PANTHER

Confirming Eligibility

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Sponsor: Imperial College London

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Study Coordination Centre: Imperial Clinical Trials Unit

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Coordinating Centre / Trial Management Team

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Introduction to PANTHER

+ An international Phase II multicentre, open-label Bayesian adaptive multi-arm platform trial.

Research questions

In patients with ARDS with hyperinflammatory and hypoinflammatory phenotypes:

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

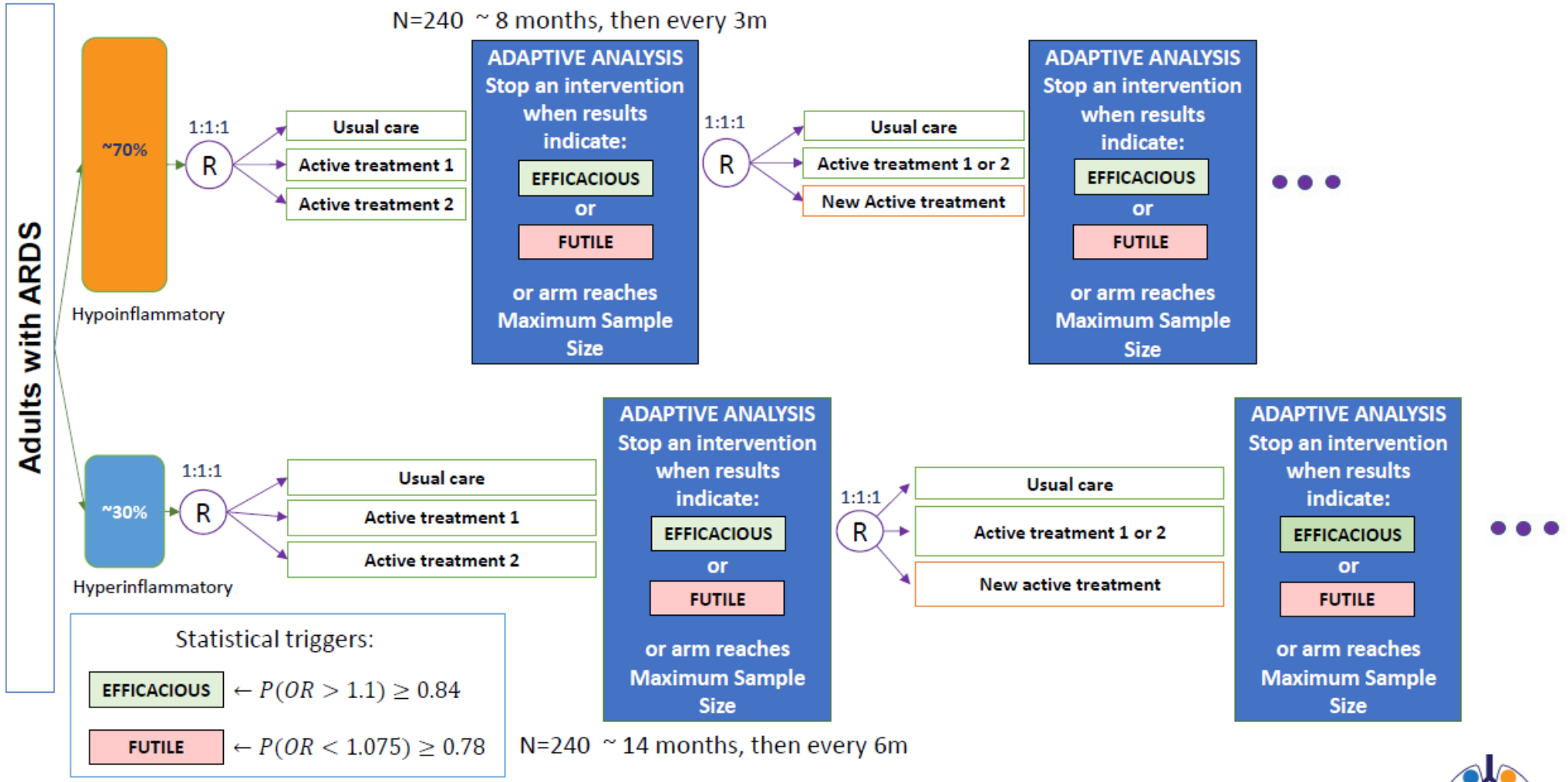
Confirming Eligibility

- As per MHRA requirements only a clinician is able to confirm whether a patient is eligible for the trial.
- The clinician confirming eligibility is required to be listed on the delegation log and must be listed on the Eligibility Check log so that the study has oversight of those clinicians who have received this training and are qualified to confirm eligibility.
- When eligibility is confirmed, this needs to be documented in the medical records.
- Please ensure a 'Eligibility Form' is completed for each eligible patient and filed in their medical records.

Study Design

Bayesian Adaptive Multi-Arm Trial design

Up to 2 active treatments recruiting in each subphenotype at any time



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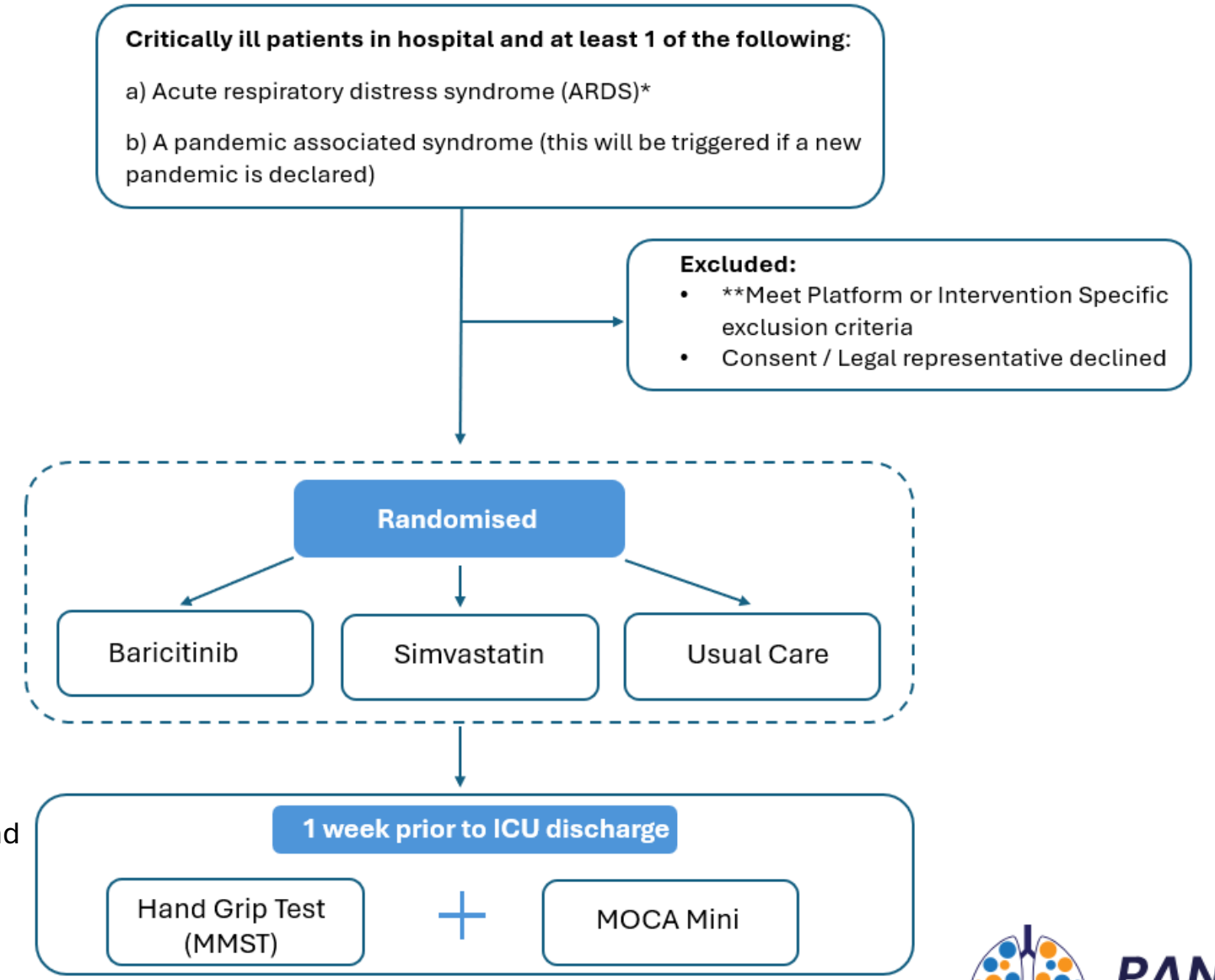
Study Flowchart



* Refer to Master Protocol for the definition of ARDS

**Refer to Master Protocol and Intervention Specific Appendices for full list

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Platform Inclusion Criteria

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

a) Acute respiratory distress syndrome (ARDS)*

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

*ARDS as defined by:-

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

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

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

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

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

Platform Exclusion Criteria

+ >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

Simvastatin - Exclusion criteria

- 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.

Baricitinib - Exclusion criteria

- 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

Good Clinical Practice (GCP)

- International, ethical and scientific quality standard to which all research involving human participants is conducted
- Comprised of 13 core principles & applies to all clinical investigations that could affect safety and well-being of human participants, providing international assurance that:
  - Data and reported results of clinical investigations are credible and accurate
  - Rights, safety and confidentiality of participants in clinical research are respected and protected
- You are encouraged to obtain GCP certification, such as that available through NIHR: https://www.nihr.ac.uk/health-and-care-professionals/learning-and-support/good-clinical-practice.htm

Principles of Good Clinical Practice (GCP)

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
4. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
6. A trial should be conducted in compliance with the protocol that has received prior Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) approval/favourable opinion.

Principles of Good Clinical Practice (GCP)

7. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task.
9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12. Investigational products should be manufactured, handled, and stored in accordance with applicable Good Manufacturing Practice(GMP). They should be used in accordance with the approved protocol.
13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.