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Research Article

Building an international precision medicine platform trial for the acute respiratory distress syndrome (ARDS): an expert consensus project report

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Abstract

Background: Almost all large-scale trials of disease-modifying therapeutic agents in critical care have failed to show benefit for patients, which may be explained in part by the clinical and biological heterogeneity inherent in virtually all critical illness syndromes. Enrichment strategies have been developed to separate responders from non-responders and better target treatments. In patients with the acute respiratory distress syndrome, a critical illness syndrome involving severe lung inflammation, latent class analysis and other clustering approaches have led to the discovery of

subgroups (phenotypes) that appear to respond differently to treatment based on retrospective analyses of published clinical trials and observational cohorts. The next step is to test these phenotypes in a prospective trial. Rapid, point-of-care analytical methods have now made such a trial possible. There is a need to advance treatment for patients with acute respiratory distress syndrome and other critical illness syndromes by incorporating a phenotype-based approach into prospective trial design. The hyperinflammatory and hypoinflammatory phenotypes, that have been identified in acute respiratory distress syndrome, will be the first to be included in such a trial, with scope for further phenotypes to be studied over time.

Future work: This Efficacy and Mechanism Evaluation report, through expert consensus, describes a new Phase II, multiarm, adaptive platform randomised controlled trial design that tests multiple pharmacological therapies in a population of patients with acute respiratory distress syndrome stratified by baseline inflammatory phenotype. This report also reviews issues to be considered in developing precision medicine trials in critical care, which are designed with newly developed clinical phenotypes in mind. This work has been used to develop the Precision medicine Adaptive Network platform Trial in Hypoxaemic acutE respiratory failuRe precision medicine trial in acute respiratory distress syndrome, which has been funded and will begin recruitment in June 2025.

Limitations: This report is the result of expert consensus review, rather than utilising strict review methodologies (e.g. Delphi consensus process). However, expert consensus has been found to generate similar results to consensus processes when a high degree of agreement is reached and > 70% agreement was reached for all included recommendations.

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Introduction

A significant challenge to developing new therapies in critical care medicine is the heterogeneity of the intensive care population.[1] Critical care medicine includes several syndromes defined by signs, symptoms and physiological measurements that are observable at the bedside but lack unifying biological pathways. Acute respiratory distress syndrome (ARDS) is a prominent example, which is a syndrome of uncontrolled lung inflammation that affects approximately 10% of the intensive care population, has no direct pharmacological treatment options (aside from the population with concurrent COVID-19 pneumonia) and carries a very high mortality rate of approximately 35–45%, depending on the patient population.[2]

Attempts to discover a unifying hypothesis for ARDS biology have been unsuccessful, which has inhibited the development of successful treatments.[3] An approach that acknowledges the heterogeneity of ARDS patients is likely to be more effective.[4] Clinical heterogeneity in ARDS can be subdivided into heterogeneity based on aetiology, patient factors, imaging and treatments.[5] In the original publication describing ARDS, Ashbaugh *et al.*[6] recognised aetiology-based heterogeneity, identifying multiple causative disease processes, including pneumonia, aspiration, pancreatitis and trauma. The recognition of aetiology-based heterogeneity has led to attempts to reclassify ARDS into 'indirect' and 'direct' ARDS, with direct ARDS being classified as damage resulting from a local lung injury and indirect ARDS occurring in systemic disorders that cause diffuse endothelial damage.[7] Patient heterogeneity in ARDS is also evident. Patients differ in age and also vary significantly with respect to underlying comorbidities.[8] ARDS has also been subdivided by the appearance on chest radiographs and computerised tomography (CT) (imaging heterogeneity), with supportive ventilation strategies tailored to 'focal' and 'non-focal' ARDS, as investigated in a large French trial.[9] Treatment-based heterogeneity refers to explainable variation in response to a specific therapy in a population of patients with a unifying clinical syndrome, such as ARDS. For example, prone positioning benefits patients with moderate-to-severe ARDS,[10] whereas the risks outweigh the treatment benefits in patients with mild ARDS.[11] Personalised ventilation strategies have been proposed to address treatment heterogeneity related to ventilatory support in ARDS.[12]

However, focusing solely on clinical heterogeneity in ARDS may be too limited because current syndromic definitions are not based on a firm understanding of underlying biology. As the biological understanding of ARDS and other critical care syndromes has advanced, it is has become increasingly evident that clinical syndromic definitions are inadequate to describe underlying heterogeneity.[1] This may be why many large randomised controlled trials (RCTs) in critical care medicine have not shown benefit despite promising preclinical or early phase signals.[13] Major advances must be based on a better understanding of underlying pathophysiology and the heterogeneity of biological events in patient populations. Trials that recruit patients based on

syndromic definitions often include a heterogeneous mix of eventual responders, non-responders and patients who experience harm from treatment and may result in a net signal for lack of treatment efficacy when in fact, there may be subgroups who respond.[5,14] The overall result is termed as 'heterogeneity of treatment effect' (HTE).

Population enrichment methods are an important tool for addressing this problem.[15,16] One method, prognostic enrichment, involves selecting a population at higher risk for an outcome of interest, such as mortality, thereby increasing the statistical power to detect benefit in a trial by increasing the absolute event rate.[17–19] Using prognostic enrichment, a trial might selectively recruit a more severe subgroup of a disease/syndrome that is at greater risk for mortality, anticipating that the reduction in mortality due to treatment will be more pronounced in this selected population with a higher baseline risk of death. This approach was taken in the Prone Position in Severe Acute Respiratory Distress Syndrome trial of prone positioning,[10] as well as the Reevaluation of Systemic Early Neuromuscular Blockade and Acute Respiratory Distress Syndrome et Curarisation Systematique trials of neuromuscular blockade,[20,21] where only populations of patients with a ratio of partial pressure of arterial oxygen to fractional inspired oxygen (PaO_2/FiO_2 ratio) of < 150 mmHg (indicating moderate-to-severe ARDS) were recruited. These prognostic enrichment approaches focused on clinical heterogeneity defined by oxygenation criteria rather than biological heterogeneity.

Predictive enrichment is an alternative approach that can be based on clinical[22] or biological heterogeneity, particularly when a proposed pathway has been identified for a new drug candidate. In the latter case, predictive enrichment involves selecting a subpopulation most likely to benefit from treatment when a marker of pathway activation can be measured at baseline[16,19] [e.g. measurement of baseline interleukin-6 (IL-6) to guide treatment with IL-6 receptor antagonists[23]]. Predictive enrichment differs from prognostic enrichment in that it relies on a supposed pathophysiological difference between the enriched population and the broader population that is targetable by the treatment of interest in the trial. Since the mechanisms underpinning critical illness syndromes remain incompletely understood, fewer examples of predictive enrichment based on biology exist. In one trial of endotoxin haemadsorption in septic shock, a predictive enrichment strategy was employed wherein only patients with high levels of circulating bacterial endotoxin were recruited.[24] Interestingly, while this trial showed no overall benefit, evidence of HTE was found in an unplanned secondary analysis.[25] In asthma research, predictive enrichment strategies have been successfully used to enrol and treat patients with type 2 inflammation with specific inhibitors of interleukin-5- and interleukin-4/-13-dependent pathways, including mepolizumab, benralizumab and dupilumab.[26–28] Adopting successful research paradigms from other fields, such as respiratory medicine and oncology, may help design predictive enrichment in critical care.[4]

Predictive enrichment and prognostic enrichment may not always align. For example, while patients in a more severe clinical subgroup might be predicted to respond to treatment better due to a greater risk of poor outcome, this may not always be the case. In a secondary analysis of a trial of vasopressin versus noradrenaline in septic shock,[29] vasopressin lowered mortality only in the less severe group with serum/plasma lactate ≤ 2 mmol/l. This beneficial effect was not observed in patients with higher serum/plasma lactate levels, suggesting a clinical 'point of no return' for the beneficial effects of vasopressin.[30] A similar phenomenon has also been observed in trials of heparin in COVID-19 and oesophageal pressure manometry-guided ventilation strategies.[22,31]

Major advancements have been made in identifying phenotypes of critical illness syndromes with differential mortality and differential responses to treatment, providing a step towards predictive enrichment.[4] In ARDS, the hypoinflammatory and hyperinflammatory phenotypes have been identified and replicated in several retrospective analyses of large interventional trials,[32–35] with highly conserved prevalence (67–74% vs. 26–33%, respectively), mortality (19–23% vs. 44–51%, respectively) and signals suggesting HTE for ventilation strategy,[32] fluid administration strategy[33] and simvastatin therapy.[34] These phenotypes have been reproduced in paediatric ARDS,[36] ARDS due to COVID-19,[37] the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE) multinational observational cohort of ARDS[38] and in a population of patients at risk for, but without ARDS.[39] In addition, uninflamed and reactive ARDS phenotypes have been described using hierarchical clustering methods on biomarker data from prospective cohort studies,[40–42] with a signal for HTE with low-dose macrolide therapy.[41] The hypoinflammatory/hyperinflammatory phenotypes and the uninflamed/reactive phenotypes were replicated in a large secondary analysis of 2499 mechanically ventilated patients with or without ARDS, demonstrating that they exist in a broader population of patients without ARDS and that the two phenotyping schemas identify approximately similar populations.[43] In COVID-19, the hyperinflammatory and hypoinflammatory phenotypes

of ARDS have been identified[44] as well as three novel phenotypes (also defined by inflammatory biomarkers) with differential responses to convalescent plasma.[45]

Multiple phenotypes have also been identified in sepsis populations, as reviewed elsewhere.[4] Phenotypes of paediatric and adult sepsis with different incidences of ARDS and clinical outcomes have been described,[46–55] although most of these identification approaches have used transcriptomic analysis rather than the clinical laboratory-based and protein-based detection methods used in ARDS.

Current disease paradigms do not adequately capture the biological complexity of ARDS and other critical illness syndromes.[1,56] Improving how we understand disease and treat patients will require a 'new age' of trial design in critical care medicine focused on precise subclassification of syndromes by underlying biology and treating these subclasses with targeted pharmacological therapies. This will require considerable rethinking of the ways that we define disease processes and the ways that we design interventional trials. International platform trials, successful in the COVID-19 pandemic, are a promising new approach.[57] These designs could be incorporated with emerging technologies that allow 'real-time' phenotyping at the point of selection or randomisation in clinical trials, thereby leveraging phenotypes for predictive enrichment. However, many questions remain about the underlying biological mechanisms of ARDS phenotypes. While HTE might suggest a conserved mechanism within a given phenotype, prospective confirmatory studies have yet to be reported, and mechanistic work remains to be done.[42,58] HTE is likely a multidimensional problem, and no single phenotyping system is likely to be the answer. Further, at the highest level of resolution, each individual patient represents their own phenotype, and as such, trial insights into precision medicine are limited by the number of patients recruited and available resources. Despite this limitation, along with the cycle of thorough and robust data exploration and validation, new innovative trial designs may allow new information to be leveraged as it comes to light. Although several barriers must be addressed before such trials become possible,[4] phenotype-stratified precision medicine trials in critical care medicine should soon become a reality.

Report of the National Institute for Health and Care Research accelerator award

The National Institute for Health and Care Research (NIHR) has awarded an 'Accelerator Award' for a project designed to develop and implement a new platform trial in ARDS, leading to the preparation of this report. The trial is now funded and is in setup phase, and it has been designated as the Precision medicine Adaptive Network platform Trial in Hypoxaemic acutE respiratory failuRe (PANTHER) trial. The aim of this project is to develop treatments for patients with ARDS and acute hypoxaemic respiratory failure (AHRF) by incorporating a phenotype-based approach. The project aims to design an international precision medicine trial in ARDS through expert discussion and consensus, which includes real-time phenotyping, biological insights into treatment efficacy and mechanisms and learnings from the COVID-19 pandemic. Here, we present a summary of the issues considered and corresponding recommendations based on expert consensus and review of recent literature. We also present *Table 1*, which outlines the work packages and deliverables described in the protocol for this project (NIHR154493). Within the text, we then reference these deliverables and work packages in *italics* to demonstrate completion and relevance to the discussion. As aforementioned, the PANTHER trial is now funded (*overall deliverable 2*).

Defining the phenotypes of interest

Evidence for HTE has been identified in secondary analyses describing the hyper-/hypoinflammatory phenotypes of ARDS,[32–34] the uninflamed/reactive phenotypes of ARDS[41] and sepsis phenotypes.[48,52] Similar phenotypes have also been identified in septic acute kidney injury.[59] While simplified classification models have been developed for these phenotyping approaches that use either a limited set of protein measurements or gene transcripts,[40,47,48,50-52,60,61] all have yet to be fully tested in a prospective cohort study using a device that can provide results on an individual patient basis in a clinically meaningful timeframe. The hyper-/hypoinflammatory phenotypes initially identified in ARDS will be the first to be tested in the Clinical Evaluation of a Point of Care Assay to Identify Phenotypes in the Acute Respiratory Distress Syndrome (PHIND, NCT04009330) study, which completed recruitment in October 2023, and emerging data from the I-SPY SPARK study also support the feasibility of rapidly identifying these phenotypes in critically ill patients.[62] Rapid identification of sepsis phenotypes should follow, with the Immune Profiling of ICU Patients to Address Chronic Critical Illness and Ensure Healthy Ageing study (ISRCTN11364482), which has been recruiting participants using a multiplex polymerase chain reaction assay to identify participant immune profiles prospectively.

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TABLE 1 Work packages and deliverables outlined in the protocol (NIHR154493)

Work package	Deliverable
WP1: Defining study population and interventions	1. Explore if clinical data alone are sufficiently robust to be used as an alternative to a point-of-care assay for phenotyping 2. Establish an independent therapeutics prioritisation group 3. Define the expected current standard of care to be implemented at trial sites
WP2: Study design and master protocol	1. Consider how additional stratification methods and intervention arms can be added over time 2. Explore the use of RAR 3. Conduct simulations to inform trial design 4. Define prespecified rules for interim analyses to allow stopping for futility, benefit or harm 5. Establish a trial design committee 6. Draft a statistical analysis plan 7. Agree an appropriate primary outcome measure 8. Determine if the methods used 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	1. Establish nominated regional leads for sponsor interaction and regulatory approval 2. Hold meetings with sponsors and regulatory authorities to ensure that all requirements can be met for regulatory approvals across multiple jurisdictions
WP4: Developing international funding models	1. Seek funding through regional leads 2. Develop collaborative funding models through interfacing with funders in multiple jurisdictions 3. Develop a guidance document on approaches to international partnered funding
WP5: Learning from and integrating with existing platform trials	1. Develop a series of standard operating procedures for trial delivery
WP6: Building capacity	1. Build research capacity through engagement with early career researchers 2. Establish agreements for recognition of academic contributions to ensure investigator participation is recognised appropriately
WP7: Engaging with industry	1. Define the standards for collecting data in an external database in an adaptive platform trial 2. Develop a standard procedure to ensure prompt reporting of AEs 3. Draft an industrial collaboration agreement
WP8: Biobanking	1. Develop a sample management guideline for trial sites 2. Establish a standard operating procedure for a centralised biobank 3. Develop an agreement for sample sharing
WP9: PPI and EDI	1. Establish a critical care precision medicine PPI and EDI working groups 2. Conduct systematic reviews of public and patient views on consent processes and methods to enhance diversity in trials 3. Conduct a survey of public attitudes to precision medicine in the critically ill 4. Ask PPI network to actively contribute to the prioritisation of therapies and review trial protocol and public-facing materials
WP10: Understanding international in vitro diagnostic regulatory environment	1. Hold meetings with regulatory authorities to ensure that all the requirements for regulatory approvals across multiple jurisdictions can be achieved
Overall deliverables	1. Draft platform trial core protocol 2. Develop application to platform grant call 3. Further develop our research network to support delivery of the trial

AE, adverse event; EDI, equality, diversity, and inclusion; PPI, patient and public involvement; RAR, response-adaptive randomisation.

'Real-time' classification models

Phenotyping patients in acute care trials carries significant challenges compared to other medical research fields. In oncology, tumour markers can be extensively categorised in days to weeks and can guide treatment choices in otherwise stable patients. In critical care medicine, phenotyping must be accomplished rapidly (e.g. in hours), limiting the available technologies.

A major barrier to operationalising the prospective use of ARDS phenotypes is the complexity of the models used to identify them. The hyperinflammatory and

hypoinflammatory phenotypes of ARDS have been identified using latent class analysis (LCA) of a mix of 20–30 clinical parameters combined with plasma markers of inflammation that are not routinely collected in clinical practice [e.g. IL-6, interleukin-8 (IL-8), soluble tumour necrosis factor receptor 1 (sTNFR1) and plasminogen activator inactivator-1)].[32–35,37] LCA is a finite mixture modelling algorithm that assumes that a data distribution comprises two or more hidden ('latent') distinct classes, or phenotypes.[63] While there is some variation depending on the degree of separation of the classes, to be confident that the LCA output is stable, the data subjected to modelling should have a sample size of > 300 subjects.[64] LCA also requires the input data to be normalised and scaled to the population mean,[63] and therefore an individual patient cannot be assigned to a phenotype without knowledge of the overall population distribution. The size of the data set required and the relative inaccessibility of biomarker measurements in the acute clinical setting currently limit this technique to retrospective analyses. The problems with this ARDS phenotyping paradigm are threefold: several specialised assays are required, the classification model is cumbersome and the model requires knowledge of the distribution of discriminant parameters based on the sample population, which is impossible in a prospective trial.

To deal with these problems, two models have been developed: simplified (parsimonious) logistic regression models using point-of-care biomarker measurements[60] and machine learning models employing readily available clinical data.[65] Both approaches have been developed using data sets comprised of thousands of patients from interventional trials in ARDS conducted in the USA, the UK and Ireland. These predictive models should be robust for use in prospective trials conducted in North America and Europe, and prospective confirmation in the PHIND study (NCT04009330) was in progress at the time of the NIHR Accelerator Award. The biomarker measurement and clinical data-based approaches have strengths and weaknesses. For ARDS phenotypes, the former requires rapid measurement of sTNFR1 and either IL-6 or IL-8, which can be combined, in parsimonious regression models, with the bicarbonate value from an arterial blood gas measurement to produce a probability of allocation to the hyperinflammatory phenotype.[60] Data on vasopressor use or plasma/serum protein C measurements can be added to the model to improve performance. For this approach, real-time measurement of plasma cytokine concentrations can be accomplished using multiplex assay systems such as the immunoanalyser device (Randox multiSTAT, Randox Laboratories, Co., Antrim, Northern Ireland) employed in the PHIND study (NCT04009330). The advantage of this approach is that an objective, quality-controlled analyser is used to measure cytokines in real time. Increases in cytokine concentration or decreases in bicarbonate cause a concomitant measurable increase in the probability of allocation to the hyperinflammatory phenotype, lending face validity. Protein biomarkers may be essential to clustering methods that identify HTE, and information may be lost by adopting models that focus only on clinical variables.[66] The downside of a protein-based approach is that expensive equipment is currently required, which may limit use in low- and middle-income countries (LMICs). A further limitation is the collinearity of cytokines used for this method, such as IL-6 and sTNFR1; introducing more protein measurements that link to different biological pathways could potentially identify more phenotypic variations.

An alternative approach to the prospective identification of clinically relevant phenotypes of ARDS uses a machine learning classifier algorithm and 24 routinely collected clinical variables.[65] The lack of additional equipment required for this approach is an important advantage. However, it remains dependent on high-quality data and selecting the 'worst' clinical data point on a given day (e.g. the lowest bicarbonate or the highest bilirubin). The output can be inaccurate if clinicians use the wrong data in the model. Furthermore, this approach for phenotyping may be slower than a cytokine-based approach in a prospective application. The necessary laboratory investigations (e.g. white blood cell count, albumin and others) may not be available in the emergency department when initial treatment decisions are made. Vasopressor use, another necessary component of the clinical classifier model, might not be initiated until intensive care unit (ICU) admission. Based on these concerns, at least initially, phenotyping by baseline cytokine measurements may be preferable (*WP1; deliverable 1*).

Temporal stability of classification models

Temporal trends in phenotype allocation are important for stratified precision medicine trial design. The hyperinflammatory and hypoinflammatory phenotypes initially described in ARDS are stable from baseline to day 3 of trial enrolment by latent transition analysis,[67] though absolute cytokine values at day 3 may differ from the baseline for individual patients. Due to this, classification models that were trained on baseline data may not perform similarly at later times. Over time, patients with the hyperinflammatory phenotype who survive might eventually transition to the lower-risk hypoinflammatory phenotype, or vice versa. Stability data beyond day 3 do not yet exist, and the time and speed of transition between phenotypes remain unknown. In the future, with

improved data, phenotype transition could be used as a surrogate outcome measure, but for the time being, early phenotyping for clinical trial enrolment is an important focus of research.

Setting the threshold for classification models

Simplified logistic regression models developed to identify ARDS phenotypes do not generate a binary class allocation but rather a numerical probability of class allocation, which is then converted to a class allocation through use of a threshold value.[60] It is also increasingly apparent that ARDS phenotypes do not necessarily form distinct categories but rather may represent points on a continuum.[68] Nevertheless, logistic regression models can be used to create a binary allocation model that is sufficient for use in a precision medicine trial, though a certain degree of subjectivity is required when choosing the optimal threshold on which to separate phenotypes. Traditionally, in parsimonious models developed for ARDS stratification, a threshold probability of 0.5 has been used, with patients above or below this threshold being allocated to the hyperinflammatory or hypoinflammatory phenotypes, respectively.[60] It is possible that this is not the optimal threshold, and as an alternative, a Youden index-derived threshold developed to maximise sensitivity for the hyperinflammatory phenotype has also been used.[44,60] Regardless of the threshold chosen, there will always be patients who fall close to the threshold and have a somewhat 'indeterminate' phenotype allocation. These patients should get careful consideration in any trial design employing regression modelling for phenotype allocation, as there is the potential for misallocation for randomised treatment. Perfect diagnostic tests for phenotyping do not exist,[69] and some patients will always be misallocated in any phenotyping approach.

Though, perhaps, not truly representative of the underlying biology, dichotomisation may be necessary to use ARDS phenotypes in a clinical trial. In such a trial, setting the threshold for phenotype allocation based on the treatment of interest would be rational. For example, a high-risk treatment that is perceived to benefit a particular phenotype preferentially could be assigned to a group defined by a highly specific threshold, thus minimising potential harm in misallocated patients. Conversely, a low-risk treatment could be allocated more broadly based using a more sensitive threshold. These threshold adjustments will influence power calculations in trial design. With a highly specific threshold, a greater treatment effect is expected but at the cost of a smaller available patient population for trial recruitment.

At this stage of stratified critical care trial design, the biology underpinning ARDS phenotypes is not completely understood, nor is the effect of varying detection thresholds on statistical power. These limitations make selecting an optimal dichotomisation threshold for ARDS phenotypes difficult. Trial designs have been proposed, which incorporate the optimisation of biomarker detection thresholds alongside therapeutic efficacy tests, called as adaptive signature designs.[70–72] One such methodology has been used in oncology, in melanoma-associated antigen 3 positive stage III melanoma, in which the first-third of patients recruited to the trial were used as a training set to develop classifier models, which were then validated on the remaining two-thirds of patients recruited to the trial after analysis of the primary outcome measure.[73] The feasibility of such a trial design for critical care medicine is an important question for future research.

Defining the population

Phenotypes in a broader population

Phenotypes initially identified in ARDS have also been described in a broader population of mechanically ventilated patients,[43] a population at risk for but without ARDS[39] and a sepsis population.[55,74,75] These data suggest that the hyperinflammatory and hypoinflammatory phenotypes are not limited to the population meeting the Berlin definition of ARDS.[76] Sepsis phenotypes are relevant for the ARDS population, as the initial evidence for Sepsis Response Signature 1 and 2 phenotypes came from a population of patients with community-acquired pneumonia,[50] which comprises the majority of patients with ARDS.[2] If phenotypes are present across various clinical syndromes and are found to be informative for the choice of clinical treatments, it will be appropriate to focus on combining the understanding of biological phenotypes with syndromic definitions.

Difficulty with clinical definitions

The Berlin definition of ARDS[76] and the Sepsis-3 definition[77] do not fully capture the underlying complexity of the syndromes they aim to define.[18,78] Diffuse alveolar damage (DAD) is considered to be the histological correlate of ARDS, but less than half of patients with ARDS have DAD on lung biopsy.[79] In a meta-analysis, the fraction of patients with DAD and ARDS had a pooled odds ratio (OR) for mortality of 1.81 [95% confidence interval (CI) 1.14 to 2.86] compared to patients with ARDS without DAD.[79] Though the proportion of patients with DAD increases to 58% when examining the autopsies of patients with severe ARDS,[80] there is still a disconnection between the clinical diagnosis of ARDS and post-mortem histology in

the lungs, in large part, because histology is not available at the onset of ARDS. The relationship between the clinical severity of ARDS and pathophysiological processes is likely to be even more complex.

Modifications to the widely used Berlin definition of ARDS (the 'global definition of ARDS') have been proposed to recognize new trends in supportive treatment and difficulties in diagnosing ARDS in resource-limited settings.[81] To make a diagnosis of ARDS with the Berlin definition requires that the patient be treated with mechanical ventilation or non-invasive ventilation with positive end-expiratory pressure (PEEP) and have arterial blood gas measurements and chest radiographs, some or all of which might not be available in resource-limited settings. The Kigali modification of the Berlin definition has been proposed to address this issue, which drops the requirement for PEEP, allows the use of the saturation of peripheral oxygen to fractional inspired oxygen (SpO_2/$FiO_{2)}$ ratio in place of the PaO_2/FiO_2 ratio and allows the use of lung ultrasound for the detection of bilateral infiltrates.[82] In a single-centre study, the Kigali definition of ARDS was used with rigorous criteria for lung ultrasound classification and had a sensitivity of 0.96 (95% CI 0.78 to 1.00) and a specificity of 0.93 (95% CI 0.88 to 0.97).[83]

There is a strong rationale for including patients on high-flow nasal oxygen (HFNO) in the definition of ARDS.[84] This inclusion reflects changes in international practice during the COVID-19 pandemic and is likely to identify some patients earlier, potentially providing a wider temporal window in which early interventions might be effective. The use of the SpO_2/FiO_2 ratio, ultrasound imaging and inclusion of patients on HFNO are components of the updated global definition of ARDS.[81] However, the inclusion of patients on HFNO in the global definition of ARDS raises questions about different clinical outcomes between ventilated ARDS patients and those treated with HFNO. The new proposed trial will prespecify 'non-intubated ARDS' as defined by the global definition as a subgroup of interest for sensitivity analysis.

Further, a secondary analysis of the LUNG SAFE study revealed that patients with AHRF having unilateral infiltrates in two chest X-ray quadrants have similar outcomes to patients with bilateral infiltrates,[85] but more studies are needed to confirm this point. Another secondary analysis of LUNG SAFE found that the attributable mortality due to ARDS increased with the number of quadrants of radiographic involvement.[86]

A phenotype-stratified trial in ARDS will adapt elements of the Berlin definition of ARDS[76] and the global definition[81] to use as inclusion criteria (*Table 2*). Adding patients on HFNO is advantageous, as this will expand the window for therapeutic benefit in a phenotype-stratified trial. It may not be necessary to include lung ultrasound and the SpO_2/FiO_2 ratio to identify ARDS (as in the global definition), because participating sites that can support a trial that identifies phenotypes of ARDS by plasma biomarkers using an immunoanalyser will have access to chest X-rays, CT and arterial blood gas measurements.

Focus on phenotypes as treatable traits

Syndromic definitions have weaknesses that limit insight into biological heterogeneity, but critical care phenotypes are likely to reflect syndrome-agnostic 'treatable traits'. The ideal stratified precision medicine trial should focus more on phenotypes as treatable traits, as they will likely have a stronger connection to the underlying biology.[1] In oncology, an analogous paradigm exists with 'basket trials' that target patients with specific oncogenic-driving mutations regardless of tumour type.[87–89] Although the development and validation of such a framework in critical care could advance the field, our understanding of underlying biology is not adequate to move in this direction at present. Therefore, trial designs should partially de-emphasise syndromes in favour of phenotypes with a view to reducing the emphasis on syndromes even further in future trials as evidence emerges.

Trial design

Platform trials

Advances in trial design can accelerate the discovery of new therapeutic agents in critical care. For example, platform trials are RCTs that can compare multiple interventions against a single control group simultaneously, sometimes incorporating predefined adaptations to trial design at interim analysis. The goal of a platform trial is to evaluate multiple treatments for a given disease, potentially across multiple strata of a target population, thereby providing an adequately powered and efficient design for identifying differential subgroup effects (as opposed to sensitivity analyses in a traditional approach).[90] The platform trial is a modification of the adaptive trial approach, commonly leveraging Bayesian statistical methods to allow multiple treatment arms and prespecified changes in trial design during the conduct of the trial in response to interim analyses.[90] Importantly, sample size calculations can be adjusted during the trial based on accruing data, and treatment arms can be closed in response to early signals for efficacy, harm or futility based on prespecified stopping criteria. These characteristics increase trial efficiency and allow for rapid reporting of results. More efficient

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TABLE 2 Proposed modification to the Berlin and global definitions of ARDS for use as inclusion criteria for a phenotype-stratified Phase II trial

ARDS criteria	Respiratory support	Timing	Chest imaging	Origin of oedema	Oxygenation
Berlin definition[65]	NIV (mild ARDS) or IMV	Within 1 week of known clinical insult or new or worsening respiratory symptoms	Bilateral opacities on CXR or CT not fully explained by effusions, lobar/lung collapse or nodules	Respiratory failure not fully explained by cardiac failure or fluid overload	ARDS • Mild – 200 mmHg < PaO_2/FiO_2 ≤ 300 mmHg with PEEP ≥ 5 cm H_2O • Moderate – 100 mmHg < PaO_2/FiO_2 ≤ 200 mm Hg with PEEP ≥ 5 cm H_2O • Severe – PaO_2/FiO_2 ≤ 100 with PEEP ≥ 5 cm H_2O
Global definition[70]	NIV/HFNO (non-intubated ARDS) or IMV		Bilateral opacities on CXR or CT, or ≥ 3 B lines per image between two ribs and/or consolidation on ultrasound; not fully explained by effusions, lobar/lung collapse or nodules		Non-intubated ARDS • PaO_2/FiO_2 ≤ 300 mmHg or SpO_2/FiO_2 ≤ 315 (if SpO_2 ≤ 97%) on HFNO > 30 LPM or NIV with PEEP ≥ 5 cmH_2O Intubated ARDS • Mild – 200 mmHg < PaO_2/FiO_2 ≤ 300 mmHg or 235 < SpO_2/FiO_2 ≤ 315 (if SpO_2 ≤ 97%) • Moderate – 100 mmHg < PaO_2/FiO_2 ≤ 200 mmHg or 148 < SpO_2/FiO_2 ≤ 235 (if SpO_2 ≤ 97%) • Severe – PaO_2/FiO_2 ≤ 100 mmHg or SpO_2/FiO_2 ≤ 148 (if SpO_2 ≤ 97%) Modified definition for resource-variable settings • SpO_2/FiO_2 ≤ 315 (if SpO_2 ≤ 97%)
Proposed modification			Bilateral opacities on CXR or CT not fully explained by effusions, lobar/lung collapse or nodules		Non-intubated ARDS • PaO_2/FiO_2 ≤ 300 mmHg or SpO_2/FiO_2 ≤ 315 (if SpO_2 ≤ 97%) on HFNO > 30 LPM or NIV with PEEP ≥ 5 cmH_2O Intubated ARDS • Mild – 200 mmHg < PaO_2/FiO_2 ≤ 300 mmHg or 235 < SpO_2/FiO_2 ≤ 315 (if SpO_2 ≤ 97%) • Moderate – 100 mmHg < PaO_2/FiO_2 ≤ 200 mmHg or 148 < SpO_2/FiO_2 ≤ 235 (if SpO_2 ≤ 97%) • Severe – PaO_2/FiO_2 ≤ 100 mmHg or SpO_2/FiO_2 ≤ 148 (if SpO_2 ≤ 97%)

Note
The proposed modification adds some recommendations from the global definition to the Berlin definition (addition of patients on HFNO) but does not incorporate ultrasound imaging and the SpO_2/FiO_2 ratio. CXR, chest X-ray; IMV, invasive mechanical ventilation; LPM, litres per minute; NIV, non-invasive ventilation.

platform trials can potentially reduce the number of underpowered Phase II trials that do not deliver decision-making results, a problem that was evident during the COVID-19 pandemic.[91]

Platform trials proved to be very useful during the COVID-19 pandemic, with the Randomised Embedded Multifactorial Adaptive Platform for Community-Acquired Pneumonia (REMAP-CAP) and Randomised Evaluation of COVID-19 Therapy (RECOVERY) trials rapidly generating evidence supporting the efficacy of IL-6 receptor antagonists[92,93] and dexamethasone.[94] Also, in COVID-19, a landmark collaboration across three platform trials led to the recommendation for therapeutic anticoagulation in non-critically ill patients and a recommendation against its use in critically ill patients,[95,96] demonstrating the utility of platform trials for identifying differential subgroup effects as well as demonstrating models for cross-trial prospective collaboration.[97,98] Successes in COVID-19 research can provide a foundation for advancing precision medicine in critical care, and platform designs can be readily adapted to phenotype-stratified designs, with numerous potential advantages.

Response-adaptive randomisation

Response-adaptive randomisation is a strategy for increasing the statistical and operational efficiency of platform trials that may lead to faster trial conclusions and better treatment of study subjects. In RAR, the ratio by which patients are allocated to treatment arms is altered, depending on interim data (*Figure 1b*).[99] By contrast, in a traditional trial, patients are allocated to treatment and control in a fixed ratio, most commonly a 1 : 1 ratio. In an adaptive trial design that uses RAR, as the trial progresses and more information is gained, this ratio can be altered to optimise statistical efficiency and improve outcomes for the average trial participant. These adjustments to the randomisation ratio can occur on a real-time basis and can be set automatically by the randomisation algorithm as the outcome data from preceding patients are obtained. This approach is designed to minimise the number of patients randomised to receive ineffective treatments while maximising the number of patients randomised to superior treatments.[100] The approach works best when multiple investigational treatment arms are included. Proponents of RAR contend that this approach can be more ethical than the traditional block randomisation because study subjects are more likely to receive an effective treatment (benefiting study subjects) and efficacy conclusions are reached faster (benefiting patients at large). The REMAP-CAP trial is an example of a critical care platform trial that used RAR,[92,95,96,101–107] whereas the RECOVERY platform trial[93,94,108–118] did not use RAR, although it might have been desirable.[119]

Response-adaptive randomisation has some important potential pitfalls.[120] Traditional RAR can introduce bias when applied to disease states in which there is a drift over time (in the primary event rate, concurrent care, disease characteristics, etc.), as summarised in Dodd *et al.*[121] For example, in trials that study rapidly changing disease processes, such as those due to infection, or in platform trials that are active for a prolonged period, such a drift could lead to imbalances between groups and the potential for over- or underestimation of the true treatment effect.[122] RAR also may reduce the statistical efficiency in two-arm trials by slowing the control event accrual (which determines statistical power). Statistical methods attempt to separate the temporal trend from the treatment effect estimate. Block RAR assigns patients to treatment in time blocks, with the randomisation ratio being adjusted per block at interim analysis rather than on a patient-by-patient basis.[123] The final data analysis is then stratified by blocks. However, such stratification approaches may require a larger patient sample than if RAR was not used, reducing its advantages.[120,124] In the case of a phenotype-stratified platform trial in respiratory failure, the issue of temporal trends is a concern, as the platform would be intended to stay active for years, and many infective causes of ARDS and AHRF are seasonal (e.g. Severe Acute Respiratory Syndrome Coronavirus 2 and influenza).

Some strategies can be considered to improve the trial efficiency without the risks of RAR. In a 'group-sequential' design, the sample size is not fixed at the beginning of the trial, as recruitment may stop early if triggered by signals for efficacy or futility.[125] Such a trial is adaptive concerning sample size but can be fixed with regard to the randomisation ratio. A 'multiarm multistage' platform design extends the group sequential design by allowing treatment arms that are stopped based on efficacy or futility signals to be replaced by new interventions. A Bayesian adaptive multiarm trial design with parallel phenotypes extends this design further (*Figure 1a*). In such designs, the randomisation ratio can either remain fixed or be varied using RAR. The success of this design depends on robust interim analyses and prespecified stopping rules for efficacy and futility. A Bayesian adaptive multiarm trial design approach without RAR may increase the trial efficiency without the added operational burden of RAR (*WP2*, *deliverable 2*).

Stopping rules

Defining stopping rules for efficacy and futility in a trial using phenotypes in critical illness is important, as thoughtful stopping rules ensure that the trial does not go on longer than needed, thereby conserving resources and avoiding harm by continued randomisation to ineffective

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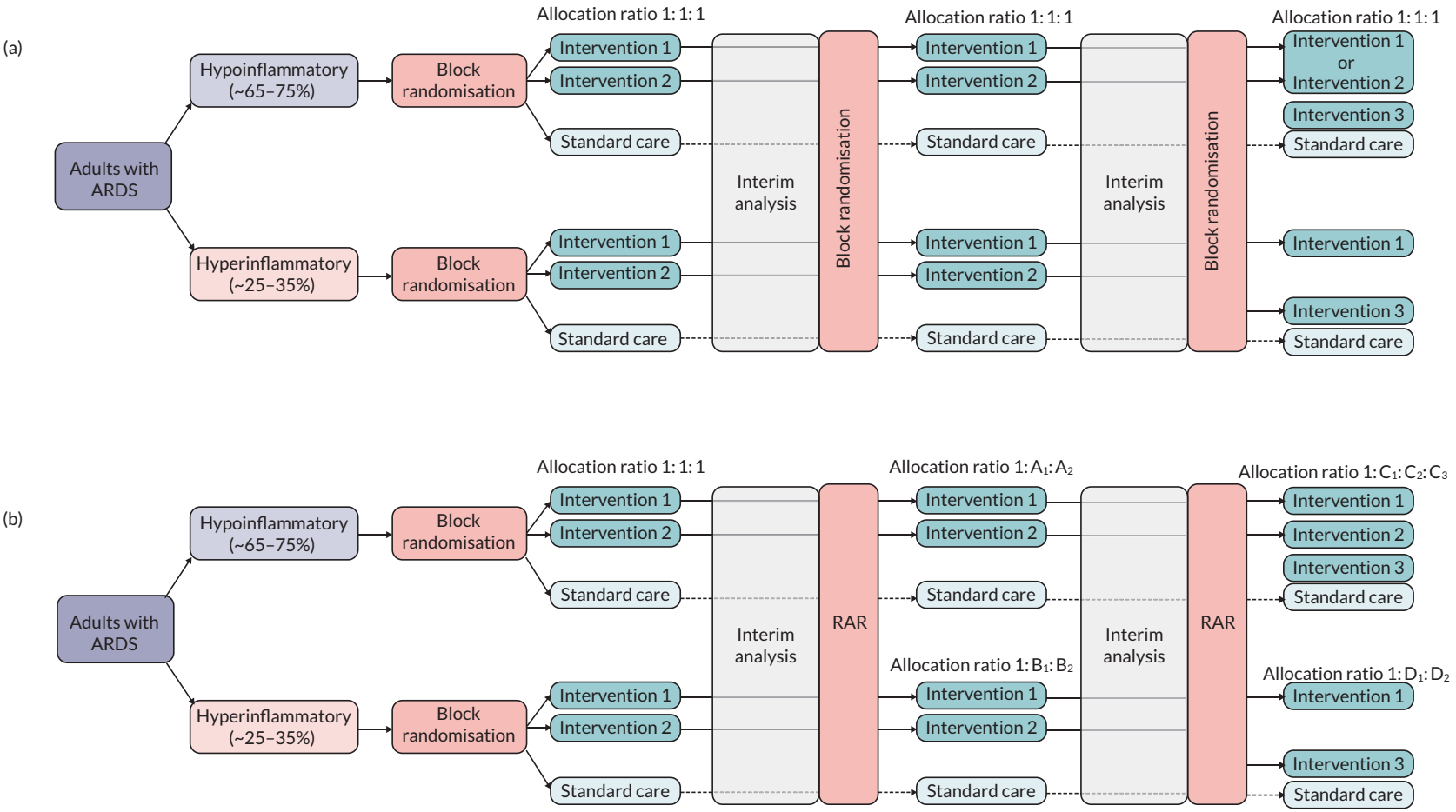


FIGURE 1 Two platform trial designs. (a) A platform trial design stratified by the hyperinflammatory and hypoinflammatory phenotypes of ARDS, which utilises continued block randomisation in a Bayesian adaptive multiarm trial design approach without RAR, stratified by phenotype. At interim analysis, interventions can be 'graduated' for efficacy or removed from the trial for futility based on prespecified stopping rules (e.g. intervention 2 at second interim analysis in the hyperinflammatory phenotype). The randomisation ratio is fixed, with up to two active interventions in each phenotype at any given time. New treatments can be added based on scientific criteria (e.g. intervention 3 after the second interim analysis). (b) A design using RAR. In this model, the trial begins with a 'burn-in' period of block randomisation. Interventions can also be stopped for futility and 'graduated' for efficacy at interim analysis. However, in this design, randomisation ratios are continuously adjusted by a statistical model following signals for efficacy or futility as patients' primary outcome measures are reported. Allocation ratios are not fixed and can be different across phenotypes and treatments.

treatments. In the case of a trial which focuses on the hyperinflammatory and hypoinflammatory phenotypes of ARDS, if at an interim adaptive analysis, a particular treatment demonstrates evidence of efficacy in one phenotype above a prespecified threshold, recruitment to that arm should cease and efficacy should be declared. This is the method used in the Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis 2 trial (I-SPY 2, NCT01042379) of neoadjuvant therapies in high-risk breast cancer, in which each phenotype/treatment combination is statistically treated as its own trial.[126–132] An alternative example of efficacy stopping rules comes from the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) series of trials in heart failure,[133–136] in which recruitment could be stopped if there was evidence of efficacy across all phenotypes, or recruitment could be stopped in a specific treatment/phenotype combination if there was evidence for efficacy in the treatment arm as well as evidence for HTE, as defined by sufficiently different relative risks across treatment/phenotype combinations. The stopping rule used in the I-SPY 2 platform is best suited to a Phase II trial, where the goal is to rapidly identify potentially effective therapeutics and progress them to Phase III, whereas the more stringent rules in CHARM are more suited to a Phase III trial. Another point to be considered is the choice of thresholds for the magnitude and probability of efficacy that are set a priori to define success. In defining these thresholds, consideration must be given to the trial's purpose, as Phase III trials require a higher probability of benefit than Phase II trials.

Early stopping rules for futility also need to be built into platform trial designs. For example, if the evidence for futility exceeds a given threshold at an adaptive analysis for a given treatment/phenotype combination, recruitment to that arm would be stopped. This approach was used by the Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination platform.[137] Interestingly, the subsequent Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination-2 platform trial used an alternative approach in which recruitment was only stopped if futility was demonstrated across all phenotypes.[138] This method focuses on maximising the number of data points to perform comparisons at the cost of slower turnover of potentially futile therapies, an approach more suited to a Phase III trial than a Phase II trial. The Precision Interventions for Severe and/or Exacerbation-Prone Asthma (NCT04129931) trial uses yet another approach, in which recruitment is stopped across all phenotypes if futility is demonstrated in the target phenotype, which was a priori deemed to be most likely to respond to treatment. Some early stopping rules used in contemporary platform trials are presented in the Online Supplement Report Supplementary Material, Table S1). Multiple stopping rules can be explored in the design phase of a trial using simulations to optimise trial operating characteristics. An executive trial design committee has been established for the PANTHER trial as well as a methodology committee (*WP2*, *deliverable 5*), which has overseen extensive simulations for the development of the trial, leading to the establishment of stopping rules for futility and efficacy, considerations for adding new intervention arms over time and evaluations of the efficacy of a platform design as compared to individual efficacy trials (*WP2*, *deliverables 1*, *3*, *4*, *8*).[139]

Blinding

Trials in which clinical staff and patients are blinded (double-blind designs) are generally considered more rigorous than open-label designs, as they limit the influence of observer and patient bias.[140] RCTs traditionally use a double-blind design to limit the risk of introducing bias into high-level evidence. Unfortunately, double-blind designs may be impractical in platform trials where multiple treatment arms are being compared against a single control group. Since the tested therapeutics may have different modes of administration, dosing regimens and contraindications, a double-blind design would require an individual control arm to be paired with each treatment arm to match the treatment characteristics and placebo administration. This would come with a significantly increased trial size and overhead cost and decreased efficiency, potentially negating the benefits of the platform trial approach. Indeed, a 2019 review identified 14 active master protocols for platform trials, 12 of which were open label and 2 of which did not report blinding design.[141] Open-label designs are usually more cost-effective and may also facilitate earlier recruitment into trials by removing delays that may be introduced by blinded drug dispensing and administration procedures, potentially maximising the therapeutic window. REMAP-CAP[92,101,102] and RECOVERY[93,94,108–118] were Phase III trials that used open-label designs to test candidate therapeutics rapidly during the COVID-19 pandemic. The influence of observer bias can be mitigated in open-label trials that use objective end points, such as organ-support free days (OSFDs) and mortality. Furthermore, significant efforts can be made to keep members of the trial team blinded in an open-label design (e.g. statisticians, trial steering committee and those involved in trial design), also mitigating bias. Delivery of usual care based on guidelines decreases the likelihood of performance bias.

Scale

With multiple active treatment arms, recruitment to a phenotype-stratified trial could be difficult in a single country. For example, if each trial arm required 200

patients to reach a result, with two active treatment arms and control, the total estimated sample size would be in the range of 2000 patients when considering that the hyperinflammatory phenotype of ARDS represents a minority of the population (~30%).[32–35] A trial of this size would be more feasible if conducted internationally and could be more generalisable. International collaboration would facilitate adequate patient recruitment and produce data representative of all populations included, particularly if patients in high-income countries and LMICs are included in the trial. It is important to recognise that international trials introduce additional levels of complexity, including ensuring a unified protocol and data collection procedures, as well as governance and data sharing issues. Nevertheless, international collaboration would facilitate innovation, strengthen international trial networks and facilitate data sharing for the secondary analyses that would be essential to develop new hypotheses to test in future trials. To facilitate international collaboration and development, additional international funding for the PANTHER trial is being sought through regional leads in high- and low-income countries (*WP4*, *deliverables 1–3*).[142] These regional leads also serve as local agents for sponsor interaction and regulatory approval (*WP3*, *deliverable 1*).

Defining the interventions

A Phase II precision-medicine platform trial in ARDS provides the unique opportunity to test a range of therapeutic options across multiple mechanisms, starting with the most promising, thereby avoiding duplication and gaps in knowledge. This was an issue during the COVID-19 pandemic when researchers were conducting parallel underpowered trials on the same therapies while ignoring other promising mechanistic targets.[91] An important point for consideration when reviewing the below proposed therapies is that, while relatively less inflamed than the hyperinflammatory phenotype, the hypoinflammatory ARDS phenotype also represents an inflamed state.[143] These two phenotypes may also be related to differential inflammatory pathways. As such, anti-inflammatory drugs may benefit one or both phenotypes to varying magnitudes. To maximise the ability to identify treatment effect, each participant in the PANTHER trial will be limited to one treatment.

Evidence for heterogeneity of treatment effect

In retrospective analyses, the hyperinflammatory and hypoinflammatory phenotypes exhibited HTE for ventilation strategies[32] in the Assessment of Low Tidal Volume and Elevated End-Expiratory Volume to Obviate Lung Injury (ALVEOLI) RCT,[144] liberal versus conservative fluid administration strategies[33] in the Fluid and Catheter Treatment Trial (FACTT) RCT,[145] simvastatin[34] in the Hydroxymethylglutaryl-CoA Reductase Inhibition with Simvastatin in Acute Lung Injury to Reduce Pulmonary Dysfunction (HARP-2) RCT[146] and non-randomised corticosteroids in COVID-19.[37] Of these, two are supportive therapies, and two are pharmacological interventions; and of the pharmacological interventions, only simvastatin was given in a randomised fashion. Simvastatin was not shown to be effective in all patients with ARDS in the HARP-2 trial despite strong preclinical evidence suggesting benefit.[146] Conversely, another steroid trial suggested benefit for early dexamethasone administration in all patients with non-coronavirus disease (COVID) moderate-to-severe ARDS,[147] though the strength of this evidence has been questioned.[148] In COVID-19 ARDS, the RECOVERY trial demonstrated benefit for dexamethasone,[94] which was supported by evidence for the beneficial effects of corticosteroids in other COVID-19 RCTs.[149] While supportive therapies have been the mainstay of intensive care for decades and have improved outcomes,[150–152] new trials are needed that shift the focus toward modifying underlying pathophysiology. Therapies that have been successful in the treatment of COVID-19 may be translatable, and several promising pharmacological therapies have the potential to modulate the immune response in non-COVID ARDS and respiratory failure.[153] Some of these candidates are discussed below.

Simvastatin

Data from murine models,[154] a human model of pulmonary inflammation induced by inhaled lipopolysaccharide (LPS),[155] and an early-phase RCT[156] supported the potential efficacy of simvastatin in ARDS. A Phase III RCT, however, showed no benefit of simvastatin in an overall population of patients with ARDS.[146] In the REMAP-CAP trial in COVID-19, simvastatin did not reach the prespecified criteria for stopping due to efficacy, but it did demonstrate a 91.9% posterior probability of superiority to standard of care, supporting further investigation.[157] A large amount of safety data exists for simvastatin in the critical care population. HARP-2 reported a statistically significantly increased incidence of AEs related to the study drug in the simvastatin group as compared to placebo (OR 2.2, 95% CI 1.1 to 4.2, $p = 0.02$), most of which included elevated creatinine kinase and hepatic aminotransferase levels. However, the number of serious AEs in the two groups was similar (12 in the simvastatin arm vs. 16 in placebo across 540 patients; OR 0.4, 95% CI 0 to 5.9, $p = 0.61$).[146] Following the publication of HARP-2, a subsequent secondary analysis demonstrated significantly higher 28-day survival in the participants with the

hyperinflammatory phenotype who were randomised to simvastatin.[34] This effect was not observed in participants with the more prevalent hypoinflammatory phenotype, providing evidence for HTE and potentially explaining the lack of benefit observed in the overall population. These data support the need to study simvastatin prospectively in a phenotype-stratified trial to provide evidence for benefit in the hyperinflammatory phenotype. Regulatory agencies such as the US Food and Drug Administration (FDA) usually require that therapies be tested in each phenotype in order to demonstrate the benefit of a predictive enrichment strategy.[158]

Baricitinib

Baricitinib is a repurposed drug approved for rheumatoid arthritis that has proven beneficial in COVID-19 pneumonia.[113] Baricitinib is an oral Janus Kinase 1 and 2 inhibitor whose mechanism of action includes modulating inflammatory signalling pathways by reducing the activation of signal transducers and activators of transcription in the signalling pathways for cytokines such as interleukin-2, IL-6, interleukin-10 and interferon-γ.[159] Baricitinib reduces the production of several proinflammatory cytokines that are important for immune cell survival, proliferation and differentiation in inflammatory disease.[160] The rationale for testing baricitinib in a non-COVID phenotype-stratified trial is its ability to reduce inflammation by modulating the production of proinflammatory cytokines and its demonstrated benefit and safety in COVID-19 and other diseases. Baricitinib has a broader mechanism of action than other drugs that target IL-6 (such as tocilizumab), lending a stronger rationale for use in a Phase II trial. ARDS biology is almost certainly more complex than a single-cytokine IL-6 mechanism,[161] and as such, a therapy like baricitinib that has more potential therapeutic targets may be more likely to be successful. Because baricitinib also has shown an overall benefit in severe COVID-19 pneumonia (a condition with a high proportion of the hypoinflammatory phenotype[44]), there is rationale to test this agent in both the hyper- and hypoinflammatory phenotypes. Infections are a concern with prolonged administration of baricitinib in rheumatoid arthritis,[162] but this concern may not be translatable to the short-term intensive care setting. The RECOVERY trial only excluded patients with known tuberculosis infection in the baricitinib arm (as opposed to all bacterial and fungal infections in the tocilizumab arm) and found no increased incidence of infections.[113]

Atibuclimab

A chimeric monoclonal antibody, atibuclimab (IC14), targets membrane and soluble CD14, a pattern recognition receptor, that is a very proximal activator of innate immunity.[163] During infection, pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) associate with toll-like receptors on circulating immune cells, activating innate immunity.[163,164] This process is facilitated by membrane-bound and soluble CD14. In COVID-19 and non-COVID ARDS, this interaction may lead to excessive cytokine release and propagation of a dysregulated inflammatory response. IC14 blocks the interaction between membrane and soluble CD14, PAMPs and DAMPs, ostensibly attenuating this dysregulated inflammatory response.[164] In a pilot study, IC14 was evaluated in hospitalised COVID-19 patients with pneumonia and hypoxaemia in a double-blind, randomised, placebo-controlled trial.[165] The trial was stopped early after recruiting 40 patients due to slow enrolment and did not show a difference in the primary end point of time to resolution of illness. However, in preplanned exploratory analyses, IC14 increased serum-soluble CD14 (a pharmacodynamic marker) and decreased macrophage inflammatory protein 1-β and tumour necrosis factor alpha (TNF-α) (biological markers). IC14 was also evaluated in the Adaptive Platform Trial to Reduce Mortality and Ventilator Requirements for Critically Ill Patients (I-SPY COVID) trial, which evaluated seven novel therapies for COVID-19 in a Phase II platform design.[166] Although the IC14 arm was stopped because it met the criteria for futility for time to recovery, a beneficial effect might have been missed because of the small sample size included in the I-SPY COVID trial design.[166] A marker of CD14 pathway activation, presepsin, identified patients who were more likely to benefit (Mabrey 2024). Based on existing biological data in relevant preclinical animal models, including non-human primates, and potential signals for efficacy in COVID-19 pneumonia,[167] further evaluation of IC14 may be warranted in non-COVID ARDS. Due to the putative effects on dampening innate immunity and cytokine release, IC14 might preferentially benefit the hyperinflammatory phenotype.

Anti-component 5a

Inhibition of the complement system, particularly complement component 5a (C5a), has had successes in COVID-19, which also could be translatable to non-COVID ARDS. C5a is a key driver of microvascular platelet aggregation and a key chemoattractant for neutrophils and monocytes to the injured lungs, causing tissue damage, inflammation of the endothelium and microthrombosis.[168,169]

In murine models, C5a blockade limits myeloid infiltration and endothelial inflammation in the injured lungs.[169] A Phase II trial demonstrated a signal for effectiveness for vilobelimab, an anti-C5a monoclonal antibody, in COVID-19.[170] This trial enrolled 368 patients on mechanical

ventilation with COVID-19 and showed a reduction in the primary outcome of all-cause mortality at day 28 in a predefined analysis that did not stratify by site [hazard ratio (HR) 0.67, 95% CI 0.48 to 0.96, $p = 0.027$]. Serious treatment-related AEs were similar in the treatment group versus the control (59% vs. 63%), the most common being acute kidney injury (20% vs. 21%). Most patients recruited in this trial had moderate ARDS (73%), and 27% had severe ARDS. A prespecified subgroup analysis suggested that the treatment effect was driven primarily by benefit in patients with severe ARDS. These data provide evidence of safety for vilobelimab in the critically ill population with COVID-19 pneumonia and provide a rationale for testing C5a inhibition in a non-COVID population with ARDS. Based on these results, the US FDA granted emergency use authorisation for vilobelimab in patients with COVID-19 on mechanical ventilation or extracorporeal membrane oxygenation.[171]

Tocilizumab

Tocilizumab is an approved monoclonal antibody that blocks the membrane and soluble forms of the IL-6 receptor and was found to improve outcomes in critically ill patients with COVID-19 pneumonia in the REMAP-CAP and RECOVERY trials.[92,93] The rationale for its use in COVID-19 is that it blocks signalling via the IL-6 mediated inflammatory pathway, which is associated with disease severity and mortality.[172,173] There is a strong rationale to test tocilizumab in a non-COVID population with respiratory failure, as IL-6 levels in ARDS patients are 10- to 200-fold higher than levels in patients with severe COVID-19 ARDS and plasma IL-6 concentrations are strongly associated with ARDS mortality.[174] Divergent levels of IL-6 in the hypoinflammatory and hyperinflammatory phenotypes suggest that these groups may respond differently to tocilizumab, supporting its study in a new platform trial. Nonetheless, the overall beneficial effect of tocilizumab in severe COVID-19 pneumonia, a condition with high rates of the hypoinflammatory ARDS phenotype, provides an additional rationale to test this agent in both hyper- and hypoinflammatory phenotypes.[44] There are some safety concerns with tocilizumab, mostly relating to a potentially increased risk of superimposed bacterial or fungal infection. As with baricitinib, this evidence largely comes from the rheumatoid arthritis literature, in which therapy is administered for years[175,176] as opposed to the short-term treatment used in patients with an acute severe illness. Indeed, most trials of tocilizumab in COVID-19 explicitly excluded patients with pre-existing infection, including the RECOVERY trial.[93,177–181] REMAP-CAP did not explicitly exclude patients based on infection but allowed investigators to exclude patients based on potential harm from treatment.[92] These concerns may not be translatable to the intensive care setting, as a meta-analysis found no increased risk of infection with tocilizumab use in COVID-19.[182] However, the results of this meta-analysis are limited due to the exclusion of patients in the analysed trials who were thought to have non-COVID infections at baseline.

Anti-tumour necrosis factor alpha

Anti-TNF-α agents, such as infliximab, are another class of drugs currently approved for immune-mediated inflammatory diseases. TNF-α inhibition reduces neutrophilic inflammation in a human model of lung inflammation induced by inhaled LPS,[183] and LPS is prominent in the lungs and circulation of patients with ARDS.[184] Patients with sepsis (many of whom will have coexisting ARDS and AHRF) and high circulating IL-6 levels treated with anti-TNF-α therapy may have improved outcomes.[185] Further, data from an early trial in patients with COVID-19 found that infliximab showed a trend towards improving time to recovery and mortality at 28 days, although these results were not statistically significant.[186] A Phase II trial did not show benefit for infliximab in COVID-19 pneumonia, though there was no signal for safety concern.[187] sTNFR1 levels in plasma are markedly higher in the hyperinflammatory phenotype than in the hypoinflammatory phenotype, indicating the potential importance of TNF-α–mediated pathways.[32–35] Together, these data provide supporting rationale to test an anti-TNF-α strategy in a phenotype-stratified trial. Infliximab is currently in extensive clinical use for inflammatory bowel disease (IBD). Extensive safety data exist in the IBD population, where neoplasia, infection and infusion reactions are a concern with prolonged administration.[188] However, these complications may be of lesser concern in an intensive care setting, as infliximab would be given as a single infusion for this indication rather than a prolonged course as in IBD.

Other candidates

Other candidate drugs for ARDS with some supporting evidence in COVID-19 focus on novel therapeutic targets. While these therapies are in earlier stages of development, they may be well suited to a Phase II platform design as they provide a broad group of therapeutic agents to investigate in a parallel-arm design.

On balance, most of the candidate treatments discussed above might be expected to preferentially benefit the hyperinflammatory phenotype in a stratified trial, but the hypoinflammatory phenotype includes approximately 70% of patients with ARDS,[32–35] so developing therapies for this subgroup is also important. One therapy that might be considered for this subgroup is imatinib, which is a small-molecule tyrosine kinase inhibitor that binds to several

tyrosine kinases known to be important in the pathogenesis of chronic myeloid leukaemia, gastrointestinal stromal tumours, systemic mastocytosis and hypereosinophilic syndromes.[189] Interestingly, many of these same tyrosine kinases regulate key functions of immune cells, particularly macrophages, T cells and dendritic cells.[190] Imatinib has shown promise in human in vitro models and in vivo murine models, effectively preventing endothelial barrier dysfunction and oedema formation.[191] This suggests a potential role in preventing or treating non-cardiogenic pulmonary oedema in ARDS. Indeed, through pathway analysis of differential gene expression data from tracheal aspirate (TA) collected from hypoinflammatory ARDS patients and healthy controls, imatinib was identified as a potential candidate drug that might shift gene expression toward a healthy control state.[58] In a secondary analysis of a cohort of patients hospitalised with COVID-19, imatinib benefited a subgroup characterised by alveolar epithelial injury and increased surfactant protein D (SP-D).[192] In causal inference analysis, this effect was determined to be mediated by a reduction in IL-6.[192] However, in a Phase IIb trial in COVID-19 ARDS, imatinib did not reduce extravascular lung water index at day 4 of trial enrolment, though there was subgroup benefit in patients characterised by high IL-6, sTNFR1 and SP-D.[193] Contrary to previous evidence, this suggests a potential benefit in the hyperinflammatory phenotype, though this result should be interpreted with caution, given that it comes from a subgroup of a small study population (n = 20).[193] Further, in a randomised trial of imatinib in patients with severe COVID-19, there was no improvement in the primary outcome of time to discontinuation of supplemental oxygen and ventilation.[194] Nonetheless, the secondary outcome of unadjusted 28-day mortality was reduced (HR 0.51, 95% CI 0.27 to 0.95), though this result was attenuated after adjustment for baseline between-group imbalances, suggesting no overall benefit (HR 0.52, 95% CI 0.26 to 1.05).[194] In the same trial, the duration of mechanical ventilation was reduced from a median of 12 days [interquartile range (IQR) 6–20] to 7 days (IQR 3–13).[194] No imatinib-related AEs were observed. Imatinib therapy would be easy to translate to a phenotype-stratified trial in non-COVID ARDS and AHRF.

A recent Phase Ib/IIa trial examined GB0139, an inhaled inhibitor of galectin-3, in hospitalised patients with COVID-19.[195] Galectin-3 is an important molecule implicated in many immune responses, being highly expressed in monocytes, macrophages, neutrophils, fibroblasts, epithelial cells and endothelial cells,[196] potentially amplifying the host inflammatory response during infection.[197] Galectin-3 also stimulates the release of interleukin-1β, IL-6 and TNF-α.[198] Hence, a galectin-3 inhibitor such as GB0139 may potentially reduce immune-mediated lung injury more than a therapy that targets a single cytokine.[199] Data from an early phase trial, while not powered for efficacy, support the safety and tolerability of GB0139. That study also presents biomarker trajectory data and cytometric analysis to suggest that GB0139 modulates inflammation in human subjects with COVID-19 pneumonia.[195] Given these data, GB0139 is another candidate for a phenotype-stratified trial. It is of particular interest due to the inhaled mode of delivery, which may reduce off-target effects and improve delivery to the lung parenchyma; however, GB0139 has yet to be tested in a critically ill population.

Defining standard of care

Comparison of treatment groups to the control group must be facilitated by ensuring that a unified standard of care is reached in the control group across international jurisdictions. A balance must be struck between rigorous definitions and acceptance of local practice variation to ensure adequate recruitment and limit the burden on participating sites. As such, in the PANTHER trial, we will define standard of care based on the European Society of Intensive Care Medicine ARDS guidelines (including lung protective ventilation and prone ventilation),[200] guidelines for weaning of vasopressors and inotropes[152] and respiratory support[201] (*WP1*, *deliverable 3*).

Prioritising interventions

There are many potential repurposed or early therapeutic candidates for evaluation in a phenotype-stratified trial in ARDS and AHRF. For many candidate therapies, relevant preclinical data are limited or co-opted from different disease models. The experience with vitamin C in sepsis, where incomplete observational data[202] led to the eventual conduct of a Phase III trial that suggested harm,[203] is a cautionary tale to this effect. As such, in a phenotype-stratified platform trial, interventions should be prioritised by an experienced and independent selection committee that can review the breadth of data supporting each proposed treatment for inclusion in the platform. Ideally, this committee should include members with scientific expertise to critically appraise existing evidence, members with pharmaceutical industry expertise to provide insight into the relevant drug development processes and members with biostatistical expertise. This committee has been established and is actively reviewing interventions for the PANTHER trial[204] (*WP1*, *deliverable 2*). A framework for therapeutics prioritisation is presented in *Figure 2*.

In this framework, an intervention for the disease of interest (ARDS) can be proposed by a trial team member, an independent academic or a pharmaceutical industry

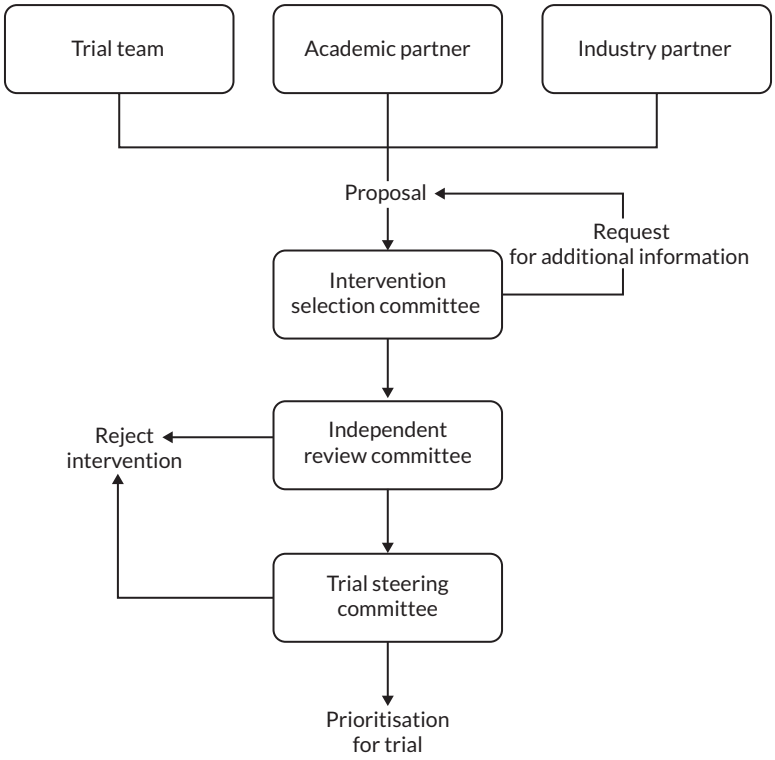


FIGURE 2 Framework for therapeutics prioritisation.

representative. The applicant submits a standardised application to the intervention selection committee (composed of academics, members with expertise in the pharmaceutical industry and biostatisticians). The intervention selection committee can approve the application and pass it on to the independent review committee or return it to the applicant requesting additional information. The independent review committee can reject or pass the application to the trial steering committee. The trial steering committee can also reject or approve the intervention and prioritise it for inclusion in the trial.

Pharmacometric considerations

The selection of candidates for clinical evaluation requires a plausible mechanism of action in the context of the pathology, relevant preclinical data demonstrating efficacy, and pharmacometric assessments that demonstrate target exposures in the relevant tissues are likely to be achieved at the proposed dose. Several issues can complicate the interpretation of preclinical data when assessing the candidacy of a pharmacological intervention. The heterogeneity of clinical disease can make preclinical models inadequate to accurately recapitulate efficacy across the full spectrum of human aetiologies.[205] The exposure–response relationship for any given pharmacological intervention is critical to success, but it is often studied independently of pharmacodynamics in animal models, if at all. In a trial, heterogeneity in clinical response may arise through interpatient variability in pharmacokinetics. For drug repurposing, pharmacokinetics in humans is usually well understood at the doses administered in the primary indication for which the medicine is already approved. Such data should be leveraged when assessing the plausibility of an agent for a new indication. For new agents, pharmacokinetic data from Phase I studies should be leveraged as far as is reasonably practicable. Broadly speaking, two distinct types of medicines are applicable to repurposing efforts in ARDS. First, the drug target may be the same in ARDS as it was for the indication(s) for which the medicine is already approved. In this scenario, there can be a reasonable certainty that the approved doses will be appropriate to achieve the target exposures in ARDS. Second, the repurposed medicine may aim to exploit a fortuitous secondary target, and as such, the achievement of adequate target exposures may not be certain at the approved dose. In these cases, a more sophisticated pharmacometric assessment may be needed to support the candidacy of the intervention and doses may need to be further optimised to achieve target engagement (particularly, where activity against the secondary target is below that of the proven target). In both scenarios, embedding pharmacokinetic and pharmacodynamic assessments into clinical trial design can help clarify the concentration-driven heterogeneity in efficacy through clarification of the exposure–response relationship.

Defining the outcomes

The choice of primary outcome in a phenotype-stratified trial is a key consideration, and the outcome should be based on the trial's goals. Many of the trials in which ARDS phenotypes have been identified come from the National Institutes of Health (US)/National Heart, Lung, and Blood Institute (US) (NIH/NHLBI) Acute Respiratory Distress Network (ARDSnet) clinical trial group [subsequently, named as the Prevention and Early Treatment of Acute Lung Injury (PETAL) network]. These trials have used outcome measures such as death before discharge while breathing without assistance,[144,206,207] ventilator-free days (VFDs) at day 28,[206–210] 28-day mortality,[211] 60-day mortality[145,212,213] and 90-day mortality.[21,214]

The primary outcomes in the trials in which HTE was observed for the hyper- and hypoinflammatory phenotypes of ARDS have been heterogeneous. The Respiratory Management in Acute Lung Injury/ARDS trial used two primary outcomes: death before discharge while breathing without assistance and VFDs at day 28.[206] ALVEOLI also used death before discharge while breathing without assistance.[144] FACTT used mortality at 60 days.[145] HARP-2, the only non-US RCT in which HTE was identified, also used 28-day VFDs as a primary outcome,[146] though HTE was identified for both survival and VFDs.[34]

A core outcome set for critical care trials has been defined, which suggests that all such trials report time of extubation, reintubation rate, duration of mechanical ventilation, duration of hospital/ICU stay, mortality at 60 days and health-related quality of life.[215] However, an interventional trial in ARDS and AHRF that focuses only on ventilated patients may miss a potential window of treatment opportunity when patients are initially treated with HFNO or non-invasive ventilation. Further, focusing only on ventilated patients does not align with the proposed new global definition of ARDS.[81] A modification of the recommended core outcome set may be preferred for a phenotype-stratified respiratory failure trial focusing on disease-modifying therapeutic agents. Furthermore, a platform trial may benefit from a relatively short-term outcome measure, such as days alive and free of ventilatory support through day 28, as this would allow more efficient adaptive analyses and prompt stopping due to efficacy or futility.

Composite outcomes

Composite outcomes combine two or more distinct component end points into a single outcome. VFDs are a commonly used composite outcome that combines mortality with duration of ventilation.[216] VFDs at day 28 have been used as a primary outcome in several ARDSnet/PETAL network trials.[206–210] Composite outcomes are attractive due to their potential to improve statistical power, reducing the probability of a type II error. Critical care trials that use mortality only as a primary end point require that a participant has died at the point of data censorship to detect an unfavourable outcome, while a trial that focuses on VFDs also identifies an unfavourable outcome if the patient is still requiring mechanical ventilation when the data are censored. Composite end points may be better suited to Phase II trials, where efficiency and detection of signals for benefit with a minimum number of recruited patients are important. This may be particularly important for the hyperinflammatory phenotype in a stratified trial, as this group comprises approximately 30% of eligible patients, requiring the recruitment of a relatively large study population to identify a signal in this subgroup. However, composite outcomes may be less desirable in a Phase III trial design. The FDA and the European Medicines Agency (EMA) provide guidance on using composite end points in trial design.[217,218] One important limitation is that a positive effect on a composite end point may be driven primarily by its least important component, with the most important component either being neutral or adversely affected. As such, the FDA and EMA recommend individualised analysis of the components of the composite end point. A trial targeted to a composite end point may be underpowered to identify the effects of individual components and may fail to reach requirements for efficacy in Phase III.

Composite outcome measures can be unreasonably combined, inconsistently defined and inadequately reported.[219] An important criticism of VFDs is the equal weighting of death and persistent mechanical ventilation so that a patient who has died and the one still on a ventilator at trial censorship are both assigned 0 VFDs,[216] although this can be addressed by assigning those who die '-1' VFD, which is worse than 0. 'Alive and Ventilator Free', is a hierarchical composite outcome proposed to address this issue, ranking mortality worse than prolonged ventilation.[220] The Alive and Ventilator Free score has been successfully used in a trial of dexamethasone in COVID-19.[221]

A further potential issue with VFDs for ARDS trials is that ARDS is a multisystem syndrome rather than solely a disease of respiratory failure. VFDs focus on detecting an early indicator of persistent lung dysfunction, but extrapulmonary organ dysfunction is also very common in ARDS, with 48.7% of non-survivors dying from multisystem organ failure.[222] An ideal composite outcome should also capture persistent non-pulmonary organ dysfunction.

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OSFDs provide an ordinal composite end point that was used by the REMAP-CAP platform trial[92,101,104] during the COVID-19 pandemic that addresses many of these issues (*WP2*, *deliverable 7*). It comprises mortality and the number of whole- or part-study days for which the patient is alive and not requiring ICU-based organ support (advanced respiratory support, vasopressors/inotropes, renal support, etc.). In this outcome, mortality is ranked lower (worse) than persistent organ support by assigning a score of −1 rather than 0.

Embedding biobanking

Biobanking is a key element of precision medicine trials, as it allows future mechanistic analyses to understand the tested therapeutics and facilitates further secondary analyses as new hypotheses are developed. Biobanking is particularly important in the era of '-omics' science (genomics, transcriptomics, proteomics and metabolomics), in which a wealth of exploratory data can be generated from stored trial samples. Data generated from stored samples can help refine the conduct of an ongoing platform trial and can help direct the design of future precision medicine trials. In the proposed trial design, biobanking should allow analyses that facilitate the future incorporation of additional biological phenotypes (such as phenotypes stratified by transcriptional profile[52] or inflammasome-associated biomarkers[223]) into the platform as further rapid assays are developed.

Blood samples

In addition to plasma required for patient phenotyping at baseline, serum and plasma should be collected and stored to facilitate exploratory cytokine measurements and proteomic analyses. Data generated from these analyses could be used to further stratify or substratify the trial population in retrospective analyses. Collection of these samples requires access to basic laboratory equipment (e.g. access to centrifuges and freezer storage at −20 °C or −80 °C). Whole blood for deoxyribonucleic acid (DNA) sequencing and ribonucleic acid (RNA) sequencing can be collected in RNA and DNA stabilisation tubes and immediately frozen for transportation to a central laboratory.[224] Peripheral blood mononuclear cells (PBMCs) also can be collected with appropriate laboratory expertise using a simplified protocol that employs cell preparation tubes (CPTs) containing Ficoll solution and a gel plug that separates the solution from blood.[225] Stored PBMCs can be used for analyses examining the immune cell population transcriptome or could be revived and used for mechanistic investigations. While significantly less labour-intensive than traditional protocols, PBMC extraction with CPTs requires laboratory expertise and access to liquid nitrogen storage.

Respiratory samples

Deep respiratory samples from intubated patients can facilitate mechanistic studies regarding cellular and biochemical changes in the airways and lung parenchyma in response to treatment/phenotype interactions. Potential procedures for collecting these samples are bronchoalveolar lavage (BAL) and non-bronchoscopic BAL (NBBAL).[226,227] BAL involves the passage of a bronchoscope by a highly experienced operator and generally returns a high sample yield. However, BAL requires significant expertise and is expensive. NBBAL is an alternative method that involves the blind passage of a catheter through an endotracheal tube into the lower airways and is less burdensome from a resource utilisation perspective. NBBAL has been used in some studies rather than BAL due to the ease of the procedure.[228] Both clinical and laboratory resources may limit the collection of deep respiratory samples, and performing the clinical procedure requires a clinician with sufficient expertise to dedicate time to the safe performance of the procedure. Collection and processing of high-quality samples require laboratory facilities (centrifuges, tissue culture hoods and microscope) and expertise in separating sample components into the liquid phase, cellular phase, RNA and DNA components.

In addition to BAL fluid, TA samples collected from routine endotracheal suctioning also may be useful, as evidenced by the work on RNA sequencing of TA samples in the hyperinflammatory and hypoinflammatory phenotypes.[58]

Considerations for biobanking

Given the necessity for international scope in a phenotype-stratified trial of ARDS, unified biobanking approaches will be challenging. Long-term sample storage during and after the trial should be a priority. Ethical considerations around safe, anonymised, long-term storage of human samples for future use must be addressed. While some patients may be concerned about the indefinite storage of samples and refuse consent for trial recruitment based on these concerns, there is a precedent for such a sample collection strategy in ARDS trials and this does not seem to have significantly affected recruitment (HARP-2;[146] PHIND, NCT04009330). There is also a considerable expense to biobanking that would require funding over multiple grant cycles. Creating national or international biobanking facilities is one solution to this problem, though harmonisation of minimum standards for access and compensation needs to be reached to facilitate this.[229] A potential framework for the collection, storage and processing of biological samples is presented in *Figure 3*

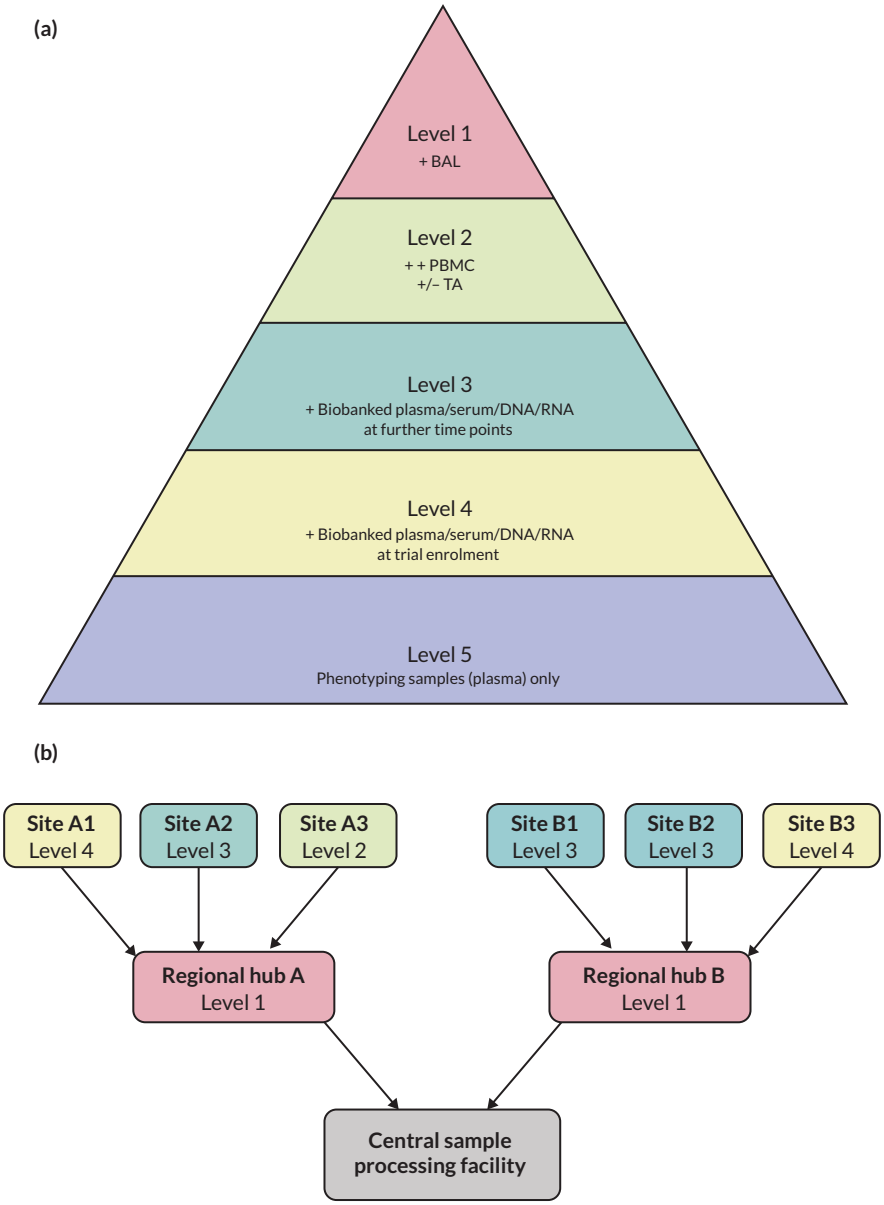


FIGURE 3 Embedded sampling approach. (a) A tiered biobanking approach based on participating site capacity. Participating sites are assigned a level based on their capacity for biological sampling. All sites participating in the trial collect biological samples (plasma) for phenotyping patients at trial enrolment (level 5). Level 4 sites will have access to −80 °C freezers and will additionally collect biobanked samples of plasma, serum, whole-blood DNA and whole-blood RNA. Level 3 sites will additionally collect biobanked samples at multiple time points. Level 2 sites will have access to tissue culture facilities and will additionally collect PBMCs +/− TA samples. Level 1 sites will additionally have access to clinical and laboratory expertise for collecting and processing BAL fluid. (b) A 'hub-and-spoke' schema to sample handling and collection for sites with limited equipment and expertise. Smaller sites (A1–A3 and B1–B3) can utilise the resources and equipment of their regional hub site (A and B) to collect and store samples. Smaller sites will generally be levels 2–5, with few expected level 5 sites. Regional hubs will generally be level 1 sites. Samples are later transferred from the regional hub to a central sample processing facility for analysis.

(*WP8*, *deliverable 2*). A sample handling guide has been drafted[230] (*WP8*, *deliverable 1).*

Stakeholders

Early career researchers

Several aspects of platform trials confer significant efficiency benefits over traditional trials, such as their prolonged nature, their capacity for broad patient inclusion and their ability to test multiple treatments in concurrent arms. However, these efficiencies could push emerging early career researchers (ECRs) out of the space. Platform trials are costly to initiate, meaning that they will initially be led by established researchers who have a demonstrated track record of delivering on large-scale funding opportunities. Without mentorship and inclusion, it is challenging for ECRs to gain experience in the delivery

of platform trials. Once platform trials are established, it is more cost-effective to add a new treatment arm than it is to initiate a new trial. Funders may support adding a new treatment arm to an existing platform rather than supporting a new trial that prominently features ECRs. Furthermore, if a new group of patients becomes of interest for a given treatment, an established platform trial could add a new domain with modified inclusion criteria for a lower price than starting a new trial. If the trial is not subject to review, it could consume most resources at recruiting sites, leaving little space for new clinical studies. Since a track record of publication and successful grant delivery is required for ECR career progression, poorly led platform trials could stifle career growth for ECRs and hinder the development of medical research. Based on these issues, there is concern that developing a platform trial may become an 'exercise in empire-building' for established investigators. New platform trials or mechanisms to include/rotate lead investigators should be required by funders to address these issues, starting from the time of trial conceptualisation and design. ECRs should be supported in trial engagement, as they will be the future leaders of the trial. Formalised efforts should be made to fairly recognise the contributions of all collaborators, including ECRs. We have established an ECR subcommittee for the PANTHER trial with engagement from a broad range of international researchers and have drafted an agreement for recognition of academic contributions (*WP6*, *deliverables 1 and 2*).

Industry partners

Platform trials provide an attractive mechanism, whereby pharmaceutical companies can rapidly screen candidate therapies, but platform trials may raise issues of concern for pharma partners. For example, platform trials may evaluate multiple candidate therapies that have intellectual property (IP) rights controlled by competing companies. In a platform trial led by academic clinicians, industry partners may have different priorities than lead investigators, such as the protection of IP and the construction of a package of evidence that is sufficient for regulatory approval and payer requirements.[231] To reach these requirements, industry partners may need to collect additional data, including more data points on each patient, veer away from composite end points and report additional safety parameters, including minor AEs. They are also likely to want to ensure that data regarding their IP are protected from competitors. While efficiency is ideal, industry partners need to be confident that academic investigators will ensure adequate safety reporting and oversight of data quality. Platform trials must balance academic interests with those of the pharmaceutical industry to ensure productive partnerships. While this is of less concern in a Phase II trial than in a standard Phase III trial targeted towards obtaining regulatory approval, these factors should be considered at the trial design phase for Phase II as well as Phase III trials. We have drafted an industrial collaboration agreement through multiple meetings with industry partners and international regulators to ensure that the needs of industry, academics and regulators are all met[232] (*WP7*, *deliverable 3)*. We have also drafted an international regulatory review document[233] (*WP3*, *deliverable 2*; *WP10*, *deliverable 1*).

Patients, families and the public

Involvement and engagement of patients and the public have become essential parts of the clinical trial process. This is particularly important in critical care where patients are critically ill, vulnerable and often unable to consent for themselves. Thus, an understanding of public and patient acceptability of critical care trial processes is essential. Public and patient involvement in the study design, conduct and material would improve acceptability and accessibility while ensuring relevance of the research question to the main beneficiaries. The public, especially post pandemic, may have some awareness of conventional Phase III clinical trials. However, in emerging designs, such as platform trials, integrating biological sample collection and stratifying patients using a precision medicine model, are newer concepts that will require public and patient engagement and involvement. Understanding their perceptions and opinions and identifying how best to co-ordinate and communicate these studies will be important tasks, with the goal of enhancing participant understanding, acceptance, recruitment and retention. Enhancing inclusivity and diversity within these activities, and the studies themselves, is challenging but essential, and focused efforts to accomplish this will be required. As part of this work, a PPI advisory group was established and supported by the European Lung Foundation (*WP9*, *deliverable 1*). PPI group meetings were regularly held and attended by ICU survivors and their families. There are two PPI co-applicants on the PANTHER grant (NIHR158714) (*WP9*, *deliverable 4*). A systematic review and large international survey (n = 9726 in 13 countries) were also undertaken, which found wide support for a precision medicine, adaptive platform trial, biological sampling and an inclusive consent process. These data are currently in preparation for publication (*WP9*, *deliverables 2*, *3*).

As aforementioned, platform trials have the potential to become 'empires' with regards to ECR involvement. Similarly, this is a concern with regards to patient access to research. Platform trials may consume significant resources at participating sites, limiting patient recruitment

to other studies. To maximise patient access to research, we propose (where scientifically feasible with regards to dilution of treatment effect) a broad coenrolment policy and a wide variety of active treatment arms in the PANTHER trial.

The patient perspective on outcome measures is also an important consideration for trial design. While short-term, unambiguous end points are important to platform trial operating characteristics, long-term quality of life outcomes may be more important to patients [such as return to work or World Health Organization (WHO) disability assessment schedule]. The PANTHER trial will include long-term quality of life outcome measures as exploratory outcomes where feasible.

Equality, diversity and inclusion

Perhaps one of the most difficult issues to address in healthcare research in general is that people often underserved by research are overlooked when it comes to trial recruitment. This problem is multifaceted and relates to language barriers, issues accessing health care and differences in how people in minority communities digest and discuss information around clinical trials. Potential solutions to this issue are multifaceted and must be endorsed from the outset in the PANTHER trial: developing trial materials with inclusion in mind, ensuring eligibility criteria do not limit participation, ensuring trial staff are culturally competent and building trusting partnerships with community organisations that work with ethnic minority groups. These recommendations are outlined in Trial Forge Guidance 3,[234] and should be employed in conjunction with a Diversity and Inclusion Plan.[235]

Learning from existing platforms

Existing critical care trials and trials in related fields have informed the development of the PANTHER trial (*WP5*, *deliverable 1*). As a reference point for future trial design, an analysis of some contemporaneous trials and design choices is presented in the Online Supplement (see *Report Supplementary Material 1, Table S1*).

The new National Institute for Health and Care Research trial

Based on the above considerations, the PANTHER Trial, an initial Phase II phenotype-stratified trial funded by NIHR is being designed based on expert consensus (> 70% agreement) and is summarised in *Table 3*. The expert committee did not utilise comprehensive processes described for the development of clinical practice guidelines, because expert consensus has been found to generate similar results to consensus processes for the development of clinical practice guidelines when a high degree of agreement is reached.[236] The PANTHER trial described here is in setup phase and in preparation for regulatory review at present.[142] A master protocol with appendices and a statistical analysis plan are in preparation for submission to regulators (*WP2*, *deliverable 6; overall deliverable 1*).

Core expert consensus principles (> 70% agreement) for designing an initial Phase II phenotype-stratified trial, The new PANTHER trial will focus on the hyper- and hypoinflammatory phenotypes of ARDS with provisions to modify the stratification approach or study new phenotypes in new domains as new evidence emerges. Initially, phenotyping will be performed using predefined clinical assessments and prospective cytokine measurements in combination with validated and parsimonious logistic regression models. A cut-off threshold of 0.5 numerical probability of phenotype assignment from logistic regression models[60] is proposed to dichotomise the hypoinflammatory and hyperinflammatory phenotypes. Based on generated data, this threshold could be varied for new treatments and domains as the trial progresses. Future domains could also use other classifier models, such as the validated clinical classifier model,[65] as more data accumulate. Due to current uncertainty about the stability of ARDS phenotypes, the trial will aim to recruit patients with the hyperinflammatory or hypoinflammatory phenotypes within the first 72 hours of meeting inclusion criteria, though phenotype also will be assessed later in the trial design.

Patients will be recruited into the trial using inclusion criteria defined by the proposed modification to the Berlin definition[76] and the global definition[81] of ARDS to maximise the potential therapeutic window (*Table 2*). Inclusion criteria can be expanded to other critical care syndromes by adding new domains as the trial progresses.

The new PANTHER trial will use a Bayesian adaptive multiarm platform design with traditional sequential block randomisation, without RAR, that enrols using a single master protocol with separate appendices for subdomains (*Figure 1a*). This approach will facilitate the study of multiple therapies in multiple phenotypes of ARDS simultaneously.[237] Stopping rules for efficacy in this trial will be built for a Phase II design, accepting a higher type I error rate than would be accepted in a Phase III design in exchange for trial efficiency. Similarly, stopping rules for futility will be decisive to allow the rapid introduction of new candidate

TABLE 3 Principles for designing an initial Phase II phenotype-stratified trial

1. Involve patients and members of the public in trial design and conduct, from planning to completion
2. Prioritise and support ECRs from the beginning of the study
3. Incorporate a Diversity and Inclusion Plan
4. Start the trial by examining the hyperinflammatory and hyperinflammatory phenotypes of ARDS
5. Start by stratifying patients using real-time cytokine measurements and a previously validated, simplified logistic regression model[59]
6. Initially, assign hyperinflammatory phenotype based on ≥ 0.5 probability of hyperinflammatory phenotype membership as generated from the regression model. Assign hypoinflammatory phenotype based on < 0.5 probability
7. Determine eligibility for the trial based on the modified criteria described in
8. Recruit patients within 72 hours of meeting inclusion criteria
9. Phenotype patients at enrolment and repeatedly determine phenotype at later time points to assess stability
10. Use a Bayesian adaptive multiarm design with traditional sequential block randomisation (see *Figure 1a*)
11. Use a single master trial protocol, with appendices for subdomains
12. Accept a higher type I error rate than traditionally used in Phase III trials when designing stopping rules for efficacy
13. Accept a higher type II error rate than traditionally used in Phase III trials when designing stopping rules for futility
14. Avoid RAR, at least initially
15. Make the trial open label, with a blinded trial steering committee
16. Recruit patients to the trial internationally
17. Have an open approach to coenrolment where feasible
18. Select candidate therapies for the trial that are potentially disease-modifying pharmaceutical agents
19. Define standard of care based on European Society of Intensive Care Medicine ARDS guidelines,[200] guidelines for weaning of vasopressors and inotropes[152] and guidelines for respiratory support[201]
20. Appoint a therapeutics prioritisation committee that has independent oversight. This group will determine therapies to include in the trial and should be composed of academics, pharmaceutical industry representatives and biostatisticians (*Figure 2*)
21. Embed pharmacometric evaluations within the trial
22. Fund the trial in an initial grant cycle for two to four treatments, with aims to add new treatments as evidence emerges
23. Use OSFDs at day 28 as the primary outcome
24. Incorporate long-term quality of life measures as exploratory outcomes
25. Make biobanking a core pillar of the trial design
26. Take a tiered approach to biobanking, allowing for sites with different equipment, expertise and capacity to collect some or all biological samples
27. Undertake biological sample analysis for the entire trial at one central, highly competent and accredited laboratory
28. Ensure biological sample collection, storage and processing adheres to multijurisdictional regulatory requirements
29. Ensure appropriate material transfer agreements for biological samples
30. Use existing national frameworks for biobanking where possible
31. Establish data-sharing agreements between academic contributors that prioritise co-operation and innovation
32. Involve ECRs from the outset of trial design through to delivery and reporting
33. Establish a trial charter outlining a mechanism for shared academic credit, a mechanism for onboarding ECRs and a mechanism for leadership transfer
34. Ensure data outputs meet industry standards
35. Harmonise platform trial design across multiple global jurisdictions
36. Consider industry requirements for regulatory approval when designing the trial
37. Ensure a transparent governance structure that ensures independence and leadership of academic investigators while engaging with industry partners
38. Establish drug-specific responsibility between sponsor and industry partners in the master protocol
39. Establish a mechanism for 'firewalling' data between competing industry partners
40. Ensure data and biological samples are owned and controlled by academic sponsors, with mechanisms for sharing with industry partners

therapeutics to the trial, once again accepting a higher type II error rate than usually employed in a Phase III design. The purpose of this platform design is to rapidly identify promising candidate therapies that could be progressed to a Phase III traditional RCT, accepting the risk that a therapy may be progressed and later show no benefit in Phase III or, conversely, that a therapy with a small positive effect might be dropped from the Phase II trial.

The PANTHER trial will use an open-label design for reasons of practicality and efficiency. However, the trial steering committee, design team and statistical team will be blinded to minimise bias in decision-making at adaptive analyses. The trial will be international in scope to facilitate recruitment and improve generalisability.

Candidate therapies studied will be potentially disease-modifying therapeutic agents rather than supportive care strategies. Therapies will be prioritised for the study by an expert committee composed of academic scientists, pharmaceutical industry representatives and biostatisticians. This group will have independent oversight. The trial will be funded in an initial grant cycle for two to four treatments, aiming to add new treatments as evidence emerges. Pharmacometric evaluations will be embedded within the trial where practicable.

To take advantage of an adaptive trial design, a shorter-term composite outcome measure incorporating non-pulmonary organ failure will be used as the primary outcome. This more immediate outcome measure will facilitate adaptive analyses and stopping rules in the proposed adaptive platform design and will allow the rapid declaration of efficacy or futility based on predefined stopping rules. A composite outcome measure considering respiratory and other organ failures is also under consideration, which could allow additional power to detect clinically meaningful significant treatment effects at this earlier time. OSFDs through day 28 will be used as a primary outcome in PANTHER. OSFDs through day 28 would score persistent respiratory, cardiovascular and renal support. Mortality would be scored lower than persistent organ support at day 28 (−1 vs. 0 on an ordinal scale). OSFDs have been successfully used as a primary end point in REMAP-CAP and correlate well with long-term survival at 180 days, indicating that success for therapy in a Phase II design based on the improvement of OSFDs suggests success in a later Phase III design that uses longer-term mortality as a primary end point.[106]

Biobanking will be a core component of the PANTHER trial design to allow further understanding of ARDS phenotypes and their response to treatment. It will also facilitate secondary analyses and the discovery of new biological phenotypes. Biobanking is not without its difficulties, and as such, a tiered approach to sample collection for clinical trial sites with variable access to equipment and levels of expertise is proposed (*Figure 3a*) (*WP8*, *deliverable 2*). Collection of recommended plasma, serum and cellular samples requires access to basic laboratory equipment (e.g. access to centrifuges and freezer storage at −20 °C or −80 °C); this should be possible at most sites. Whole blood for DNA sequencing and RNA sequencing can be easily collected in RNA and DNA stabilisation tubes and can be immediately frozen for transportation to a central laboratory.[224] This should be possible at most sites. Most sites should be able to collect these samples at the baseline of trial enrolment, and a subset of sites should be able to collect longitudinal samples at repeated times. PBMC extraction will be employed at select sites to facilitate studies of circulating immune cell populations. Although it is significantly less labour-intensive than traditional protocols, PBMC extraction with premade CPTs would require lab expertise and access to liquid nitrogen storage. Deep respiratory samples will also be collected at selected sites to facilitate mechanistic work demonstrating cellular and biochemical changes in the target tissue in response to treatment/phenotype interactions. For those sites unable to collect deep respiratory samples, TA samples will be collected as a surrogate, with the caveat that upper airway respiratory samples may not represent changes at the alveolar level.

Collected samples must adhere to multijurisdictional regulatory requirements and will require appropriate material transfer agreements, which are currently in development (*WP8*, *deliverable 3*). Collected trial samples will be analysed at one centralised, highly competent and accredited laboratory to minimise variability and maximise rigour. Regional lead centres may have more access to the expertise and equipment for biological sampling that can be shared with smaller sites. Accordingly, a 'hub-and-spoke model' for sample collection and processing is detailed in *Figure 3b* (*WP8*, *deliverable 2*). Biobanking efforts will build on and leverage existing national frameworks where possible while adhering to the master protocol for sample handling and collection. Efforts will be made to obtain ethical approval to store samples indefinitely.

The ECRs will be involved from the outset of trial design to delivery and reporting. A trial was established at the outset that outlines a mechanism for shared academic credit, a mechanism for adding ECRs with innovative ideas to the trial team and a mechanism for transferring trial leadership from established to emerging investigators as the platform progresses (*WP6*, *deliverables 1 and 2*).

An effort has been made to balance the priorities of academic investigators with industry partners from trial outset. Data outputs will meet industry standards (*WP7*, *deliverable 1*). Contemporary platform trials in different global jurisdictions should endeavour to collaborate and harmonise on key areas such as patient selection, minimum data sets, sample collection and trial end points. Though not of primary concern in a Phase II trial, the platform's design will consider requirements for multijurisdictional regulatory approval. The trial's governance structure is designed to be transparent and robustly engage industry partners while ensuring the independence and leadership of academic investigators. Details of drug-handling responsibility and AE reporting between the industry partner and the trial sponsor will be prespecified (*WP7*, *deliverable 2*), as well as mechanisms by which data can be 'firewalled' between industry partners, thereby protecting the IP rights. The ownership and management of biological samples will rest with the academic sponsor, with prespecified agreements for data and material transfer to industry partners.

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Conclusions

With the advent of real-time patient classification methods that use readily available clinical data and rapid blood-based measurements, a phenotype-stratified precision medicine trial is now possible in critical care respiratory failure, with an initial emphasis on ARDS. The new PANTHER trial will focus initially on the hyperinflammatory and hypoinflammatory phenotypes first identified in ARDS[32] with a view to later expanding the target population to patients with AHRF (with or without ARDS). A summary of this trial framework is shown in *Table 3*. An advantage of this framework is that other phenotyping strategies and treatments can be added to the platform over time as new evidence emerges in the form of new platform domains.

A phenotype-stratified trial such as PANTHER will require a large international collaboration and extensive work between academics, regulatory agencies, government sponsors and pharmaceutical industry collaborators. Recent platform trial successes in COVID-19 have paved the way for such collaborations. Designing a phenotype-stratified platform trial will involve multiple complex considerations, as it will require the inclusion of industry-supported diagnostic tests and pharma-supported repurposed and novel therapeutics. These diagnostics and therapeutics will be used in multiple jurisdictions, creating potential regulatory challenges.

There is still much to learn about the mechanistic underpinnings of critical care and ARDS phenotypes, and there is a strong rationale to test several therapies in a stratified trial design. Rigorous, transparent procedures for therapeutics prioritisation are necessary, and the interventions discussed above will provide an initial starting point, with a view to incorporating more novel interventions as the platform progresses.

Embedding biobanking of samples from the blood, plasma and air spaces is a key underpinning of the PANTHER phenotype-stratified trial, given our early but limited understanding of the hyperinflammatory and hypoinflammatory ARDS phenotypes as well as how biology may provide new insights when patients treated with HFNO are included. While biobanked samples will be stored centrally to ensure consistency, open access to samples and data generated across collaborators is of key importance (*WP8*, *deliverable 3*). Analysis of these samples may guide the introduction of new therapies to the platform and further the understanding of critical illness syndromes.

Through learning from and building on existing platform trials, the new PANTHER Phase II phenotype-stratified platform trial will accelerate the pace of critical care research and expand our understanding of the pathophysiology of critical illness. This new platform trial will involve global cooperation and shared credit with a goal of remaining active for years. At present, the PANTHER trial collaborative includes a diverse array of researchers from the UK, the USA, Canada, Japan, Germany, France, Italy, Ireland, Australia, New Zealand, the United Arab Emirates, Brazil, Colombia and representatives for LMICs in Asia and Africa.[142] This collaborative is actively expanding membership (*overall deliverable 3*). Broad engagement across academics and industry, across ECRs and late career researchers, across patient demographics and across the globe should allow efficient and inclusive testing of multiple candidate therapies in a stratified critically ill population, thereby improving outcomes for patients through identifying promising therapies that can be confirmed in traditional double-blind placebo-controlled Phase III trials. Using this approach, precision medicine in critical care will make important strides toward reality.

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List of supplementary material

Report supplementary material 1
Supplementary material

Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/TTND8896).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

AE	adverse event
AHRF	acute hypoxaemic respiratory failure
ALVEOLI	Assessment of Low Tidal Volume and Elevated End-Expiratory Volume to Obviate Lung Injury
ARDS	acute respiratory distress syndrome
ARDSnet	Acute Respiratory Distress Network
BAL	bronchoalveolar lavage
C5a	complement component 5a
CHARM	Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity
CI	confidence interval
CIHR	Canadian Institutes of Health Research
COVID	coronavirus disease
COVID-19	coronavirus disease discovered in 2019
CPT	cell preparation tube
CT	computerised tomography
DAD	diffuse alveolar damage
DAMP	damage-associated molecular pattern
DNA	deoxyribonucleic acid
ECR	early career researcher
EMA	European Medicines Agency
FACTT	Fluid and Catheter Treatment Trial
FDA	Food and Drug Administration
FIO_2	fractional inspired oxygen
HARP-2	Hydroxymethylglutaryl-CoA Reductase Inhibition with Simvastatin in Acute Lung Injury to Reduce Pulmonary Dysfunction
HFNO	high-flow nasal oxygen
HR	hazard ratio
HTE	heterogeneity of treatment effect
IBD	inflammatory bowel disease
IC14	atibuclimab
ICU	intensive care unit
IL-6	interleukin-6
IL-8	interleukin-8
IP	intellectual property
I-SPY 2	Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis 2
I-SPY COVID	Adaptive Platform Trial to Reduce Mortality and Ventilator Requirements for Critically Ill Patients
LCA	latent class analysis
LMICs	low- and middle-income countries
LPS	lipopolysaccharide
LUNG SAFE	large observational study to understand the global impact of severe acute respiratory failure
NBBAL	non-bronchoscopic bronchoalveolar lavage
NHLBI	National Heart, Lung, and Blood Institute (US)
NIH	National Institutes of Health (US)
NIHR	National Institute for Health and Care Research

OR	odds ratio
OSFD	organ-support free day
PAMP	pathogen-associated molecular pattern
PANTHER	Precision medicine Adaptive Network platform Trial in Hypoxaemic acutE respiratory failuRe
PaO_2	partial pressure of arterial oxygen
PBMC	peripheral blood mononuclear cell
PEEP	positive end-expiratory pressure
PETAL	Prevention and Early Treatment of Acute Lung Injury
PHIND	Clinical Evaluation of a Point of Care Assay to Identify Phenotypes in the Acute Respiratory Distress Syndrome
RAR	response-adaptive randomisation
RCT	randomised controlled trial
RECOVERY	Randomised Evaluation of COVID-19 Therapy
REMAP-CAP	Randomised Embedded Multifactorial Adaptive Platform for Community-Acquired Pneumonia
RNA	ribonucleic acid
SP-D	surfactant protein D
SpO_2	saturation of peripheral oxygen
sTNFR1	soluble tumour necrosis factor receptor 1
TA	tracheal aspirate
TNF-A	tumour necrosis factor alpha
VFD	ventilator-free day
WHO	World Health Organization

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