temperature Monitoring	Labelling	Accountability	Returns & destruction
Simvastatin	✓	X	SmPC	Local Process	No additional labelling required	At pharmacy level	Local Process
Baricitinib	✓	X	SmPC	Local Process	No additional labelling required	At pharmacy level	Local Process

Additional guidance regarding the preparation and administration of each intervention can be found in the intervention specific appendices and pharmacy manual.

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Visit Schedule

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	Baseline (24 hours pre randomisation)	**Day 0** (post randomisation)	**D2**	**D6**	**Up to D28**	**Hosp D/C**	**D90**	**D180**	**D365**
Screening	X								
Informed Consent	Patient / PerLR / ProLR will be obtained initially. Retrospective patient consent will be obtained when the patient has recovered capacity to consent.								
Inclusion / Exclusion criteria	X								
Phenotyping	X								
Randomisation	X								
Research samples	X		X	X					
Intervention administration					X				

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Visit Schedule – Data Collection

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	Baseline (24 hours pre randomisation)	Day 0 (post randomisation)	D2	D6	Up to D28	HospD/C	D90	D180	D365
Baseline data	X								
Data collection / follow up		X	X	X	X	X	X	X	X
Physical function (MMST)						X			
MOCA Mini						X	X	X	
Data collection in ICU (up to day 90 max)							X		
Vital status							X		
Data collection in hospital (up to day 90 max)							X		
EQ-5D-5L							X	X	
HADS							X	X	
Social and Wellbeing (SF-36)							X	X	
Impact of Events Scale							X	X	
Care and wellbeing needs							X	X	
Long-term follow-up									X

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Sample Collection and Management

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- There are different tiers of sampling in PANTHER.
- Sites may choose which level of sampling they wish to participate in.
- The different tiers are described here:
- Sample kits will be provided by the sponsor.
- More details in the sample collection guide.

Tier	Biological Samples
0	Phenotyping sample only (Li heparin)
1	- Phenotyping sample - Day 0 bloods = plasma/serum/Paxgene RNA - Other Day 0 samples = nasopahyngeal swab (NPS)/ tracheal aspirate in patients on invasive mechanical ventilation
2	- Tier 1 samples PLUS - Longitudinal samples: plasma/serum/RNA plus - Longitudinal NPS/ tracheal aspirate sampling in patients on invasive mechanical ventilation
3	- Tier 2 samples PLUS - Day 0 and longitudinal CPT samples
4	Tier 2 or 3 PLUS BAL where possible (selected sites only)

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Consent Process

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Is patient competent to consent prior to screening procedures?

No

1. Personal LR present?
2. Professional LR present?

No

Is treatment start urgent and enrolment beneficial for the patient?

Written consent possible from patient / PerLR?

No

Yes

Prospective consent

Yes

Deferred consent

Yes

Delayed consent

Verbal consent (in person)
Remote verbal (telephone)

Consent must be obtained from Patient/PerLR/ProLR as soon as possible after screening procedures, ideally within 24hrs

Patient consent must be obtained when patient becomes capacitated

With impartial witness

Follow up with written consent if/when possible

IMPORTANT: All consent discussions should be documented in the patients' medical notes. If it is not written down, it did not happen.

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Consent

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Retrospective Consent

- If the patient regains capacity, ensure Retrospective consent is obtained.
- If the patient is discharged prior to obtaining retrospective consent, then please contact the patient/family member and use the Telephone/Postal/ e-consent option.

ensure the family member/patient is aware of the study before discharge

ensure the participation of the patient is documented in the GP discharge letter

Additional support materials on the consent process can be found on www.panthertrial.org.uk

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Telephone / Postal / e-Consent

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Has patient been discharged?

Yes

Call the patient using the telephone agreement form

Explain the study and allow the patient to ask any questions. Are they happy to continue to take part in the study & for the consent form to be posted?

No

Please update the consent section on the eCRF if the patient chooses to withdraw

No

Approach the patient in hospital to gain retrospective consent. Follow the consent flowchart if unable to obtain.

Yes

Post form / send e-consent link

If the patient is happy, they can sign and return the consent form which will then be countersigned by yourself/ the person who discussed the study with them.

REMINDER
Please always document any conversation with the patient in the patients notes

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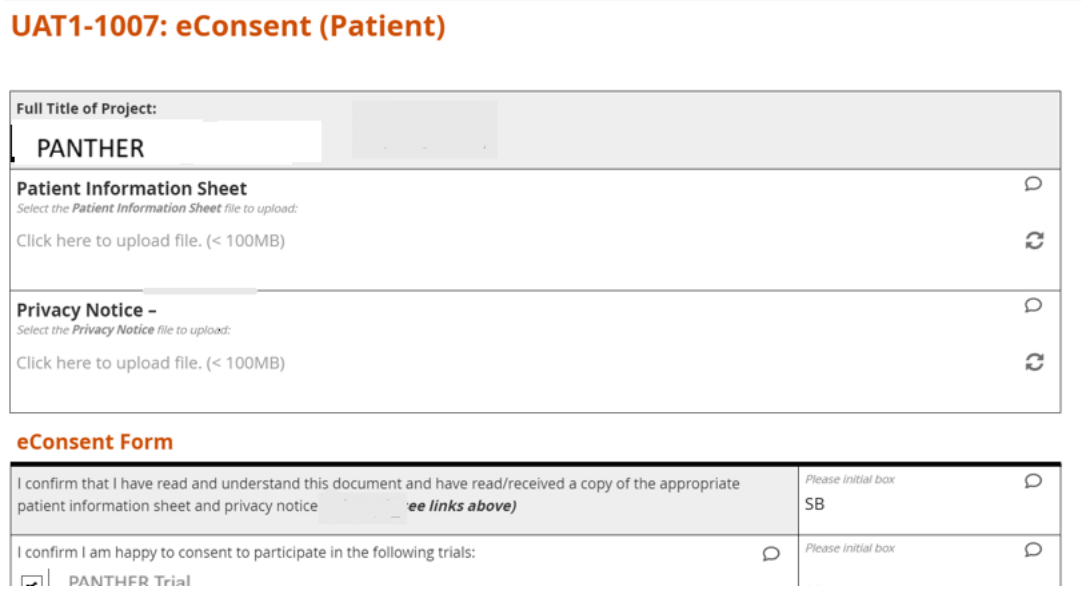
eConsent



1. Add form to OpenClinica
2. Enter email address for patient/family member completing the form
3. The patient/family member receives a link to complete
4. Once complete this will appear in the eCRF where the research nurse will countersign

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Inclusion

Research needs to include everyone to make sure that it is robust and applicable to the whole community. Here are some suggestions to help inclusivity in research:

- Every **eligible** patient (and their family, where relevant) on the ICU **should be offered the opportunity to take part in the trial.**
- Screen all patients for eligibility and it is **best not to make assumptions** that a patient would find it difficult or would not be able/want to take part.
- Be culturally aware and **consider changing language or approach** after the initial meeting with the patient and relatives, if another would be more suitable **to build trust and rapport with them**. See if there is a member of the team who may be more able to connect with them. Consider the use of trained interpreters.
- **Check if the patient and family or friend have any communication requirements e.g. disability, low literacy or vision.** Consider language, verbal and expressions used in communication.

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Inclusion

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- **Don’t assume a patient’s gender** and use gender-neutral terms until preferred pronouns can be confirmed.
- **Don’t assume patients’ marital status**. Don’t assume patients’ sexuality and ensure to use gender-neutral terms to refer to their partners/relationships when their gender is not known.
- Have trial **materials in a variety of formats** to offer choices to best suit the patient and their relatives (such as video/audio/translation etc). Do not make assumptions about literacy levels.
- Do not stereotype and **be aware that you may have your own sub-conscious biases**. Question your own assumptions.
- Ensure there is an **appropriate environment when taking consent**, there is time to discuss the research and there is some privacy. You can check with the clinical team when it might be best to approach a patient. Always give thinking time between initial approach and consent and check retention of information.

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Inclusion

More information and resources on inclusion in clinical trials can be found here:

- Improving inclusion of under-served groups in clinical research: Guidance from INCLUDE project | NIHR

- TRIAL FORGE – Improving Trial Diversity

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Randomisation

- Screening, randomisation and data collection will all be via the OpenClinica database
- Randomisation emails should be saved in the eISF and in the medical records
- Data Entry :
  - Phenotyping, Baseline (vital signs, imaging results, lab results), demography, co-enrolment, samples, consent
  - Day 1 to 28 – organ support, lab results, IMP given
  - Follow ups – D90, D180, 1 year
- Protocol Deviations
- Serious Adverse Events

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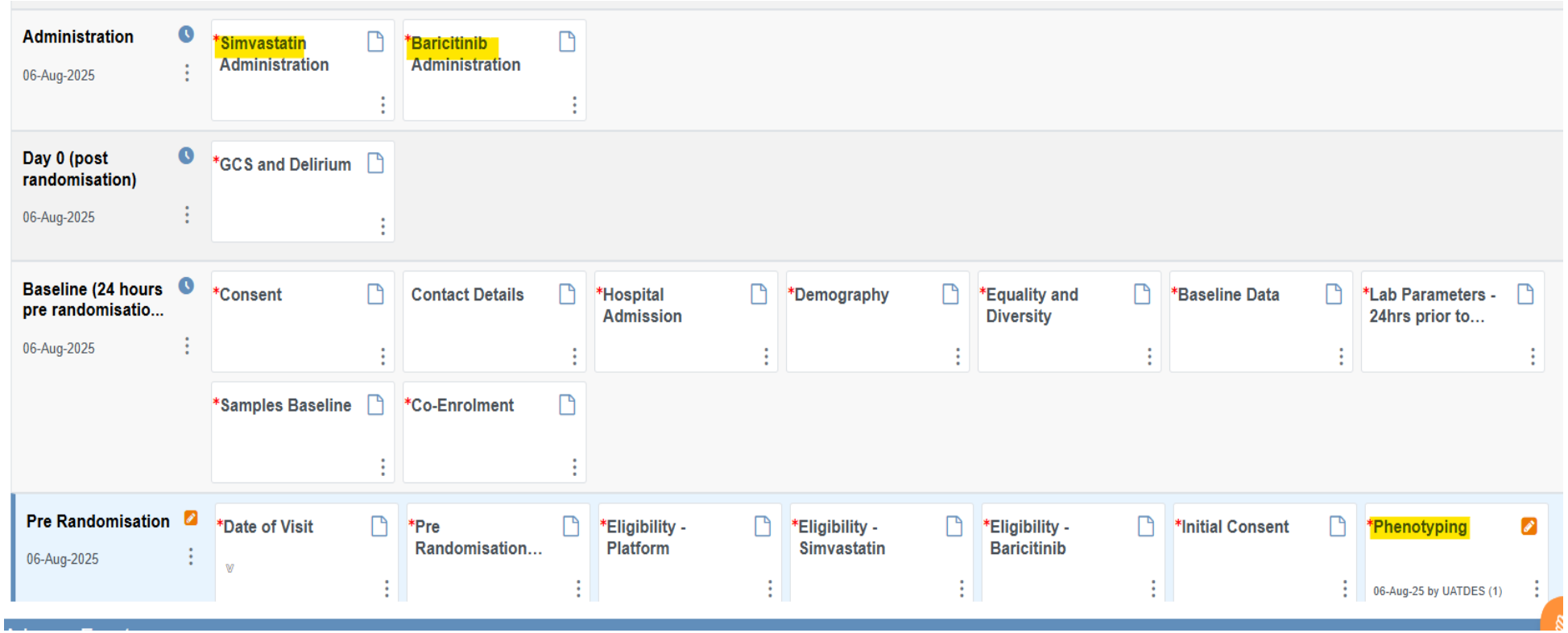
Data Collection

- Data is collected via OpenClinica
- Enter IL-6, sTNFR1 and sodium bicarbonate and randomise the patient
- Data is entered daily
- Intervention administration data forms are separate



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Withdrawal & Lost to Follow-up

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Withdrawal and LTFU

If the patient/family member chooses to withdraw from the study:

- Amend the consent form page to ‘no consent’ or ‘consent to use partial data’ and confirm if the patient/family would like to keep data already collected
- Complete the End of Study form, if not complete select ‘no’ and the reason:-

Primary reason for Withdrawal

- ◯ Adverse Event
- ◯ Consent Withdrawn
- ◯ Subject did not meet Inclusion/Exclusion Criteria
- ◯ Lost to follow-Up
- ◯ Sponsor Decision
- ◯ Investigator Decision
- ◯ Other

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Recruitment & Follow-up

- The database will notify you when D90 and D365 follow up requires completion.

REMINDER

Day 90 – no need to contact patient – status obtained from records

Day 180 - no need to contact patient, will be completed by the central team when required

Day 365 - 1 year post randomisation – no need to contact patient - status obtained from records

**there is a +/-14-day window on each follow up*

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Overview Safety Reporting

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Adverse Events - Due to the population of patients AEs are expected, therefore only SAEs are collected.

Abnormal Test Results - Similarly due to the population these are expected and so not reported.

Serious Adverse Events

An SAE is defined as any event that:

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

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Overview Safety Reporting

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- In PANTHER there may be intervention specific SAEs, please refer to the Intervention Specific Appendix for details.
- The PI or staff member must enter the SAE on the eCRF immediately of becoming aware or within 24hrs of occurring during the patient's ICU stay up to a maximum of 28 days.
- The SAE should be followed up to resolution or discharge.
- The sponsor should be notified of any potential serious breaches immediately.
- SAEs will be reported using MedDRA coding by the trial team.

NB – The RSI in this study is the SmPC for each intervention – MHRA approved version

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Expectedness and MedDRA

- Reporting of an SAE – the PI can delegate this task to a site study member as long as they are delegated this task on the delegation log are suitably qualified and are GCP trained.
- In PANTHER the PI will assess the expectedness and causality of any SAE
- All SAEs are medically coded in the eCRF using the MedDRA coding system
- MedDRA coding will be completed by the PANTHER study team

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Safety Reporting – Safety Outcomes

The following events are captured as outcomes and so **do not need to be captured as SAEs***:

- Elevated Creatine Kinase more than 10 times the upper limit of normal
- Alanine Transaminase or Aspartate Transaminase more than 8 times the upper limit of normal
- Severe thrombocytopenia, out of keeping with clinical disease
- Severe neutropenia, out of keeping with clinical disease
- Serious infection defined as a positive blood cultures requiring treatment and pulmonary aspergillosis requiring treatment
- Venous thromboembolism
- Stroke
- Myocardial infarction
- Ischaemic bowel
- Gastrointestinal perforation
- Clinically important gastrointestinal (GI) bleeding.
  Defined as overt bleeding on GI endoscopy, developing as a complication in the ICU and accompanied by 1 or more of the following features within 24 hours:-
  - Spontaneous drop of systolic, mean arterial pressure or diastolic blood pressure of 20mmHg or more
  - Start of vasopressor or a 20% increase in vasopressor dose
  - Decrease in haemoglobin of at least 2 g/dl o Transfusion of 2 unites of packed RBC or more

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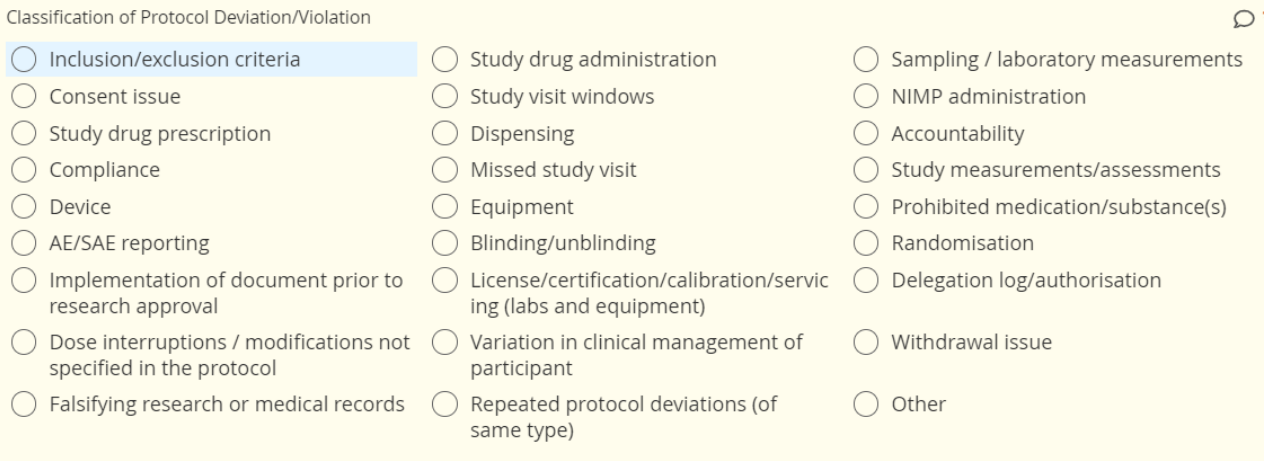
Protocol Deviations and Violations

- All protocol deviations and violations will be entered on the eCRF
- If in doubt, please contact the Trial Team



- Please refer to the pharmacy manual for protocol deviations relating to missed doses

Definitions

Protocol Deviation = a procedure/treatment is not followed as per protocol (non-serious).

Protocol Violation = a serious deviation that reduces quality/completeness of data, incorrect consent process, impacts patient safety.

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Co-enrolment

Yes	No
GuARDS (Simvastatin only)	ADCAP
Awake Prone	AnakARDS
RELEASE	Rhu-pGSN for Acute Respiratory Distress Syndrome (ARDS)
NAVA	

NB Co-enrolment must be documented in the medical notes and eCRF
Full co-enrolment list is on www.panthertrial.org.uk

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Site Training

- Study training
  - SIV
  - OpenClinica full users and randomisation users
  - Study training log we have study specific training for:-
    - Eligibility assessors
    - Randomisation users
    - eCRF
    - Simvastatin
    - Baricitinib

  - All training materials will be available on our study website:- www.panthertrial.org.uk

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Delegation Logs

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- All site staff listed on the delegation log **must be GCP trained**.

<u>Delegated Tasks – PI is ultimately responsible for the study</u>

- Obtaining consent **(YES)** - Only those listed on the delegation log with the delegated task of 'obtaining consent' can take consent from the patient/legal representative.

- Eligibility **(YES)** – this must be confirmed by a clinician. The individual **does** need to be listed on the delegation log; However a shortened slide deck is available which includes GCP training. We have generated an eligibility worksheet this should be completed and signed for each patient and filed in the ISF.

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Monitoring

Plan to adapt a <u>combined approach</u> to monitoring:

- On site – each site will receive an onsite visit during the 1st year opening to the study.
- Remote - if acceptable to the site, remote visits will be offered as an option for subsequent visits– see further detail below.
- Central - central monitoring will be used throughout the study, we will take this approach to pull reports from the data base and remote/central consent checks.

<u>Remote/Central monitoring tools</u>

Egress Account/nhs.net email – allows the review of consents and secure data

Access to source data – if the Trust allows access (as per the new MHRA guidance/requirements)

Checklists – provision of eISF and consent checklists

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Study Management

The following study procedure manuals/guidelines are available:-

- eCRF Completion Guidelines
- OpenClinica Manual
- Sample Management and Collection Guide
- Sample Shipping Form
- Device Manual
- Pharmacy Manual – specifics on how to handle the IMP
- Randomisation/screening log

- All study documentation is available on our website:- www.panthertrial.org.uk

All websites and emails will include **UK** for PANTHER UK – as this is an international trial, please ensure you are using the correct details.

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eISF, PSF and Archiving

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- This study will use an eISF called Florence. Separate training for those who will maintain and use Florence is required.
- Please ensure these are well maintained and kept up to date.
- The PSF will also be on Florence.
- Prior to Green Light the PANTHER study team will arrange a session with the site eISF admin to transfer the eISF and walkthrough the filing.

Archiving

The Sponsor Trial team will inform sites when archiving will take place. This will usually be once the close out visit is complete. As per the IRAS application and privacy notice, the archive period for this study is at least 10 years.

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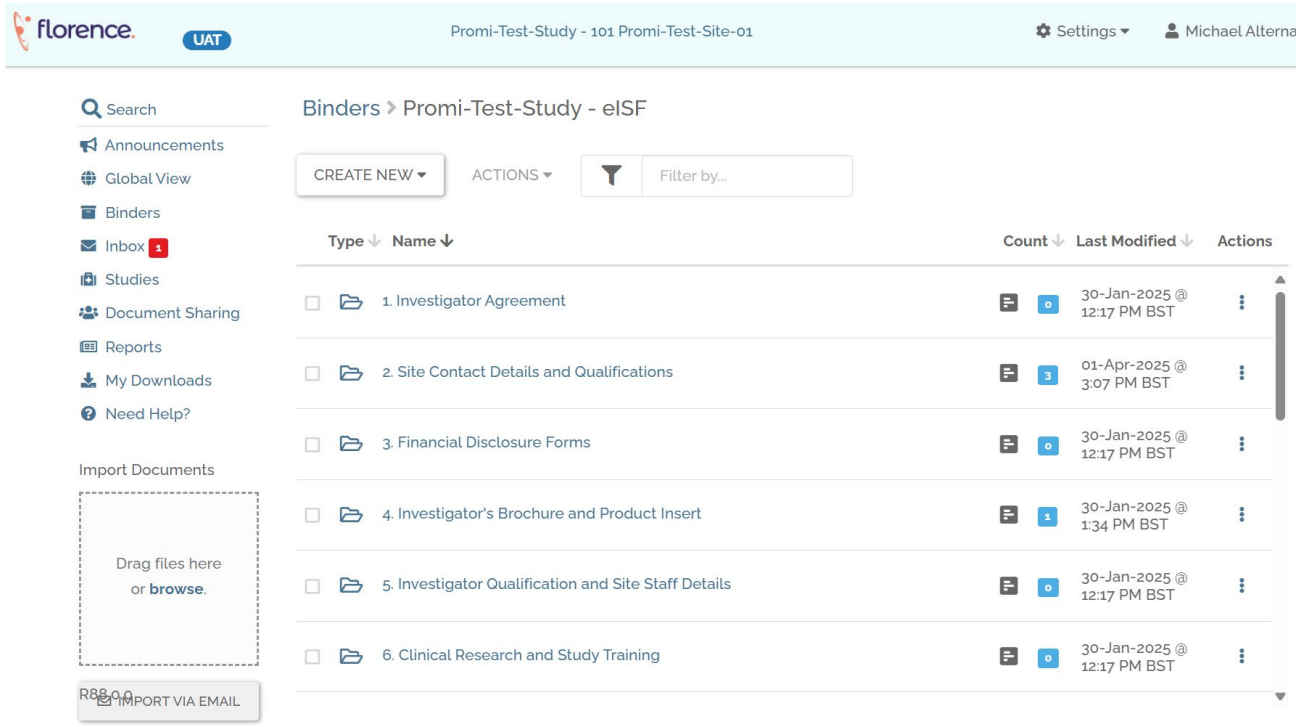
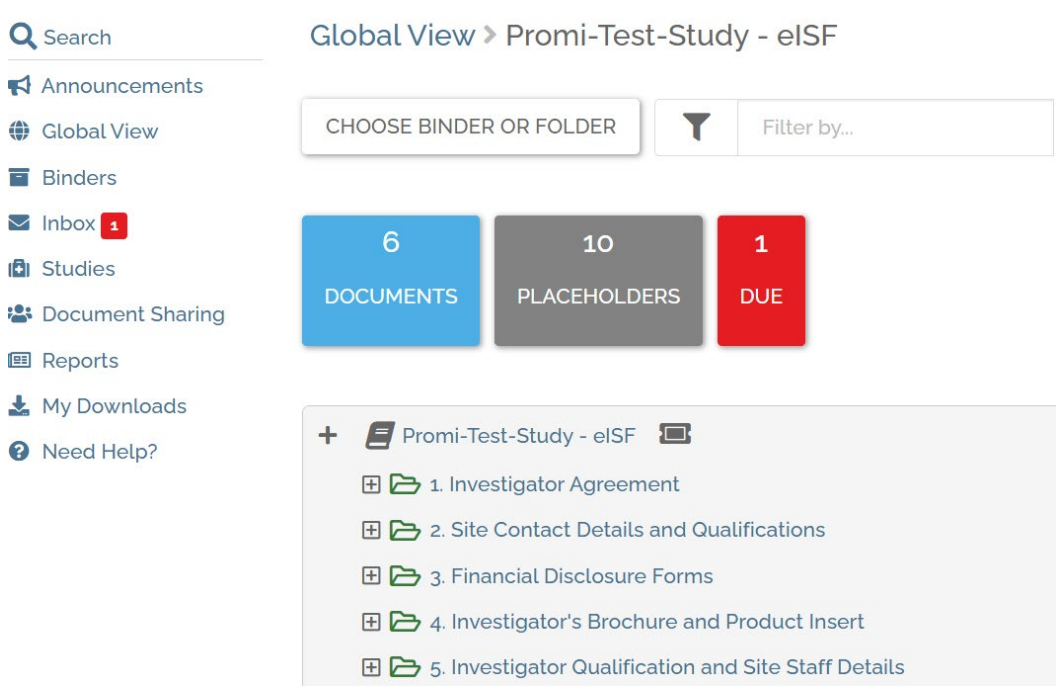
Florence





- Florence training involves a series of short courses and demonstrations on an easy-to-use portal.
- Your dedicated trial team will be on hand to support sites with implementation.

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Site Activation and Green Light

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- Fully executed mNCA
- SIV Attendance Log
- PI signed protocol signature pages
- Site sampling choice page
- Completed delegation log (all site trial team listed and signed off by the PI)
- Signed and dated CVs and valid GCPs for all those listed on the delegation log
- Localised copies of all PIS/ICFs
- Lab normal ranges and accreditation certificates
- Staff Training (OpenClinica, SIV, Interventions)
- CCC from R&D

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PANTHER Team

UK Trial Management Contacts:

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