1. **+Building an international precision medicine platform trial for the acute respiratory distress syndrome (ARDS)**

2. **Summary of Research (abstract)**

The acute respiratory distress syndrome (ARDS) is a heterogeneous clinical syndrome characterised by acute hypoxaemic respiratory failure. The “syndromic” definition of ARDS ignores the significant clinical and biological heterogeneity within ARDS. A novel precision medicine approach to identifying pharmacological treatments for ARDS, targeting ARDS phenotypes which are linked to the host biological response, is urgently required.

The objective of this application is to support the development of an international precision medicine platform trial aiming to efficiently test several pharmacological interventions in biological phenotypes in ARDS.

This will be achieved by undertaking a series of interlinked work packages which will aim to:
1) define the best approach to phenotyping patients and prioritising initial interventions to be tested.
2) develop the study design and draft platform trial core (master) protocol and analysis plan.
3) undertake collaborative work with international regulators, sponsors and funders to define their individual requirements in the delivery of a UK led platform trial.
4) Incorporate learning from existing platform trials.
5) build research capacity for clinical trial delivery.
6) engage with industry to develop pathways for testing novel agents and for sustainable funding.
7) develop a framework to embed biobanking globally within the platform trial.
8) ensure the patient and public voice is incorporated in every aspect of the trial design and execution.

This project will be delivered over a 12 month period by a world class team.

This project will establish the infrastructure to deliver an international precision medicine platform trial for ARDS.

3. **Background and rationale**

The acute respiratory distress syndrome (ARDS) is a heterogeneous clinical syndrome characterised by acute diffuse, inflammatory lung injury resulting in acute hypoxaemic respiratory failure due to non-cardiogenic pulmonary oedema (1). ARDS has significant global burden and high mortality. Consensus definitions for ARDS provided standardised recruitment to clinical trials and have led to the development of effective supportive therapies such as lung protective ventilation. However, this “syndromic” approach ignores the significant clinical and biological heterogeneity within ARDS which has contributed to the failure to date to translate pre-clinical research to effective therapies in patients with ARDS (2). Using the syndromic definition of ARDS does not provide information on which subgroups of patients are likely to respond effectively and safely to a given pharmacological treatment.

Much as oncology has moved towards treating patients based on tumour biology and linked biomarkers, a new paradigm in critical care suggests that de-emphasising syndromic definitions and focusing on phenotypes more closely linked to the host biological response is the key to identifying effective and safe therapeutics (3), which remains a significant area of unmet need. Considerable recent progress has been made towards identifying biological ARDS phenotypes that appear to respond differently to specific interventions in secondary analysis of completed randomised controlled trials (4-6). This application aims to design an adaptive platform trial which stratifies ARDS patients based on their biological phenotype, enabling a “precision medicine” approach to the pharmacological management of ARDS (7).

Proof of concept for ARDS biological phenotypes

In recent years, distinct subgroups (biological phenotypes) of patients with ARDS have been identified in multiple clinical trials and clinical cohorts. These phenotypes exhibit divergent clinical and biological characteristics and have different outcomes as well as differential responses to treatments (8). These phenotypes are largely distinguishable by inflammatory biomarkers, suggesting that patients with a specific phenotype may have a more homogeneous inflammatory response.

Although several methods of identifying biological phenotypes within critical illness syndromes have been reported (4, 9-15), the initial focus of this project will be on the “hyperinflammatory” and “hypoinflammatory” phenotypes first identified in ARDS by members of our research team (4). The project will focus on these phenotypes because they have been replicated in 8 separate cohorts with a high degree of concordance and appear to respond differently to several therapeutic interventions (5, 6). The hyperinflammatory phenotype is characterised by higher circulating levels of inflammatory markers (IL-6, IL-8, sTNFR1, and PAI-1), lower circulating protein C levels, vasopressor requirement and more metabolic acidosis. The hyperinflammatory phenotype is less prevalent than the hypoinflammatory phenotype (26-33% vs. 67-74%) but has significantly higher mortality (44-51% vs. 19-23%).

Treatments may have different effects within these phenotypes and may be more likely to improve outcomes in the hyperinflammatory phenotype with a higher mortality, although this hypothesis remains

unproven. In contrast treatment responsive phenotypes have also been reported in the less severely ill with lower mortality (16). Secondary analyses of several randomised controlled trials suggest these phenotypes respond differently to positive end-expiratory pressure (PEEP), fluid therapy, and simvastatin. Secondary analysis of observational data supported these findings for PEEP and also suggested differential response to corticosteroids in COVID-19 by phenotype (17). These data indicate that these phenotypes may represent useful targets for therapeutic trials.

Proof of concept that timely identification of ARDS phenotypes is feasible

Our team have worked with industry to help develop and validate a near-patient test to identify these biological phenotypes in ARDS in an Innovate-UK funded project. As a result, these phenotypes can now be accurately classified in real-time using this near-patient test, facilitating stratified randomisation in a precision medicine trial (18)(PHIND study; NCT04009330; unpublished data – see uploaded paper). Real-time identification of phenotypes is required to start therapies in patients who are critically ill with ARDS as soon as possible. As an alternative approach, clinical data may also be used in a machine learning analysis to identify the phenotypes (19). These potentially complementary approaches will be explored further in one of the work packages for this proposal (WP1).

Proof of concept for potential therapies.

The proposed trial design will enrol patients with both hyper- and hypo-inflammatory ARDS phenotypes, stratifying patients in real-time. While we have biological rationale to hypothesize that our current proposed treatments may be more effective in the hyperinflammatory phenotype, we also recognise that rather than being mutually exclusive classes, these phenotypes may partially overlap, especially when accounting for the dynamic illness trajectory of ARDS. Furthermore, though inflammatory markers are lower in the hypoinflammatory phenotype, they are nonetheless elevated compared with healthy states. We have therefore elected to enrol both phenotypes, specifically to acknowledge uncertainty about the optimal match between biological phenotype and pharmacotherapy, and to enable unanticipated insights to emerge. This approach was informed by successful adaptive platform trials in other conditions, including the ISPY2 study in breast cancer (20), and the PrecISE study in asthma (21) which have taken a similar approach.

Initially, we propose studying three treatments compared to standard care: these are simvastatin, tocilizumab, and infliximab.

Data from murine models (22), a human model of pulmonary inflammation induced by inhaled lipopolysaccharide (23), and an early phase RCT (24) supported the potential efficacy of simvastatin in ARDS. The EME funded HARP-2 trial however showed no benefit for simvastatin in an overall population of patients with ARDS (25). However, in a subsequent EME funded secondary retrospective analysis of HARP-2, patients with the hyperinflammatory phenotype demonstrated significantly higher 28-day survival when randomised to simvastatin, supporting the need to study simvastatin in a phenotype-stratified trial (5).

Tocilizumab is a monoclonal antibody that blocks the IL-6 receptor. Tocilizumab has been found to improve outcomes in critically-ill patients with COVID-19 by our team and others (26, 27). The rationale for its use in COVID-19 is through dampening of the IL-6 mediated inflammatory pathway, which is associated with disease severity and mortality (28, 29). There is strong rationale to test tocilizumab in a non-COVID ARDS population, as IL-6 levels in this group are 10 to 200 fold higher than levels in patients with severe COVID-19 ARDS, and plasma IL-6 concentrations strongly associate with ARDS mortality (30). Widely divergent levels of IL-6 in the hypoinflammatory and hyperinflammatory phenotypes would suggest that these groups may respond differently to tocilizumab, supporting its study in the proposed platform trial. Nonetheless, the overall beneficial effect of tocilizumab in severe COVID-19 pneumonia, a condition with a high rate of hypoinflammatory ARDS phenotype, provides rationale to test this agent in both hyper- and hypoinflammatory phenotypes (18).

Anti-TNF drugs, such as infliximab, are another class of drugs currently approved in immune-mediated inflammatory disease. TNF inhibition reduces neutrophilic inflammation in the human model of ARDS induced by inhaled lipopolysaccharide (31). Patients with sepsis (many of whom will have co-existing ARDS) and high IL-6 treated with anti-TNF therapy may have improved outcomes (32). Recent unpublished data from the National Institute for Health supported ACTIV-1 Immune Modulators clinical trial in patients with COVID-19 found infliximab improved time to recovery and mortality at 28 days, although these results were not statistically significant (33). Soluble TNF-receptor-1 levels in plasma are markedly higher in the hyperinflammatory ARDS phenotype than in the hypoinflammatory phenotype, indicating the potential importance of this pathway. Together these data provide supporting rationale to test infliximab in a phenotype-stratified trial in patients with ARDS.

4. Aims and objectives

The aim of this application is to support the development of an international precision medicine platform trial aiming to efficiently test several pharmacological interventions in hyperinflammatory and hypoinflammatory phenotypes in ARDS. The platform will be led by the UK, but will recruit internationally and involve collaboration with investigators in the United States, Canada, Ireland, the Netherlands, Germany, France, Italy, Japan and

Australia. We will also involve participants in low- and middle-income countries (LMICs). Our research team has the required networks to achieve this goal.

The objective of this project is to build an international platform trial which will build stronger collaboration to enable involvement of greater diversity of participants, avoid unnecessary duplication of efforts, and produce clinical evidence that is generalisable to a larger number of populations and places.

5. Research plan/methods

The aims of this Application Acceleration Award will be met by undertaking a number of work packages (WP) to develop a platform trial application for the planned funding call in May 2023. These WP are detailed below with the WP lead(s) although each WP will include broad representation from within the research team.

WP1: Defining study population and interventions [McAuley, Calfee]

The planned study population will be patients with hypoinflammatory and hyperinflammatory ARDS phenotypes. Phenotypes will be identified by point-of-care biomarker measurement (18)(PHIND study; NCT04009330; unpublished data – see uploaded paper). We will also explore if additional approaches to the identification of these biological phenotypes, using clinical data alone as previously described (19), are sufficiently robust to be used as an alternative to point-of-care biomarker measurement, as this approach could enhance generalisability.

We will establish an independent therapeutics prioritisation group which will include members of the study team that will discuss our proposed treatments, as well as review emerging evidence for alternative treatments and consider future treatments to be tested within the platform trial. This approach was used successfully during the COVID-19 pandemic for the UK national platform trials (34). The suggested treatments to be tested may be more likely to be effective in the hyperinflammatory phenotype (although this remains unproven). We recognise that this represents a smaller proportion of patients, albeit with the highest mortality. Therefore a priority for the therapeutics group will be to identify therapies with proof of concept data to indicate potential benefit in the hypoinflammatory phenotype to be tested in the platform trial.

In addition we will define expected current standard of care to be implemented at trial sites.

WP2: Study Design and Master protocol [Cornelius, Wheeler, Norrie]

The platform trial will compare intervention arms to a shared control arm. We will consider how additional stratification methods and intervention arms can be added over time and we will explore the use of response adaptive randomisation to maximise the number of patients exposed to the most effective treatments.

We will use a Bayesian approach for trial conduct and data analysis which requires significant modelling and simulation work in advance of commencing the trial to determine the rules for adaptation and target sample size. We will simulate the usefulness of response adaptive randomisation to improve trial efficiency. The pre-specified rules for interim analyses to allow stopping for futility, benefit or harm within phenotypes, and also for adapting randomisation ratios across treatments (35), will be developed through extensive simulation work and input from collaborators and stakeholders. Based on available proof of concept data for efficacy, we may define different stopping rules for futility in each phenotype. A hierarchical model will be used to examine treatment effects within phenotypes. The ability to adopt new stratification methods and new treatment options within the platform trial also need to be considered in our simulation work (36).

A trial design committee will be established, led by Cornelius, Wheeler, and Norrie. A full design summary, including operating characteristics from simulation studies, and a draft statistical analysis plan will be the key outputs from WP2. Another key output from WP2 will be to agree an appropriate primary outcome measure. As a starting point, we will propose to use respiratory support-free days at day 60, but will explore other outcome measures (37). This will consider clinician acceptability as well as patient and public views aligned with WP7.

There is an assumption that platform trials are more efficient in delivering answers to multiple research questions. As part of WP2, we will determine if methods to demonstrate the efficiency of platform studies compared to a series of individual efficacy trials can be embedded within the trial.

WP3: Understanding international regulatory/sponsor environment [Ferguson, Ichihara, Grasselli]

An ambitious international platform trial such as this will necessitate involvement of sponsors and regulatory authorities across multiple jurisdictions. WP3 will be led by investigators with experience in the conduct of large-scale interventional trials in critical care in their respective jurisdictions and interaction with regulatory bodies (38, 39). Within each participating jurisdiction, a nominated regional lead will be responsible for sponsor interaction and regulatory approval. Meetings will be held with sponsors and regulatory authorities to ensure all the requirements can be met for the regulatory approvals across multiple jurisdictions to be in place to deliver a start date for the trial in Q2 2024.

WP4: Developing international funding models [Marshall, Annane]

This trial will be led from the UK and funding for its oversight and its conduct in the UK will be sought from the EME programme. Funding in international jurisdictions will be sought through regional leads. WP4 will be led by Prof. Marshall (Canada) and Prof. Annane (France), who have a strong track record in funding trials within their jurisdictions and internationally. Prof. Marshall leads the InFACT collaboration, which is a platform to promote international collaboration in acute care research. A fundamental challenge in funding international trials involving multiple funders is the need for the trial to undergo assessment in multiple jurisdictions with the risk that different funding decisions might be made. A key aim of WP4 is to develop collaborative funding models through interfacing with funders in multiple jurisdictions to determine if it is possible to harmonise funding decisions. We will review current funding models used by international funders to support international collaborations, and engage with trialists who have undertaken international trials to understand challenges.

A key output from WP4 will be a guidance document on approaches to international partnered funding. Examples of this approach exist between NIHR and the Australian National Health and Medical Research Council, which will be used to develop this model of funding. This will address issues including the need for agreement on data ownership, data sharing, and intellectual property rights.

WP5: Learning from and integrating with existing platform trials [Gordon]

Prof. Gordon, with other members of our research team, continues to lead the REMAP-CAP trial in COVID-19, which is the most successful international critical care platform trial ever undertaken, having completed over 17,000 randomisations across 57 interventions at the time of writing of this application. This experience has provided invaluable insight into leading platform trials. For example, work on REMAP-CAP has improved our understanding of the methodological challenges with response-adaptive randomisation approaches and highlighted the need to include longer-term outcome measures and embedded tissue sampling in the study design. Experience from REMAP-CAP will also inform our approach to including participants in low- and middle-income countries. The I-SPY COVID trial (a phase 2 adaptive platform designed to simultaneously evaluate pharmacological therapies) (40), in which several members of our research team are involved, will provide additional opportunities for learning in relation to the conduct of our planned trial.

Much of the experience gained through the management of these platform trials will be immediately transferrable to this trial. This integration ensures we design a platform protocol that builds on the successes and learns from the pitfalls of previous platform trials. We will learn from this expertise to overcome barriers associated with obtaining regulatory approvals in different jurisdictions. This experience will also facilitate the production of draft collaboration, data management and intellectual property management agreements that meets individual international regulatory, sponsor and funder requirements (aligned with **WP3** and **WP4**).

A key outcome from WP5 will be a series of standard operating procedures for trial delivery.

WP6: Building capacity [Bos, Reddy]

The success of an ambitious trial such as this depends on the co-operation of numerous clinical sites and investigators across regions. The establishment of a large international team of researchers to deliver this trial is essential. WP6 will be led by Dr. Bos and Dr. Reddy. The key aims of WP6 are to build research capacity through engagement with early career researchers to participate in research, including within LMICs, as well as to enhance diversity within the research team. To achieve these aims a complimentary application to fund clinical research fellows in different jurisdictions will be developed. Through participation in the trial management, these clinical research fellows will develop clinical trial management skills. The aim will be to build international capacity for the delivery of clinical trials. WP6 will also establish agreements for recognition of academic contributions to ensure investigator participation is recognised appropriately.

WP7: Engaging with industry [Fowler]

Platform trials aim to improve the efficiency of the drug development process, which is attractive to industry. However, there are some key challenges to be addressed with regards to engaging with industry and meeting industry needs in a platform trial design.

This trial will necessitate multiple sponsors across jurisdictions. Defining how an industry partner can operate in this framework will be critical. This may, for example, necessitate a governance committee including representatives from all sponsors and key stakeholders.

High quality data in the required format is fundamental for a successful drug registration. Considerable resources need to be applied to ensure data compatibility, quality, completeness, and readiness for inspection. A key aim of WP7 will be to define the standards for collecting data in an external database in an adaptive platform trial design. Experts in data management, statistical programming, biostatistics and quality will be engaged as needed.

Platform studies in which there may be multiple stakeholders result in complexity to the pharmacovigilance efforts. A standard procedure to ensure prompt reporting of adverse events and appropriate assignment of

causality will be defined. To address this, experts in safety and pharmacovigilance will be engaged to provide feedback on plans for safety reporting.

An appropriate balance between platform trial conduct and the commercialisation considerations that are relevant to industry partners including data access and IP will need to be maintained. An approach to supply agreements between multiple partners will also need to be considered.

Key outcomes from WP7 will be a draft industrial collaboration agreement as well as a series of standard operating procedures for industrial collaboration.

WP8: Biobanking [O'Kane]

A key element of this platform trial will be the integration of tissue sampling. These samples may include plasma, peripheral blood mononuclear cells, whole blood RNA, whole blood DNA, tracheal aspirate, bronchoalveolar lavage fluid, and urine. Samples will be collected at multiple timepoints (and biobanked). These samples will be used to investigate the mechanisms by which phenotypes may exhibit differential response to randomised treatments. Prof O'Kane will lead WP8 and has extensive experience in embedding tissue sampling in clinical trials. A key output from WP8 will be to develop a sampling management guideline for trial sites as well as establish a standard operating procedure for a centralised biobank. An agreement for sample sharing will also be established.

WP9: Patient and Public Involvement (PPI) and Equality, Diversity, and Inclusion (EDI) [Williams, Nichol]

The application of precision medicine is novel in the context of care of the critically ill patient. To date public and patient opinions regarding precision medicine in the critically ill have not been systematically assessed but it is necessary to understand patient/public views of precision medicine given they represent the central stakeholders for this programme of work. We have extensive experience in public, patient and relative engagement in influenza and COVID-19, which are common causes of ARDS (41-43). We conducted a systematic review of consent models (41), conducted focus groups (42) and completed an international survey in 8 countries (6800 respondents, including the UK) (43). These results demonstrated public acceptance of critical care research, very high levels of satisfaction of the current models of consent used for trials in the ICU, and acceptability of taking biological samples for future use.

Our established PPI network includes representatives from all participating regions in this application and is chaired by Prof Nichol and our PPI co-applicant Mr Barry Williams. In addition, we have established an international network of public patient panels to provide ongoing advice, input and tailoring of all aspects of trial design, patient facing trial documents and public/patient accessible trial results documents.

As part of WP9 we will establish a critical care precision medicine PPI and EDI working group with patient, public and investigator representation for all participating regions. To inform the conduct of the platform trial, we will conduct systematic reviews of public and patient views on consent processes and methods to enhance diversity in trials recruiting critically ill patients. We will also undertake a survey of public attitudes to precision medicine in the critically ill (including current understanding, consent models, methods to enhance diversity, optimal outcome measure, use of data and samples for future use and prioritisation of potential trial interventions). Finally we will ask our PPI network to actively contribute to the prioritisation of therapies to be tested within the platform trial as well as inform the selection of the primary outcome for the trial. Our PPI group will also review patient/public relevant sections of the trial protocol and public-facing trial materials.

WP10: Understanding international in-vitro diagnostic regulatory environment [Shankar-Hari]

The proposed trial will initially use a near-patient diagnostic test to stratify patients to the hyperinflammatory and hypoinflammatory phenotypes. Understanding the regulatory framework for the in vitro diagnostic tests across multiple jurisdictions will therefore be critical to the delivery of this trial. Meetings will be held with regulatory authorities to ensure all the requirements for the regulatory approvals across multiple jurisdictions can be achieved to deliver a start date for the trial in Q2 2024.

Overall project deliverables

Finally, a key deliverable from the project will be a draft platform trial core (master) protocol that may be followed across collaborating centres, is acceptable to all stakeholders, and is robust to international differences in research environments. This protocol will inform the development of a stage 1 application to be submitted to the subsequent platform grant call in May 2023, which will be another key deliverable. This protocol will be developed at up to 2 face-to-face investigator meetings. Although many of the investigators already actively collaborate, an additional aim of these investigator meetings will be to further develop our research network to support the delivery of the platform trial.

6. Dissemination, outputs and anticipated impact

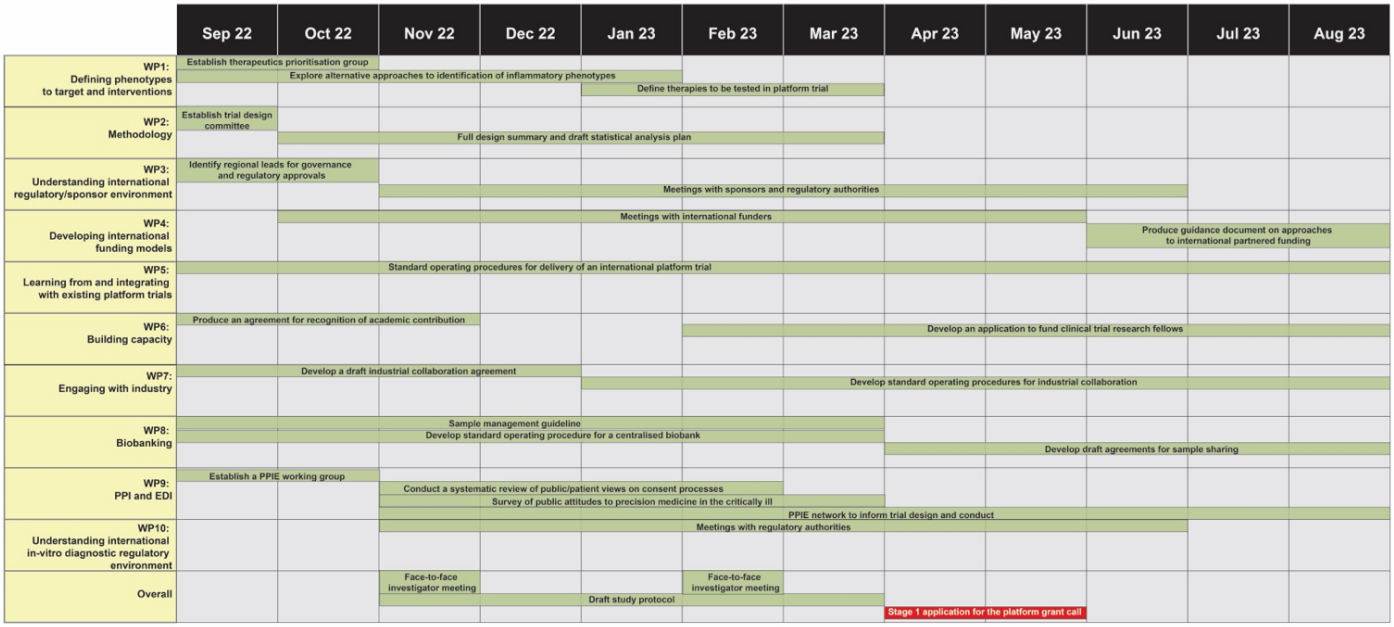
Dissemination will take multiple routes including publication in international journals, presentation at relevant national and international conferences, communication with participant and family networks as well as through social media and the lay press. Learning from this project will be shared as a template for future precision medicine trials in critical care.

The development of effective treatments in ARDS has been hampered by a broad syndromic definition. Our team's paradigm-shifting description of phenotypes, clinical trial experience, and experience in global collaboration allow us to finally deliver the promise of precision medicine in ARDS.

This project will determine if a precision medicine approach in ARDS can increase trial efficiency and deliver effective treatments to a cohort of patients with high unmet healthcare needs, reducing death, disability and healthcare costs, and in the process will also develop a ground-breaking template for future precision medicine trials in critical care. Treatments which are found to be efficacious in this platform trial will subsequently be tested in a clinical effectiveness trial, either as a stand-alone phase 3 trial or as part of a phase 3 platform trial.

An important additional impact of this platform trial is that it could be rapidly re-purposed to test potential therapies in the event of a future pandemic of a respiratory pathogen associated with severe respiratory failure.

7. Project/research timetable



8. Project management

The project will be coordinated by the UKCRC registered Imperial Clinical Trials Unit (ICTU) (https://www.imperial.ac.uk/clinical-trials-unit/), which has a track record of successfully delivering large scale ICU trials. The ICTU Director, Professor Victoria Cornelius, is a co-applicant.

A Project Management Group will be established which will be chaired by McAuley and include co-applicants to oversee the management of the work packages. The management group will meet on a monthly basis and WP leads will provide updates on progress. Communication between meetings will be via telephone and email as needed. The project manager will manage the day-to-day project activity and be a single dissemination point for project communications between WPs.

9. Ethics/regulatory approvals

None of the activities in the planned work packages require Ethics or regulatory approvals

10. Project/research expertise

The research team's expertise in clinical trials in ARDS, phenotyping in the critically ill, international collaboration and trials methodology (evident in their submitted CVs), means we are uniquely placed to deliver an international precision medicine platform trial in ARDS. In addition to the named co-applicants, a broader group of co-investigators (Mary Cross, Operational Manager Imperial Clinical Trials Unit; Dr Matthew Rowland, Novartis; Dr Pratik Sinha, Washington University School of Medicine in St. Louis; Dr Nuala Meyer, University of Pennsylvania; Professor Djillali Annane, Université Paris Saclay – UVSQ; Dr David Maslove, Queen's University Ontario; Professor Shigeki Fujitani and Dr Hiroki Saito, St. Marianna University; Mr. Barry Williams, PPI Representative) have made substantial contributions to the proposal and are committed to supporting this project.