



Research Article

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

Kiran Reddy^{1*}, Neil Aggarwal², Narges Alipanah-Lechner³, Djillali Annane⁴, David B Antcliffe⁵, Daphne Babalis⁶, J Kenneth Baillie⁷, Abigail Beane⁷, Lieuwe DJ Bos⁸, Aidan Burrell⁹, Carolyn S Calfee³, Kiki Cano-Gamez¹⁰, Victoria R Cornelius⁶, Mary Cross⁶, Emma Davenport¹¹, Lorenzo del Sorbo¹², Laura Esserman¹³, Eddy Fan¹², Vito Fanelli¹⁴, Niall D Ferguson¹², D Clark Files¹⁵, Christoph Fisser¹⁶, Shigeki Fujitani¹⁷, Ewan C Goligher¹², Anthony C Gordon⁵, Giacomo Grasselli¹⁸, Fergus Hamilton¹⁹, Rashan Haniffa⁷, Andrea Haren²⁰, Daniel JR Harvey²¹, Leanne M Hays²², Anna Heath²³, Nicholas Heming⁴, Susanne Herold²⁴, Tim Hicks²⁵, Nao Ichihara²⁶, Vinod Jaiswal²⁷, Jun Kataoka²⁸, Julian C Knight²⁹, Patrick R Lawler^{30,31}, Kathleen Liu³, John C Marshall³¹, David M Maslove³², Michael A Matthay³³, Daniel F McAuley¹, Nuala J Meyer³⁴, Jonathan A Millar⁷, Holger Müller-Redetzky³⁵, Alistair Nichol³⁶, John Norrie³⁷, Marlies Ostermann³⁸, Andrew Owen³⁹, Cecilia M O’Kane¹, Dhruv Parekh⁴⁰, Rachel Phillips⁶, Duncan Richards⁴¹, Bram Rochweg⁴², Anthony J Rostron⁴³, Hiroki Saito⁴⁴, Romit J Samanta⁴⁵, Vittorio Scaravilli⁴⁶, Wesley Self⁴⁷, Manu Shankar-Hari⁷, A John Simpson⁴², Pratik Sinha⁴⁸, Marry R Smit⁸, Jonathan Stewart¹, B Taylor Thompson⁴⁹, István Vadasz²⁴, Ed Waddingham⁶, Steve Webb⁹, Graham Wheeler⁶, D Martin Witzenrath³⁴, Mark M Wurfel⁵⁰ and Thomas R Martin⁵⁰

¹Wellcome-Wolfson Institute for Experimental Medicine, Queen’s University Belfast, Belfast, UK

²Division of Pulmonary Sciences and Critical Care, Department of Medicine, University of Colorado, Aurora, CO, USA

³Division of Pulmonary, Critical Care, Allergy, and Sleep Medicine, Department of Medicine, University of California San Francisco, San Francisco, CA, USA

⁴INSERM U1173, Université de Versailles SQY-Université Paris Saclay, Garches, France

⁵Department of Surgery & Cancer, Faculty of Medicine, Imperial College London, London, UK

⁶School of Public Health, Faculty of Medicine, Imperial College London, London, UK

⁷Centre for Inflammation Research, Deanery of Clinical Sciences, University of Edinburgh, Midlothian, UK

⁸Department of Intensive Care and Laboratory of Experimental Intensive Care and Anaesthesiology, Amsterdam UMC, Amsterdam, The Netherlands

⁹School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia

¹⁰Department of Clinical and Biomedical Sciences, University of Exeter, Exeter, UK

¹¹Wellcome Sanger Institute, Cambridgeshire, UK

¹²Interdepartmental Division of Critical Care Medicine, University of Toronto, Li Ka Shing Knowledge Institute, Toronto, Canada

¹³Department of Surgery, University of California San Francisco, San Francisco, CA, USA

¹⁴Anesthesiology and Intensive Care Division, Surgical Sciences Department, Città della Salute e della Scienza, University of Turin, Turin, Italy

¹⁵Section of Pulmonary, Critical Care, Allergy, and Immunology, School of Medicine, Wake Forest University, Winston-Salem, NC, USA

- ¹⁶Department of Internal Medicine II, University Hospital Regensburg, Regensburg, Germany
- ¹⁷Department of Emergency and Critical Care Medicine, St. Marianna University School of Medicine, Kanagawa, Japan
- ¹⁸Department of Emergency, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
- ¹⁹Department of Population Health Sciences, University of Bristol, Bristol, UK
- ²⁰Department of Anaesthesiology and Intensive Care, St. Vincent's University Hospital, Dublin, Ireland
- ²¹Division of Anaesthesia and Intensive Care, School of Medicine, The University of Nottingham, Nottingham, UK
- ²²University College Dublin Clinical Research Centre, St. Vincent's University Hospital, Dublin, Ireland
- ²³Division of Biostatistics, Dalla Lana School of Public Health, University of Toronto, Toronto, Canada
- ²⁴Department of Internal Medicine V, University of Giessen and Marburg Lung Center, Giessen, Germany
- ²⁵NIHR Newcastle In Vitro Diagnostics Co-operative, Newcastle University, Newcastle upon Tyne, UK
- ²⁶Osaka University, Osaka, Japan
- ²⁷Department of Intensive Care, Mediclinic City Hospital, Dubai, United Arab Emirates
- ²⁸Department of Pulmonary and Critical Care Medicine, Tokyo Bay Urayasu Ichikawa Medical Center, Urayasu, Japan
- ²⁹Wellcome Centre for Human Genetics, Nuffield Department of Medicine, University of Oxford, Oxford, UK
- ³⁰Cardiology Division, McGill University Health Centre, McGill University, Montreal, Canada
- ³¹Department of Surgery, University of Toronto, Toronto, Canada
- ³²Department of Critical Care Medicine, School of Medicine, Queen's University, Kingston, Canada
- ³³Department of Medicine, Cardiovascular Research Institute, University of California San Francisco, San Francisco, CA, USA
- ³⁴Pulmonary, Allergy, and Critical Care Division, School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
- ³⁵Department of Infectious Diseases, Respiratory Medicine and Critical Care, Charité-Universitätsmedizin Berlin, Berlin, Germany
- ³⁶Department of Critical Care Medicine, School of Medicine, University College Dublin, Health Sciences Centre, Dublin, Ireland
- ³⁷Edinburgh Clinical Trials Unit, University of Edinburgh, Edinburgh, UK
- ³⁸Department of Critical Care Medicine, King's College London, Guy's & St Thomas Hospital, London, UK
- ³⁹Centre of Excellence in Long-acting Therapeutics (CELT), Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, UK
- ⁴⁰Birmingham Acute Care Research Group, Institute of Inflammation and Ageing, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK
- ⁴¹Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Disorders, University of Oxford, Oxford, UK
- ⁴²Faculty of Health Sciences, McMaster University, Hamilton, Canada
- ⁴³Translation and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK
- ⁴⁴Department of Emergency and Critical Care Medicine, St. Marianna University Yokohama Seibu Hospital, Yokohama, Japan
- ⁴⁵Department of Medicine, School of Clinical Medicine, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK
- ⁴⁶Department of Biomedical, Surgical, and Dental Sciences, University of Milano, Milan, Italy
- ⁴⁷Department of Emergency Medicine, School of Medicine, Vanderbilt University, Nashville, TN, USA
- ⁴⁸Department of Anesthesiology, Washington University in St. Louis, St. Louis, WA, USA
- ⁴⁹Division of Pulmonary and Critical Care, Department of Medicine, Harvard University, Boston, MA, USA
- ⁵⁰Division of Pulmonary and Critical Care, Department of Medicine, University of Washington, Seattle, WA, USA

*Corresponding author k.reddy@qub.ac.uk

Published July 2025

DOI: 10.3310/TTND8896

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.

Funding: This article presents independent research funded by the (NIHR) Efficacy and Mechanism Evaluation programme as award number NIHR154493.

A plain language summary of this research article is available on the NIHR Journals Library Website <https://doi.org/10.3310/TTND8896>.

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 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 ($\text{PaO}_2/\text{FiO}_2$ 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 clinical²² 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 antagonists²³]. 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 strategy³³ 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 ARDS³⁸ 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 identified⁴⁴ 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 acuteE 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 ARDS⁴¹ 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.

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

Work package	Deliverable
WP1: Defining study population and interventions	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 1. Develop a series of standard operating procedures for trial delivery
WP6: Building capacity	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 1. Hold meetings with regulatory authorities to ensure that all the requirements for regulatory approvals across multiple jurisdictions can be achieved
Overall deliverables	<ol style="list-style-type: none"> 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 measurements⁶⁰ 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 ARDS³⁹ 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 ARDS⁷⁶ and the Sepsis-3 definition⁷⁷ 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 ($\text{SpO}_2/\text{FiO}_2$) ratio in place of the $\text{PaO}_2/\text{FiO}_2$ 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 $\text{SpO}_2/\text{FiO}_2$ 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 ARDS⁷⁶ and the global definition⁸¹

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 $\text{SpO}_2/\text{FiO}_2$ 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

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 <ul style="list-style-type: none"> Mild – $200 \text{ mmHg} < \text{PaO}_2/\text{FiO}_2 \leq 300 \text{ mmHg}$ with $\text{PEEP} \geq 5 \text{ cm H}_2\text{O}$ Moderate – $100 \text{ mmHg} < \text{PaO}_2/\text{FiO}_2 \leq 200 \text{ mmHg}$ with $\text{PEEP} \geq 5 \text{ cm H}_2\text{O}$ Severe – $\text{PaO}_2/\text{FiO}_2 \leq 100$ with $\text{PEEP} \geq 5 \text{ cm H}_2\text{O}$
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 <ul style="list-style-type: none"> $\text{PaO}_2/\text{FiO}_2 \leq 300 \text{ mmHg}$ or $\text{SpO}_2/\text{FiO}_2 \leq 315$ (if $\text{SpO}_2 \leq 97\%$) on HFNO $> 30 \text{ LPM}$ or NIV with $\text{PEEP} \geq 5 \text{ cmH}_2\text{O}$ Intubated ARDS <ul style="list-style-type: none"> Mild – $200 \text{ mmHg} < \text{PaO}_2/\text{FiO}_2 \leq 300 \text{ mmHg}$ or $235 < \text{SpO}_2/\text{FiO}_2 \leq 315$ (if $\text{SpO}_2 \leq 97\%$) Moderate – $100 \text{ mmHg} < \text{PaO}_2/\text{FiO}_2 \leq 200 \text{ mmHg}$ or $148 < \text{SpO}_2/\text{FiO}_2 \leq 235$ (if $\text{SpO}_2 \leq 97\%$) Severe – $\text{PaO}_2/\text{FiO}_2 \leq 100 \text{ mmHg}$ or $\text{SpO}_2/\text{FiO}_2 \leq 148$ (if $\text{SpO}_2 \leq 97\%$) Modified definition for resource-variable settings <ul style="list-style-type: none"> $\text{SpO}_2/\text{FiO}_2 \leq 315$ (if $\text{SpO}_2 \leq 97\%$)
Proposed modification			Bilateral opacities on CXR or CT not fully explained by effusions, lobar/lung collapse or nodules		Non-intubated ARDS <ul style="list-style-type: none"> $\text{PaO}_2/\text{FiO}_2 \leq 300 \text{ mmHg}$ or $\text{SpO}_2/\text{FiO}_2 \leq 315$ (if $\text{SpO}_2 \leq 97\%$) on HFNO $> 30 \text{ LPM}$ or NIV with $\text{PEEP} \geq 5 \text{ cmH}_2\text{O}$ Intubated ARDS <ul style="list-style-type: none"> Mild – $200 \text{ mmHg} < \text{PaO}_2/\text{FiO}_2 \leq 300 \text{ mmHg}$ or $235 < \text{SpO}_2/\text{FiO}_2 \leq 315$ (if $\text{SpO}_2 \leq 97\%$) Moderate – $100 \text{ mmHg} < \text{PaO}_2/\text{FiO}_2 \leq 200 \text{ mmHg}$ or $148 < \text{SpO}_2/\text{FiO}_2 \leq 235$ (if $\text{SpO}_2 \leq 97\%$) Severe – $\text{PaO}_2/\text{FiO}_2 \leq 100 \text{ mmHg}$ or $\text{SpO}_2/\text{FiO}_2 \leq 148$ (if $\text{SpO}_2 \leq 97\%$)

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 $\text{SpO}_2/\text{FiO}_2$ 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

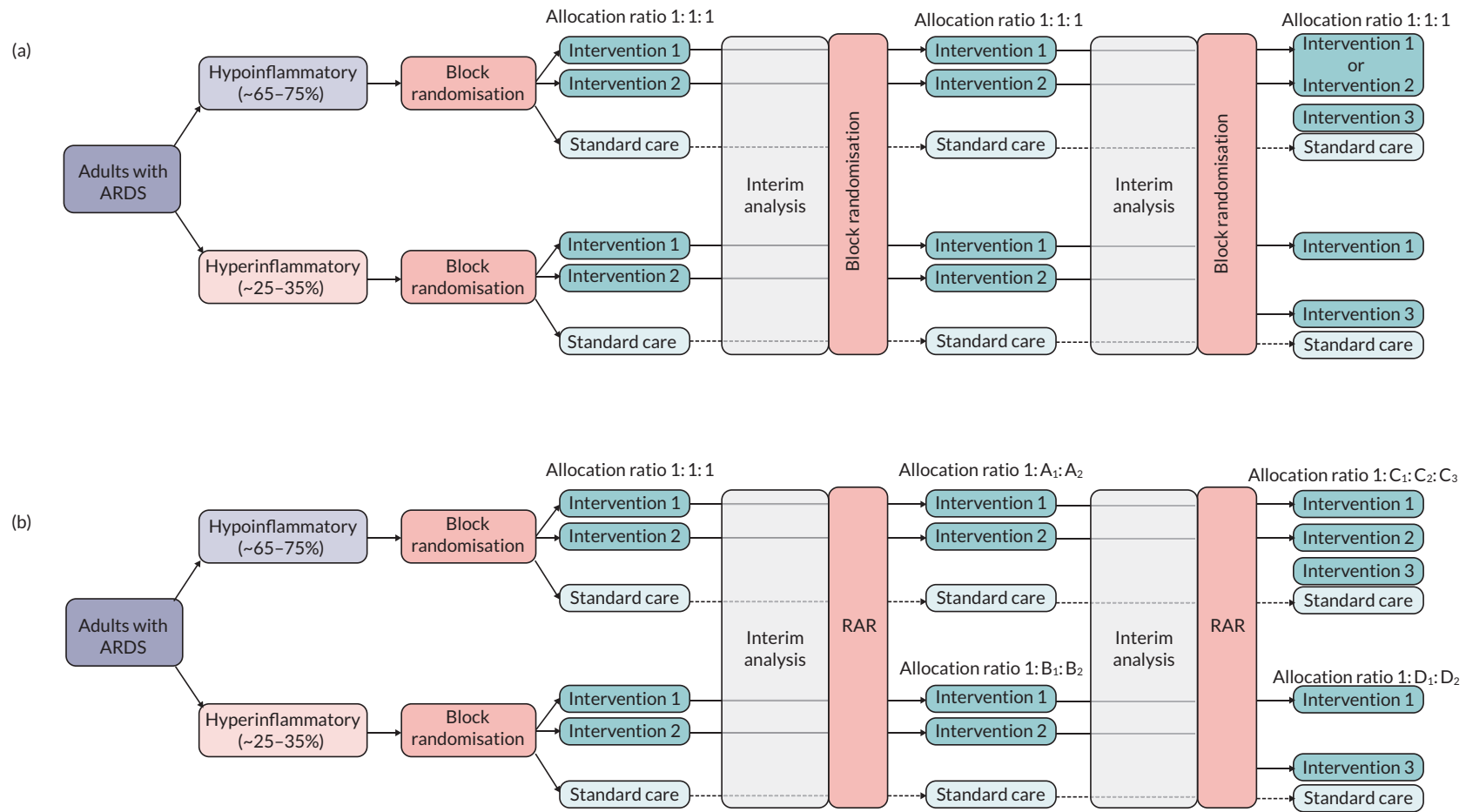


FIGURE 1 Two platform trial designs. (a) A platform trial design stratified by the hyperinflammatory and hypoinflammatory phenotypes of ARDS, which utilises continued block randomisation in a Bayesian adaptive multiarm trial design approach without RAR, stratified by phenotype. At interim analysis, interventions 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 strategies³² in the Assessment of Low Tidal Volume and Elevated End-Expiratory Volume to Obviate

Lung Injury (ALVEOLI) RCT,¹⁴⁴ liberal versus conservative fluid administration strategies³³ in the Fluid and Catheter Treatment Trial (FACTT) RCT,¹⁴⁵ simvastatin³⁴ in the Hydroxymethylglutaryl-CoA Reductase Inhibition with Simvastatin in Acute Lung Injury to Reduce Pulmonary Dysfunction (HARP-2) RCT¹⁴⁶ 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 RCT¹⁵⁶ 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 phenotype⁴⁴), 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

Atibuclelimab

A chimeric monoclonal antibody, atibuclelimab (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/Ila 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-1 β , 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 inotropes¹⁵² and respiratory support²⁰¹ (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 data²⁰² 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 trial²⁰⁴ (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

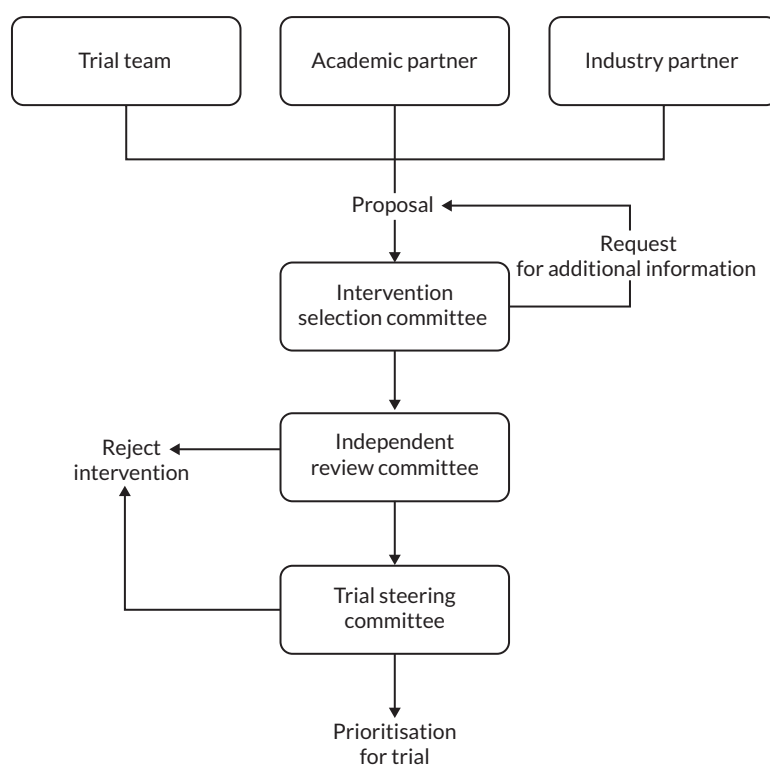


FIGURE 2 Framework for therapeutics prioritisation.

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.

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 profile⁵² or inflammasome-associated biomarkers²²³) 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*

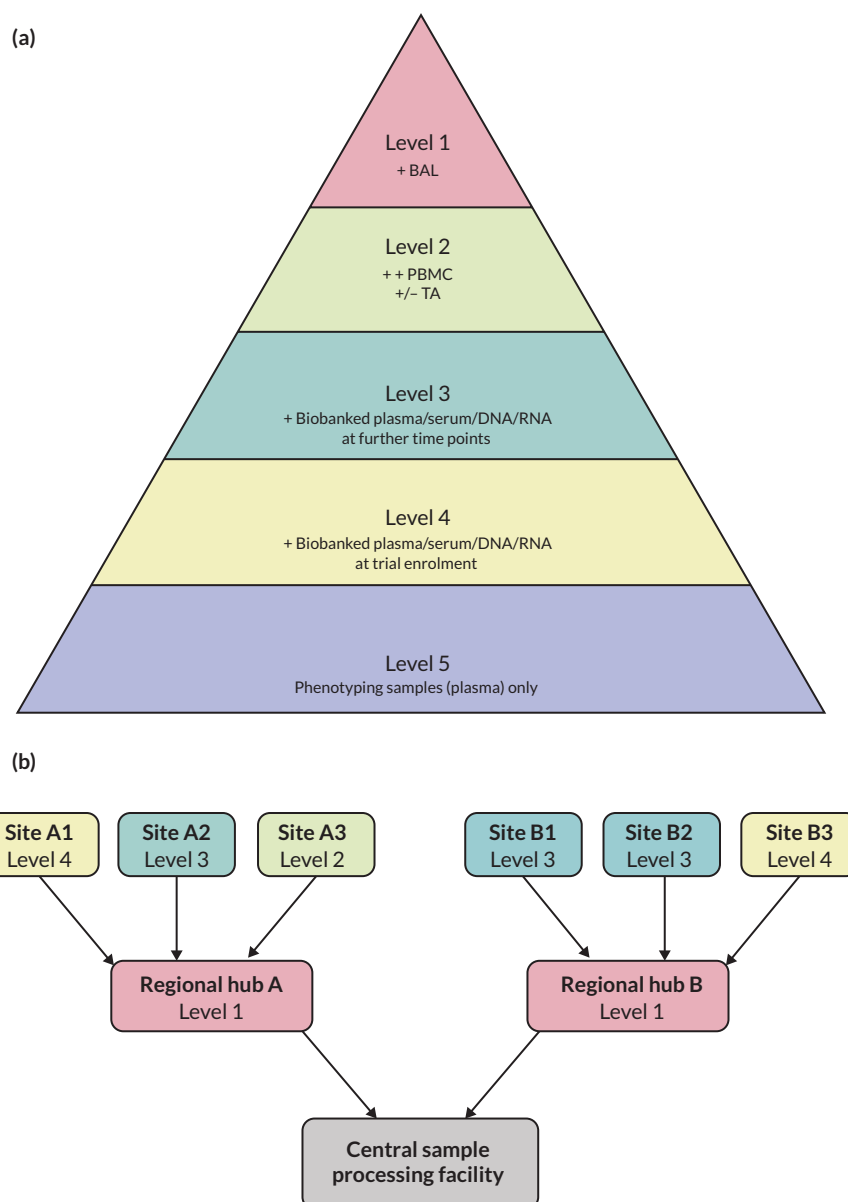


FIGURE 3 Embedded sampling approach. (a) A tiered biobanking approach based on participating site capacity. Participating sites are assigned a level based on their capacity for biological sampling. All sites participating in the trial collect biological samples (plasma) for phenotyping patients at trial 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 drafted²³⁰ (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 met²³² (WP7, deliverable 3). We have also drafted an international regulatory review document²³³ (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 enrolment 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 models⁶⁰ 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 definition⁷⁶ and the global definition⁸¹ 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 enrolls 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 model⁵⁹
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 inotropes¹⁵² and guidelines for respiratory support²⁰¹
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.

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 ARDS³² 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.

Additional information

CRedit contribution statement

Kiran Reddy (<https://orcid.org/0000-0002-1621-1481>): Conceptualisation (equal), Funding acquisition (supporting), Writing – original draft (lead), Writing – review & editing (lead).

Neil Aggarwal (<https://orcid.org/0000-0002-0922-8824>): Conceptualisation (equal), Funding acquisition (supporting), Writing – review & editing (supporting).

Narges Alipanah-Lechner (<https://orcid.org/0000-0002-8381-5701>): Conceptualisation (equal), Writing – review & editing (supporting).

Djillali Annane (<https://orcid.org/0000-0001-6805-8944>): Conceptualisation (equal), Funding acquisition (supporting), Writing – review & editing (supporting).

David B Antcliffe (<https://orcid.org/0000-0002-1846-9160>): Conceptualisation (equal), Writing – review & editing (supporting).

Daphne Babalis (<https://orcid.org/0000-0001-9654-4130>): Conceptualisation (equal), Funding acquisition (supporting), Project administration (lead), Writing – review & editing (supporting).

J Kenneth Baillie (<https://orcid.org/0000-0001-5258-793X>): Conceptualisation (equal), Writing – review & editing (supporting).

Abigail Beane (<https://orcid.org/0000-0001-7046-1580>): Conceptualisation (equal), Funding acquisition (supporting), Writing – review & editing (supporting).

Lieuwe DJ Bos (<https://orcid.org/0000-0003-2911-4549>): Conceptualisation (equal), Funding acquisition (supporting), Writing – review & editing (supporting).

Aidan Burrell (<https://orcid.org/0000-0001-8430-9678>): Conceptualisation (equal), Funding acquisition (supporting), Writing – review & editing (supporting).

Carolyn S Calfee (<https://orcid.org/0000-0001-9208-6865>): Conceptualisation (equal), Funding acquisition (supporting), Writing – review & editing (supporting).

Kiki Cano-Gamez (<https://orcid.org/0000-0003-2753-1226>): Conceptualisation (equal), Writing – review & editing (supporting).

Victoria R Cornelius (<https://orcid.org/0000-0002-0080-1065>): Conceptualisation (equal), Funding acquisition (supporting), Methodology (equal), Writing – review & editing (supporting).

Mary Cross (<https://orcid.org/0000-0002-9663-7270>): Conceptualisation (equal), Project administration (supporting), Writing – review & editing (supporting).

Emma Davenport (<https://orcid.org/0000-0002-8768-346X>): Conceptualisation (equal), Writing – review & editing (supporting).

Lorenzo del Sorbo (<https://orcid.org/0000-0003-3294-9838>): Conceptualisation (equal), Writing – review & editing (supporting).

Laura Esserman (<https://orcid.org/0000-0001-9202-4568>): Conceptualisation (equal), Writing – review & editing (supporting).

Eddy Fan (<https://orcid.org/0000-0002-1210-9914>): Conceptualisation (equal), Writing – review & editing (supporting).

Vito Fanelli (<https://orcid.org/0000-0002-1647-2411>): Conceptualisation (equal), Writing – review & editing (supporting).

Niall D Ferguson (<https://orcid.org/0000-0002-6213-5264>): Conceptualisation (equal), Funding acquisition (supporting), Writing – review & editing (supporting).

D Clark Files (<https://orcid.org/0000-0002-1595-4080>): Conceptualisation (equal), Funding acquisition (supporting), Writing – review & editing (supporting).

Christoph Fisser (<https://orcid.org/0000-0001-5833-1230>): Conceptualisation (equal), Writing – review & editing (supporting).

Shigeki Fujitani (<https://orcid.org/0000-0001-6327-682X>): Conceptualisation (equal), Writing – review & editing (supporting).

Ewan C Goligher (<https://orcid.org/0000-0002-0990-6701>): Conceptualisation (equal), Funding acquisition (supporting), Writing – review & editing (supporting).

Anthony C Gordon (<https://orcid.org/0000-0002-0419-547X>): Conceptualisation (equal), Funding acquisition (supporting), Writing – review & editing (supporting).

Giacomo Grasselli (<https://orcid.org/0000-0002-1735-1400>): Conceptualisation (equal), Funding acquisition (supporting), Writing – review & editing (supporting).

Fergus Hamilton (<https://orcid.org/0000-0002-9760-4059>): Conceptualisation (equal), Writing – review & editing (supporting).

Rashan Haniffa (<https://orcid.org/0000-0002-8288-449X>): Conceptualisation (equal), Writing – review & editing (supporting).

Andrea Haren: Conceptualisation (equal), Writing – review & editing (supporting).

Daniel JR Harvey (<https://orcid.org/0000-0002-5165-3277>): Conceptualisation (equal), Writing – review & editing (supporting).

Leanne M Hays (<https://orcid.org/0000-0002-6936-1459>): Conceptualisation (equal), Funding acquisition (supporting), Writing – review & editing (supporting).

Anna Heath (<https://orcid.org/0000-0002-7263-4251>): Conceptualisation (equal), Methodology (supporting), Writing – review & editing (supporting).

Nicholas Heming (<https://orcid.org/0000-0002-4537-7595>): Conceptualisation (equal), Writing – review & editing (supporting).

Susanne Herold (<https://orcid.org/0000-0001-6343-0911>): Conceptualisation (equal), Funding acquisition (supporting), Writing – review & editing (supporting).

Tim Hicks (<https://orcid.org/0000-0002-0942-696X>): Conceptualisation (equal), Writing – review & editing (supporting).

Nao Ichihara (<https://orcid.org/0000-0002-6902-2342>): Conceptualisation (equal), Writing – review & editing (supporting).

Vinod Jaiswal (<https://orcid.org/0000-0001-8365-6758>): Conceptualisation (equal), Writing – review & editing (supporting).

Jun Kataoka (<https://orcid.org/0000-0002-2881-1644>): Conceptualisation (equal), Writing – review & editing (supporting).

Julian C Knight (<https://orcid.org/0000-0002-0377-5536>): Conceptualisation (equal), Writing – review & editing (supporting).

Patrick R Lawler (<https://orcid.org/0000-0001-5155-5071>): Conceptualisation (equal), Writing – review & editing (supporting).

Kathleen Liu (<https://orcid.org/0000-0003-4891-8649>): Conceptualisation (equal), Writing – review & editing (supporting).

John C Marshall (<https://orcid.org/0000-0002-7902-6291>): Conceptualisation (equal), Writing – review & editing (supporting).

David M Maslove (<https://orcid.org/0000-0002-0765-7158>): Conceptualisation (equal), Writing – review & editing (supporting).

Michael A Matthay (<https://orcid.org/0000-0003-3039-8155>): Conceptualisation (equal), Funding acquisition (supporting), Writing – review & editing (supporting).

Daniel F McAuley (<https://orcid.org/0000-0002-3283-1947>): Conceptualisation (equal), Funding acquisition (lead), Writing – review & editing (supporting).

Nuala J Meyer (<https://orcid.org/0000-0003-4597-5584>): Conceptualisation (equal), Writing – review & editing (supporting).

Jonathan A Millar (<https://orcid.org/0000-0002-4853-9377>): Conceptualisation (equal), Writing – review & editing (supporting).

Holger Müller-Redetzky (<https://orcid.org/0000-0002-0434-9061>): Conceptualisation (equal), Writing – review & editing (supporting).

Alistair Nichol (<https://orcid.org/0000-0002-4689-1238>): Conceptualisation (equal), Funding acquisition (supporting), Writing – review & editing (supporting).

John Norrie (<https://orcid.org/0000-0001-9823-9252>): Conceptualisation (equal), Writing – review & editing (supporting).

Marlies Ostermann (<https://orcid.org/0000-0001-9500-9080>): Conceptualisation (equal), Writing – review & editing (supporting).

Andrew Owen (<https://orcid.org/0000-0002-9819-7651>): Conceptualisation (equal), Writing – review & editing (supporting).

Cecilia M O’Kane (<https://orcid.org/0000-0002-7138-5396>): Conceptualisation (equal), Funding acquisition (supporting), Writing – review & editing (supporting).

Dhruv Parekh (<https://orcid.org/0000-0002-1508-8362>): Conceptualisation (equal), Writing – review & editing (supporting).

Rachel Phillips (<https://orcid.org/0000-0002-3634-7845>): Conceptualisation (equal), Writing – review & editing (supporting).

Duncan Richards (<https://orcid.org/0000-0002-8093-7084>): Conceptualisation (equal), Writing – review & editing (supporting).

Bram Rochweg (<https://orcid.org/0000-0002-8293-7061>): Conceptualisation (equal), Writing – review & editing (supporting).

Anthony J Rostron (<https://orcid.org/0000-0002-9336-1723>): Conceptualisation (equal), Writing – review & editing (supporting).

Hiroki Saito (<https://orcid.org/0000-0002-6477-8204>): Conceptualisation (equal), Writing – review & editing (supporting).

Romit J Samanta (<https://orcid.org/0000-0003-0828-3183>): Conceptualisation (equal), Writing – review & editing (supporting).

Vittorio Scaravilli (<https://orcid.org/0000-0003-0877-7626>): Conceptualisation (equal), Writing – review & editing (supporting).

Wesley Self (<https://orcid.org/0000-0002-9300-3045>): Conceptualisation (equal), Writing – review & editing (supporting).

Manu Shankar-Hari (<https://orcid.org/0000-0002-5338-2538>): Conceptualisation (equal), Writing – review & editing (supporting).

A John Simpson (<https://orcid.org/0000-0003-4731-7294>): Conceptualisation (equal), Writing – review & editing (supporting).

Pratik Sinha (<https://orcid.org/0000-0003-3751-9079>): Conceptualisation (equal), Writing – review & editing (supporting).

Marry R Smit (<https://orcid.org/0000-0001-9938-6035>): Conceptualisation (equal), Writing – review & editing (supporting).

Jonathan Stewart (<https://orcid.org/0000-0001-5649-9355>): Conceptualisation (equal), Writing – review & editing (supporting).

B Taylor Thompson (<https://orcid.org/0000-0001-6391-0448>): Conceptualisation (equal), Writing – review & editing (supporting).

István Vadász (<https://orcid.org/0000-0003-1370-9783>): Conceptualisation (equal), Writing – review & editing (supporting).

Ed Waddingham (<https://orcid.org/0000-0002-0479-5125>): Conceptualisation (equal), Methodology (equal), Writing – review & editing (supporting).

Steve Webb (<https://orcid.org/0000-0001-9134-9045>): Conceptualisation (equal), Writing – review & editing (supporting).

Graham Wheeler (<https://orcid.org/0000-0002-3254-5991>): Conceptualisation (equal), Writing – review & editing (supporting).

D Martin Witzenrath (<https://orcid.org/0000-0002-9787-5633>): Conceptualisation (equal), Writing – review & editing (supporting).

Mark M Wurfel: Conceptualisation (equal), Writing – review & editing (supporting).

Thomas R Martin (<https://orcid.org/0000-0002-8193-909X>): Conceptualisation (equal), Writing – original draft (supporting), Writing – review & editing (lead).

Data-sharing statement

All data cited in this manuscript are available in the public domain. For unpublished data, please contact the corresponding author.

Ethics statement

As this manuscript is the result of expert consensus review, no ethical approval was required.

Information governance statement

No personal information was handled in the preparation of this manuscript.

Disclosure of interest statement

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at <https://doi.org/10.3310/TTND8896>.

Primary conflicts of interest: All authors declare an interest in describing and justifying the above trial for which they have sought funding. Kiran Reddy reports grants from the Wellcome Trust, the NIHR EME programme and the Association of Anaesthetists. He reports travel support from the Queen's University Belfast. Neil Aggarwal reports grants from the NIH and an uncompensated leadership role on the steering committee for Pfizer-Paxlovid US. Narges Alipanah-Lechner reports grants from the NHLBI. Djillali Annane reports grants from Programme Hospitalier de Recherche Clinique, Programme

d'Investissements d'Avenir, France 2030 and ERA PerMed. He also reports personal fees from Beckman-Coulter, Alexion and Baxter. He participates on Data Safety Monitoring Boards and Advisory Boards for Fab'entech, Pfizer, Janssen, Viatrix, and Hillrom. David B Antcliffe reports grants from the NIHR EME programme, outside of the submitted work. He is a board member of the National Outreach Forum. Daphne Babalis reports grants from the NIHR EME programme. J Kenneth Baillie reports no additional competing interests. Abigail Beane reports grants from Wellcome Innovations CRIT Care Asia-Africa and support for attending meetings/travel from the WHO ECO Implementation Advisory Group. Lieuwe DJ Bos reports grants from the Dutch Lung Foundation, Health Holland, the IMI COVID-19 initiative, an Amsterdam UMC fellowship, an ERS Gold Medal for ARDS, Santhera and ZonMW. He reports consultancy fees from Scailyte, Sobi, Exvastat, Santhera, Pfizer, Astra Zeneca and Johnson & Johnson. Aidan Burrell reports no additional competing interests. Carolyn S Calfee reports grants from the NIH, Roche-Genentech and the Quantum Leap Healthcare Collaborative. She reports consulting fees from Vasomune, Gen1e Life Sciences, NGM Bio, Cellenkos, Calcimedica, Arrowhead, EnliTISA, Novartis, Aerogen, Boehringer and Merck. She reports honoraria for a presentation from Fisher-Paykel. She also reports a patent for metagenomic sequences for sepsis diagnosis (corecipient) issues to Regents University of California and Chan Zuckerberg BioHub. She reports an uncompensated leadership role on the International Sepsis Forum. Eddie Cano-Gamez reports grants from the Danaher Beacon Programme. Victoria R Cornelius reports grants from the NIHR EME programme. Mary Cross reports no additional competing interests. Emma Davenport reports grants from the Wellcome Trust. Lorenzo Del Sorbo reports a patent licensed to SQI Diagnostic for a precision medicine diagnostic assay in critical care. Laura Esserman reports an uncompensated leadership role on the Quantum Leap Healthcare Collaborative board of directors. Eddy Fan reports consulting fees from Aerogen, Mallinckrodt, Baxter, Boehringer Ingelheim, Getinge, Inspira and Vasomune. He reports honoraria for lectures from Getinge. Vito Fanelli reports no additional competing interests. Niall D Ferguson reports no additional competing interests. D Clark Files reports grants from the NIH. He also reports consulting fees from Novartis. Christoph Fisser reports no additional competing interests. Shigeki Fujitani reports no additional competing interests. Ewan C Goligher reports grants from the Canadian Institutes of Health Research (CIHR) and the NSA. He reports consulting fees from LungPacer, BioAge, Stimit, Zoll, Getinge and Baxter. He reports honoraria for lectures from Vyair, Draeger and Getinge. He participates on Data Safety Monitoring Boards of Advisory Boards for Getinge, Lungpacer, Heecap and the HiOX-SR trial. He reports receipt of equipment/materials from Vyair, Lungpacer and Timpel. Anthony C Gordon reports grants from the NIHR. He reports consulting fees from AstraZeneca, Novartis and Beckman Coulter. He participates on

Data Safety and Monitoring Boards and Advisory Boards for 30 Respiratory. He is Director of the NIHR National Research Collaboration Programme. Giacomo Grasselli reports grants from Pfizer and MSD. He also reports personal fees from Getinge, Draeger Medical, Fisher & Paykel, Mundipharma and Pfizer. He reports travel support from Biotest and Getinge. He participates on Data Safety Monitoring Boards and Advisory Boards for GlaxoSmithKline and Viatrix. Fergus Hamilton reports no additional competing interests. Rashan Haniffa reports grants from the Wellcome Trust. He participates on Data Safety Monitoring Boards or Advisory Boards for the WHO. He is Director (honorary) for the NICS-MORU and Trustee (honorary) for the NICST. Andrea Haren reports no additional competing interests. Daniel JR Harvey reports no additional competing interests. Leanne M Hays reports grants from the Health Research Board Clinical Trials Network. Anna Heath reports grants from the Natural Sciences and Engineering Research Council of Canada. She participates on Data Safety and Monitoring Boards and Advisory Boards for the FAAN-C trial and the INSITE-DME trial. She is Canada Research Chair in Statistical Trial Design. Nicholas Heming reports no additional competing interests. Susanne Herold reports grants from the German Research Foundation (DFG), the German Ministry of Education and Research (BMBF), the German Center for Lung Research (DZL) and the Institute for Lung Health (ILH). She reports consulting fees from and has participated in advisory boards for AstraZeneca and Janssen. Tim Hicks reports no additional competing interests. Nao Ichihara reports grants from the Japan Society for the Promotion of Science. Vinod D Jaiswal reports grants and receipt of equipment from Abionic. Jun Kataoka reports no additional competing interests. Julian Knight reports grants from the MRC and the NIHR BRC. Patrick R Lawler reports no additional competing interests. Kathleen Liu reports grants from the National Institutes of Health Quantum Leap Healthcare Collaborative, outside of the submitted work. She also reports consulting fees from AM Pharma, Biomerieux, Seastar Biomedical, UpToDate and Baxter. She reports payments for lectures and travel support from the American Society of Nephrology. She participates on Data Safety Monitoring Boards and Advisory Boards for BOA Medical and Novartis. She reports stock in Amgen. She is the Associate Journal Editor for the American Thoracic Society. John C Marshall reports grants from the CIHR. He reports honoraria for lectures from Matisse Pharma. He participates on Data Safety Monitoring Boards for AM Pharma and the SHIPSS trial. He is the Chair of the International Forum for Acute Care Trialists (InFACT). David M Maslove reports salary support from the Southeastern Ontario Academic Medical Organisation. He reports stake in a relevant patent issued to the Queen's University Belfast. Michael A Matthay reports grants from the NIH/NHLBI, US Department of Defence, The California Institute of Regenerative Medicine, Roche Genentech and Quantum Health, outside of the submitted work. He reports consulting fees from Citius Pharmaceuticals,

Novartis, Johnson & Johnson and Gilead Pharmaceuticals. Daniel F McAuley reports grants from the NIHR EME programme. He also reports grants from the NIHR, Innovate UK, the MRC, Novavax, the Northern Ireland HSC R&D Division, Radox Ltd and the Wellcome Trust, outside of the submitted work. He reports consulting fees from Bayer, Aptarion, Direct Biologics, Aviceda, GlaxoSmithKline, Boehringer Ingelheim, Novartis, Eli Lilly and SOBI. He reports honoraria for lectures from GlaxoSmithKline. He participates on Data Safety and Monitoring Boards and Advisory Boards for Vir Biotechnology Inc and Faron Pharmaceuticals. His spouse has received payments and consultancy fees from Insmad and the California Institute for Regenerative Medicine. He is coholder of a patent licensed to the Queen's University Belfast for a novel treatment of inflammatory disease (USB962032). He is Codirector of Research for the Intensive Care Society, former director of the NIHR/MRC EME programme and current Scientific Director for NIHR programmes. Nuala J Meyer reports grants from the NIH. She reports consulting fees from Novartis and AstraZeneca. She reports honoraria for lectures from Yale University and Johns Hopkins University. She reports travel support for attending a meeting from the Sixth International ARDS Conference (Dublin, Ireland). She reports two US provisional patents (63/182531 and 63/650523). She participates in Data Safety Monitoring Boards or Advisory Boards for the CAVIARDS trial and the SPIROMICS II/SOURCE trial. Jonathan A Millar reports grants from the Academy of Medical Sciences and the MRC, outside of the submitted work. Holger Müller-Redetzky reports no additional competing interests. Alistair Nichol reports grants from the Health Research Board Clinical Trials Network. He participates on Data Safety Monitoring Boards and Advisory Boards for the SHORTER trial, the MARCH trial, the VITDALIZE UK trial, the GOAL-ARC trial, the REST trial, the POPART trial and the A2B trial. John Norrie reports grants from the NIHR. He is the former chair of the NIHR EME funding board (2019–24), which funded this work. Marlies Ostermann reports no additional competing interests. Andrew Owen reports grants from Tandem Nano Ltd, ViiV Healthcare and Gilead Sciences, outside of the submitted work. He reports consulting fees from Tandem Nano Ltd and Assembly Biosciences. He reports travel support from the University of Liverpool. He is coinventor of multiple patents issued to the University of Liverpool. He is Director of Tandem Nano Ltd and A&D Consulting. Cecilia M O'Kane reports grants from the NIHR, Innovate UK, the MRC, Novavax, the Northern Ireland HSC R&D Division, Radox and the Wellcome Trust. She is member of grant review panels for the California Institute of Regenerative Medicine and the MRC. Her spouse has received consultancy fees from Aptarion, Direct Biologics, Aviceda, GlaxoSmithKline, Boehringer Ingelheim, Novartis, Eli Lilly and SOBI. Her spouse participates on Data Safety Monitoring Boards for Vir Biotechnology Inc, Faron Pharmaceuticals and GlaxoSmithKline. Dhruv Parekh reports grants from the NIHR and the MRC, outside of the submitted work. He is on the faculty

of the Intensive Care Medicine Board, the NIHR HTA Committee and the NCEPOD Steering Committee. Rachel Phillips reports grants from the NIHR EME programme. Duncan Richards reports consulting fees from OMASS Therapeutics and Avicenna Bio. Bram Rochweg reports no additional competing interests. Anthony J Rostron reports no additional competing interests. Hiroki Saito reports no additional competing interests. Romit J Samanta reports grants from the NIHR, the NIHR Cambridge Biomedical Research Centre and GlaxoSmithKline. He reports travel support from the University of Cambridge. Vittorio Scaravilli reports grants from the Fondazione Ricerca Fibrosi Cistica, outside of the submitted work. He reports honoraria from Biomedica Srl and travel support from Biomerieux Spa. He reports stake in two relevant patents (TO2014A001096 and 102015000017412). Wesley Self reports no additional competing interests. Manu Shankar-Kari reports no additional competing interests. A John Simpson reports grants from the NIHR and the MRC. He is the Programme Director for the NIHR EME Programme, previous Deputy Chair of the MRC Clinical Training and Career Development Panel, Director of the NIHR Healthtech Research Centre for Diagnostic and Technology Evaluation and an NIHR Senior Investigator. He reports receipt of equipment/materials from Clinigen, Partner Therapeutics and Aerogen. Pratik Sinha reports grants from the NIH. He reports consulting fees from AstraZeneca and Prenosis Inc. Marry R Smit reports no additional competing interests. Jonathan Stewart reports no additional competing interests. B Taylor Thompson reports grants from the NHLBI and PCORI. He reports consulting fees from Bayer, Novartis, Direct Biologics, Genentech, Regeneron and Merck. He participates in numerous Data Safety Monitoring Boards outside of the submitted work. He reports stock options in Direct Biologics. He reports authorship on an UpToDate article on the diagnosis of pulmonary embolism. István Vadász reports no additional competing interests. Ed Waddingham reports no additional competing interests. Steve Webb reports no additional competing interests. Graham Wheeler is an employee of GlaxoSmithKline. He participates on Data Safety and Monitoring Boards and Advisory Boards for the PERSEUS1 trial, the ADaPT trial, the SeluDex trial and the TRAFIC trial. He reports stock in GlaxoSmithKline. D Martin Witzenrath reports grants from Biotest, Pantherna, Vaxxilon and Aptarion. He reports personal fees from Biotest, Pantherna, Vaxxilon, Aptarion, AstraZeneca, Chiesi, Insmmed, Gilead and Boehringer. Mark M Wurfel reports no additional competing interests. Thomas R Martin reports consulting fees from Direct Biologics Inc, Novartis and the Quantum Leap Healthcare Collaborative. He participates on Data Safety Monitoring and Advisory Boards for Direct Biologics Inc and the Quantum Leap Healthcare Collaborative.

Professor Anthony C Gordon and Professor A John Simpson are National Institute for Health and Care Research (NIHR) Senior Investigators

Department of Health and Social Care disclaimer

This publication presents independent research commissioned by the National Institute for Health and Care Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, MRC, NIHR Coordinating Centre, the Efficacy and Mechanism Evaluation programme or the Department of Health and Social Care.

This article was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Study registration

This is an expert consensus report and as such the study was not prospectively registered.

Funding

This article presents independent research funded by the National Institute for Health and Care Research (NIHR) Efficacy and Mechanism Evaluation programme as award number NIHR154493.

This article provided an overview of the research award *Building an international precision medicine platform trial for the acute respiratory distress syndrome (ARDS)*. For other articles from this thread and for more information about this research, please view the award page (www.fundingawards.nihr.ac.uk/award/NIHR154493).

About this article

The contractual start date for this research was in September 2022. This article began editorial review in November 2023 and was accepted for publication in February 2025. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The Efficacy and Mechanism Evaluation editors and publisher have tried to ensure the accuracy of the authors' article and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this article.

Copyright

Copyright © 2025 Reddy *et al.* This work was produced by Reddy *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health and Social Care. This is an Open Access publication distributed under the terms of the Creative Commons Attribution CC BY 4.0 licence, which permits unrestricted use, distribution, reproduction and adaptation in any medium and for any purpose provided that it is properly attributed. See: <https://creativecommons.org/licenses/by/4.0/>.

For attribution the title, original author(s), the publication source – NIHR Journals Library, and the DOI of the publication must be cited.

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	atibucimab
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

References

- Maslove DM, Tang B, Shankar-Hari M, Lawler PR, Angus DC, Baillie JK, *et al.* Redefining critical illness. *Nat Med* 2022;**28**:1141–8.
- Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, *et al.*; LUNG SAFE Investigators. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA* 2016;**315**:788–800.
- Sinha P, Bos LD. Pathophysiology of the acute respiratory distress syndrome: insights from clinical studies. *Crit Care Clin* 2021;**37**:795–815.
- Reddy K, Sinha P, O’Kane CM, Gordon AC, Calfee CS, McAuley DF. Subphenotypes in critical care: translation into clinical practice. *Lancet Respir Med* 2020;**8**:631–43.
- Martin TR, Zemans RL, Ware LB, Schmidt EP, Riches DWH, Bastarache L, *et al.* New insights into clinical and mechanistic heterogeneity of the acute respiratory distress syndrome: summary of the Aspen Lung Conference 2021. *Am J Respir Cell Mol Biol* 2022;**67**:284–308.
- Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. *Lancet* 1967;**2**:319–23.
- Ware LB, Matthay MA. The acute respiratory distress syndrome. *N Engl J Med* 2000;**342**:1334–49.
- Bierman AS, Tinetti ME. Precision medicine to precision care: managing multimorbidity. *Lancet* 2016;**388**:2721–3.
- Constantin JM, Jabaudon M, Lefrant JY, Jaber S, Quenot JP, Langeron O, *et al.*; AZUREA Network. Personalised mechanical ventilation tailored to lung morphology versus low positive end-expiratory pressure for patients with acute respiratory distress syndrome in France (the LIVE study): a multicentre, single-blind, randomised controlled trial. *Lancet Respir Med* 2019;**7**:870–80.
- Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, *et al.*; PROSEVA Study Group. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013;**368**:2159–68.
- Albert RK. Prone ventilation for patients with mild or moderate acute respiratory distress syndrome. *Ann Am Thorac Soc* 2020;**17**:24–9.
- Pelosi P, Ball L, Barbas CSV, Bellomo R, Burns KEA, Einav S, *et al.* Personalized mechanical ventilation in acute respiratory distress syndrome. *Crit Care* 2021;**25**:250.
- Santacruz CA, Pereira AJ, Celis E, Vincent JL. Which multicenter randomized controlled trials in critical care medicine have shown reduced mortality? A systematic review. *Crit Care Med* 2019;**47**:1680–91.
- Senn S. Mastering variation: variance components and personalised medicine. *Stat Med* 2016;**35**:966–77.
- Shankar-Hari M, Rubenfeld GD. Population enrichment for critical care trials: phenotypes and differential outcomes. *Curr Opin Crit Care* 2019;**25**:489–97.

16. Ware LB, Matthay MA, Mebazaa A. Designing an ARDS trial for 2020 and beyond: focus on enrichment strategies. *Intensive Care Med* 2020;**46**:2153–6.
17. Wong HR. Intensive care medicine in 2050: precision medicine. *Intensive Care Med* 2017;**43**:1507–9.
18. Prescott HC, Calfee CS, Thompson BT, Angus DC, Liu VX. Toward smarter lumping and smarter splitting: rethinking strategies for sepsis and acute respiratory distress syndrome clinical trial design. *Am J Respir Crit Care Med* 2016;**194**:147–55.
19. Stanski NL, Wong HR. Prognostic and predictive enrichment in sepsis. *Nat Rev Nephrol* 2020;**16**:20–31.
20. Papazian L, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, *et al.*; ACURASYS Study Investigators. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 2010;**363**:1107–16.
21. Moss M, Huang DT, Brower RG, Ferguson ND, Ginde AA, Gong MN, *et al.*; National Heart, Lung, and Blood Institute PETAL Clinical Trials Network. Early neuromuscular blockade in the acute respiratory distress syndrome. *N Engl J Med* 2019;**380**:1997–2008.
22. Goligher EC, Lawler PR, Jensen TP, Talisa V, Berry LR, Lorenzi E, *et al.*; REMAP-CAP, ATTACC, and ACTIV-4a Investigators. Heterogeneous treatment effects of therapeutic-dose heparin in patients hospitalized for COVID-19. *JAMA* 2023;**329**:1066–77.
23. Galván-Román JM, Rodríguez-García SC, Roy-Vallejo E, Marcos-Jiménez A, Sánchez-Alonso S, Fernández-Díaz C, *et al.*; REINMUN-COVID Group. IL-6 serum levels predict severity and response to tocilizumab in COVID-19: an observational study. *J Allergy Clin Immunol* 2021;**147**:72–80.e8.
24. Dellinger RP, Bagshaw SM, Antonelli M, Foster DM, Klein DJ, Marshall JC, *et al.*; EUPHRATES Trial Investigators. Effect of targeted polymyxin B hemoperfusion on 28-day mortality in patients with septic shock and elevated endotoxin level: the EUPHRATES randomized clinical trial. *JAMA* 2018;**320**:1455–63.
25. Klein DJ, Foster D, Walker PM, Bagshaw SM, Mekonnen H, Antonelli M. Polymyxin B hemoperfusion in endotoxemic septic shock patients without extreme endotoxemia: a post hoc analysis of the EUPHRATES trial. *Intensive Care Med* 2018;**44**:2205–12.
26. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, *et al.*; MENSA Investigators. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014;**371**:1198–207.
27. FitzGerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, *et al.*; CALIMA Study Investigators. Benralizumab, an anti-interleukin-5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2016;**388**:2128–41.
28. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, *et al.* Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med* 2018;**378**:2486–96.
29. Russell JA, Walley KR, Singer J, Gordon AC, Hébert PC, Cooper DJ, *et al.*; VASST Investigators. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med* 2008;**358**:877–87.
30. Russell JA, Lee T, Singer J, Boyd JH, Walley KR; Vasopressin and Septic Shock Trial (VASST) Group. The septic shock 3.0 definition and trials: a vasopressin and septic shock trial experience. *Crit Care Med* 2017;**45**:940–8.
31. Sarge T, Baedorf-Kassis E, Banner-Goodspeed V, Novack V, Loring SH, Gong MN, *et al.*; EPVent-2 Study Group. Effect of esophageal pressure-guided positive end-expiratory pressure on survival from acute respiratory distress syndrome: a risk-based and mechanistic reanalysis of the EPVent-2 trial. *Am J Respir Crit Care Med* 2021;**204**:1153–63.
32. Calfee CS, Delucchi K, Parsons PE, Thompson BT, Ware LB, Matthay MA; NHLBI ARDS Network. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. *Lancet Respir Med* 2014;**2**:611–20.
33. Famous KR, Delucchi K, Ware LB, Kangelaris KN, Liu KD, Thompson BT, Calfee CS; ARDS Network. Acute respiratory distress syndrome subphenotypes respond differently to randomized fluid management strategy. *Am J Respir Crit Care Med* 2017;**195**:331–8.
34. Calfee CS, Delucchi KL, Sinha P, Matthay MA, Hackett J, Shankar-Hari M, *et al.*; Irish Critical Care Trials Group. Acute respiratory distress syndrome subphenotypes and differential response to simvastatin: secondary analysis of a randomised controlled trial. *Lancet Respir Med* 2018;**6**:691–8.
35. Sinha P, Delucchi KL, Thompson BT, McAuley DF, Matthay MA, Calfee CS; NHLBI ARDS Network. Latent class analysis of ARDS subphenotypes: a secondary analysis of the statins for acutely injured lungs from sepsis (SAILS) study. *Intensive Care Med* 2018;**44**:1859–69.
36. Dahmer MK, Yang G, Zhang M, Quasney MW, Sapru A, Weeks HM, *et al.*; RESTORE and BALI Study Investigators. Identification of phenotypes in paediatric patients with acute respiratory distress syndrome: a latent class analysis. *Lancet Respir Med* 2022;**10**:289–97.
37. Sinha P, Furfaro D, Cummings MJ, Abrams D, Delucchi K, Maddali MV, *et al.* Latent class analysis reveals

- COVID-19-related acute respiratory distress syndrome subgroups with differential responses to corticosteroids. *Am J Respir Crit Care Med* 2021;**204**:1274–85.
38. Maddali MV, Churpek M, Pham T, Rezoagli E, Zhuo H, Zhao W, *et al.*; LUNG SAFE Investigators and the ESICM Trials Group. Validation and utility of ARDS subphenotypes identified by machine-learning models using clinical data: an observational, multicohort, retrospective analysis. *Lancet Respir Med* 2022;**10**:367–77.
 39. Kitsios GD, Yang L, Manatakis DV, Nourai M, Evankovich J, Bain W, *et al.* Host-response subphenotypes offer prognostic enrichment in patients with or at risk for acute respiratory distress syndrome. *Crit Care Med* 2019;**47**:1724–34.
 40. Bos LD, Schouten LR, van Vught LA, Wiewel MA, Ong DSY, Cremer O, *et al.*; MARS Consortium. Identification and validation of distinct biological phenotypes in patients with acute respiratory distress syndrome by cluster analysis. *Thorax* 2017;**72**:876–83.
 41. Simonis FD, de Iudicibus G, Cremer OL, Ong DSY, van der Poll T, Bos LD, Schultz MJ; MARS Consortium. Macrolide therapy is associated with reduced mortality in acute respiratory distress syndrome (ARDS) patients. *Ann Transl Med* 2018;**6**:24.
 42. Bos LDJ, Scicluna BP, Ong DSY, Cremer O, van der Poll T, Schultz MJ. Understanding heterogeneity in biologic phenotypes of acute respiratory distress syndrome by leukocyte expression profiles. *Am J Respir Crit Care Med* 2019;**200**:42–50.
 43. Heijnen NFL, Hagens LA, Smit MR, Cremer OL, Ong DSY, van der Poll T, *et al.* Biological subphenotypes of ARDS show prognostic enrichment in mechanically ventilated patients without ARDS. *Am J Respir Crit Care Med* 2021;**203**:1503–11.
 44. Sinha P, Calfee CS, Cherian S, Brealey D, Cutler S, King C, *et al.* Prevalence of phenotypes of acute respiratory distress syndrome in critically ill patients with COVID-19: a prospective observational study. *Lancet Respir Med* 2020;**8**:1209–18.
 45. Fish M, Rynne J, Jennings A, Lam C, Lamikanra AA, Ratcliff J, *et al.*; REMAP-CAP Immunoglobulin Domain UK Investigators. Coronavirus disease 2019 subphenotypes and differential treatment response to convalescent plasma in critically ill adults: secondary analyses of a randomized clinical trial. *Intensive Care Med* 2022;**48**:1525–38.
 46. Wong HR, Cvijanovich N, Lin R, Allen GL, Thomas NJ, Willson DF, *et al.* Identification of pediatric septic shock subclasses based on genome-wide expression profiling. *BMC Med* 2009; **7**:34.
 47. Wong HR, Cvijanovich NZ, Allen GL, Thomas NJ, Freishtat RJ, Anas N, *et al.* Validation of a gene expression-based subclassification strategy for pediatric septic shock. *Crit Care Med* 2011;**39**:2511–7.
 48. Wong HR, Cvijanovich NZ, Anas N, Allen GL, Thomas NJ, Bigham MT, *et al.* Developing a clinically feasible personalized medicine approach to pediatric septic shock. *Am J Respir Crit Care Med* 2015;**191**:309–15.
 49. Wong HR, Sweeney TE, Hart KW, Khatri P, Lindsell CJ. Pediatric sepsis endotypes among adults with sepsis. *Crit Care Med* 2017;**45**:e1289–91.
 50. Davenport EE, Burnham KL, Radhakrishnan J, Humburg P, Hutton P, Mills TC, *et al.* Genomic landscape of the individual host response and outcomes in sepsis: a prospective cohort study. *Lancet Respir Med* 2016;**4**:259–71.
 51. Burnham KL, Davenport EE, Radhakrishnan J, Humburg P, Gordon AC, Hutton P, *et al.* Shared and distinct aspects of the sepsis transcriptomic response to fecal peritonitis and pneumonia. *Am J Respir Crit Care Med* 2017;**196**:328–39.
 52. Antcliffe DB, Burnham KL, Al-Beidh F, Santhakumaran S, Brett SJ, Hinds CJ, *et al.* Transcriptomic signatures in sepsis and a differential response to steroids. From the VANISH randomized trial. *Am J Respir Crit Care Med* 2019;**199**:980–6.
 53. Scicluna BP, van Vught LA, Zwinderman AH, Wiewel MA, Davenport EE, Burnham KL, *et al.*; MARS Consortium. Classification of patients with sepsis according to blood genomic endotype: a prospective cohort study. *Lancet Respir Med* 2017;**5**:816–26.
 54. Sweeney TE, Azad TD, Donato M, Haynes WA, Perumal TM, Henao R, *et al.* Unsupervised analysis of transcriptomics in bacterial sepsis across multiple datasets reveals three robust clusters. *Crit Care Med* 2018;**46**:915–25.
 55. Evrard B, Sinha P, Delucchi K, Hendrickson CM, Kangelaris KN, Liu KD, *et al.* Causes and attributable fraction of death from ARDS in inflammatory phenotypes of sepsis. *Crit Care* 2024;**28**:164.
 56. Lawler PR, Fan E. Heterogeneity and phenotypic stratification in acute respiratory distress syndrome. *Lancet Respir Med* 2018;**6**:651–3.
 57. Vanderbeek AM, Bliss JM, Yin Z, Yap C. Implementation of platform trials in the COVID-19 pandemic: a rapid review. *Contemp Clin Trials* 2022;**112**:106625.
 58. Sarma A, Christenson SA, Zha BS, Pisco AO, Neyton LPA, Mick E, *et al.* Hyperinflammatory ARDS is characterized by interferon-stimulated gene expression, T-cell activation, and an altered meta-transcriptome in tracheal aspirates [published online ahead of print April 5 2022]. *medRxiv*. <https://doi.org/10.1101/2022.03.31.22272425>

59. Wiersema R, Jukarainen S, Vaara ST, Poukkanen M, Lakkisto P, Wong H, *et al.* Two subphenotypes of septic acute kidney injury are associated with different 90-day mortality and renal recovery. *Crit Care* 2020;**24**:150.
60. Sinha P, Delucchi KL, McAuley DF, O’Kane CM, Matthay MA, Calfee CS. Development and validation of parsimonious algorithms to classify acute respiratory distress syndrome phenotypes: a secondary analysis of randomised controlled trials. *Lancet Respir Med* 2020;**8**:247–57.
61. Wong HR, Sweeney TE, Lindsell CJ. Simplification of a septic shock endotyping strategy for clinical application. *Am J Respir Crit Care Med* 2017;**195**:263–5.
62. Files DC, Gibbs K, Matthay MA, Calfee CS, Youssef FA, Liu K, *et al.* Real-time prospective classification of biologic sub-phenotypes in severe acute respiratory failure: an interim report on the SPARC study (abstract). *Am J Respir Crit Care Med* 2024;**209**:A5512.
63. Sinha P, Calfee CS, Delucchi KL. Practitioner’s guide to latent class analysis: methodological considerations and common pitfalls. *Crit Care Med* 2021;**49**:e63–79.
64. Henson JM, Reise SP, Kim KH. Detecting mixtures from structural model differences using latent variable mixture modeling: a comparison of relative model fit statistics. *Struct Equ Model: Multidiscip J* 2007;**14**:202–26.
65. Sinha P, Churpek MM, Calfee CS. Machine learning classifier models can identify acute respiratory distress syndrome phenotypes using readily available clinical data. *Am J Respir Crit Care Med* 2020;**202**:996–1004.
66. Sinha P, Spicer A, Delucchi KL, McAuley DF, Calfee CS, Churpek MM. Comparison of machine learning clustering algorithms for detecting heterogeneity of treatment effect in acute respiratory distress syndrome: a secondary analysis of three randomised controlled trials. *eBioMedicine* 2021;**74**:103697.
67. Delucchi K, Famous KR, Ware LB, Parsons PE, Thompson BT, Calfee CS; ARDS Network. Stability of ARDS subphenotypes over time in two randomised controlled trials. *Thorax* 2018;**73**:439–45.
68. Reddy K, Hardin CC, McAuley DF. COVID-19-related acute respiratory distress syndrome subphenotypes and differential response to corticosteroids: time for more precision? *Am J Respir Crit Care Med* 2021;**204**:1241–3.
69. Šimundić AM. Measures of diagnostic accuracy: basic definitions. *EJIFCC* 2009;**19**:203–11.
70. Jiang W, Freidlin B, Simon R. Biomarker-adaptive threshold design: a procedure for evaluating treatment with possible biomarker-defined subset effect. *J Natl Cancer Inst* 2007;**99**:1036–43.
71. Freidlin B, Simon R. Adaptive signature design: an adaptive clinical trial design for generating and prospectively testing a gene expression signature for sensitive patients. *Clin Cancer Res* 2005;**11**:7872–8.
72. Bhattacharyya A, Rai SN. Adaptive signature design: review of the biomarker guided adaptive phase-III controlled design. *Contemp Clin Trial Commun* 2019;**15**:100378.
73. Dreno B, Thompson JF, Smithers BM, Santinami M, Jouary T, Gutzmer R, *et al.* MAGE-A3 immunotherapeutic as adjuvant therapy for patients with resected, MAGE-A3-positive, stage III melanoma (DERMA): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol* 2018;**19**:916–29.
74. Sinha P, Kerchberger VE, Willmore A, Chambers J, Zhuo H, Abbott J, *et al.* Identifying molecular phenotypes in sepsis: an analysis of two prospective observational cohorts and secondary analysis of two randomised controlled trials. *Lancet Respir Med* 2023;**11**:965–74.
75. Shankar-Hari M, Santhakumaran S, Prevost AT, Ward JK, Marshall T, Bradley C, *et al.* Defining phenotypes and treatment effect heterogeneity to inform acute respiratory distress syndrome and sepsis trials: secondary analyses of three RCTs. *Eff Mech Eval* 2021;**8**:1–104.
76. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, *et al.*; ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin definition. *JAMA* 2012;**307**:2526–33.
77. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, *et al.* The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016;**315**:801–10.
78. Leligowicz A, Matthay MA. Heterogeneity in sepsis: new biological evidence with clinical applications. *Crit Care* 2019;**23**:80.
79. Cardinal-Fernández P, Bajwa EK, Dominguez-Calvo A, Menéndez JM, Papazian L, Thompson BT. The presence of diffuse alveolar damage on open lung biopsy is associated with mortality in patients with acute respiratory distress syndrome: a systematic review and meta-analysis. *Chest* 2016;**149**:1155–64.
80. Thille AW, Esteban A, Fernández-Segoviano P, Rodríguez JM, Aramburu JA, Peñuelas O, *et al.* Comparison of the Berlin definition for acute respiratory distress syndrome with autopsy. *Am J Respir Crit Care Med* 2013;**187**:761–7.
81. Matthay MA, Arabi Y, Arroliga AC, Bernard G, Bersten AD, Brochard LJ, *et al.* A new global definition of acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2023;**209**:37–47.

82. Riviello ED, Kiviri W, Twagirumugabe T, Mueller A, Banner-Goodspeed VM, Officer L, *et al.* Hospital incidence and outcomes of the acute respiratory distress syndrome using the Kigali modification of the Berlin definition. *Am J Respir Crit Care Med* 2016;**193**:52–9.
83. Vercesi V, Pisani L, van Tongeren PSI, Lagrand WK, Leopold SJ, Huson MMA, *et al.*; Lung Ultrasound Consortium. External confirmation and exploration of the Kigali modification for diagnosing moderate or severe ARDS. *Intensive Care Med* 2018;**44**:523–4.
84. Matthay MA, Thompson BT, Ware LB. The Berlin definition of acute respiratory distress syndrome: should patients receiving high-flow nasal oxygen be included? *Lancet Respir Med* 2021;**9**:933–6.
85. Pham T, Pesenti A, Bellani G, Rubenfeld G, Fan E, Bugeo G, *et al.* Outcome of acute hypoxaemic respiratory failure: insights from the LUNG SAFE study. *Eur Respir J* 2020;**57**:2003317.
86. Saha R, Pham T, Sinha P, Maddali MV, Bellani G, Fan E, *et al.*; LUNG-SAFE Investigators. Estimating the attributable fraction of mortality from acute respiratory distress syndrome to inform enrichment in future randomised clinical trials. *Thorax* 2023;**78**:990–1003.
87. Marabelle A, Le DT, Ascierto PA, Di Giacomo AM, De Jesus-Acosta A, Delord JP, *et al.* Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase II KEYNOTE-158 study. *J Clin Oncol* 2020;**38**:1–10.
88. Drilon A, Laetsch TW, Kummar S, DuBois SG, Lassen UN, Demetri GD, *et al.* Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. *N Engl J Med* 2018;**378**:731–9.
89. Doebele RC, Drilon A, Paz-Ares L, Siena S, Shaw AT, Farago AF, *et al.*; Trial Investigators. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1–2 trials. *Lancet Oncol* 2020;**21**:271–82.
90. Berry SM, Connor JT, Lewis RJ. The platform trial: an efficient strategy for evaluating multiple treatments. *JAMA* 2015;**313**:1619–20.
91. Park JJH, Mogg R, Smith GE, Nakimuli-Mpungu E, Jehan F, Rayner CR, *et al.* How COVID-19 has fundamentally changed clinical research in global health. *Lancet Glob Health* 2021;**9**:e711–20.
92. REMAP-CAP Investigators. Interleukin-6 receptor antagonists in critically ill patients with COVID-19. *N Engl J Med* 2021;**384**:1491–502.
93. Collaborative Group RECOVERY. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021;**397**:1637–45.
94. Collaborative Group RECOVERY, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, *et al.* Dexamethasone in hospitalized patients with COVID-19. *N Engl J Med* 2021;**384**:693–704.
95. Goligher EC, Bradbury CA, McVerry BJ, Lawler PR, Berger JS, Gong MN, *et al.*; REMAP-CAP Investigators. Therapeutic anticoagulation with heparin in critically ill patients with COVID-19. *N Engl J Med* 2021;**385**:777–89.
96. Lawler PR, Goligher EC, Berger JS, Neal MD, McVerry BJ, Nicolau JC, *et al.*; ATTACC Investigators. Therapeutic anticoagulation with heparin in non-critically ill patients with COVID-19. *N Engl J Med* 2021;**385**:790–802.
97. Lawler PR, Hochman JS, Zarychanski R. What are adaptive platform clinical trials and what role may they have in cardiovascular medicine? *Circulation* 2022;**145**:629–32.
98. Lawler PR. Models for evidence generation during the COVID-19 pandemic: new opportunities for clinical trials in cardiovascular medicine. *Circulation* 2023;**147**:187–9.
99. Hu F, Rosenberger WF. *The Theory of Response-Adaptive Randomization in Clinical Trials*. London: John Wiley & Sons; 2006.
100. Berry DA. Adaptive clinical trials: the promise and the caution. *J Clin Oncol* 2011;**29**:606–9.
101. REMAP-CAP Investigators. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. *JAMA* 2020;**324**:1317–29.
102. Angus DC, Berry S, Lewis RJ, Al-Beidh F, Arabi Y, van Bentum-Puijk W, *et al.* The REMAP-CAP (Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia) study. rationale and design. *Ann Am Thorac Soc* 2020;**17**:879–91.
103. Arabi YM, Gordon AC, Derde LPG, Nichol AD, Murthy S, Beidh FA, *et al.*; REMAP-CAP Investigators. Lopinavir-ritonavir and hydroxychloroquine for critically ill patients with COVID-19: REMAP-CAP randomized controlled trial. *Intensive Care Med* 2021;**47**:867–86.
104. Writing Committee for the REMAP-CAP Investigators. Effect of convalescent plasma on organ support-free days in critically ill patients with COVID-19: a randomized clinical trial. *JAMA* 2021;**326**:1690–702.
105. REMAP-CAP Investigators. Effect of antiplatelet therapy on survival and organ support-free days in critically ill patients with COVID-19: a randomized clinical trial. *JAMA* 2022;**327**:1247–59.

106. REMAP-CAP Investigators. Long-term (180-day) outcomes in critically ill patients with COVID-19 in the REMAP-CAP randomized clinical trial. *JAMA* 2023;**329**:39–51.
107. REMAP-CAP Investigators. Effect of angiotensin-converting enzyme inhibitor and angiotensin receptor blocker initiation on organ support-free days in patients hospitalized with COVID-19: a randomized clinical trial. *JAMA* 2023;**329**:1183–96.
108. Horby PW, Mafham M, Bell JL, Linsell L, Staplin N, Emberson J, *et al.* Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2020;**396**:1345–52.
109. RECOVERY Collaborative Group, Horby P, Mafham M, Linsell L, Bell JL, Staplin N, *et al.* Effect of hydroxychloroquine in hospitalized patients with COVID-19. *N Engl J Med* 2020;**383**:2030–40.
110. Abaleke E, Abbas M, Abbasi S, Abbott A, Abdelaziz A, Abdelbadee S, *et al.* Azithromycin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021;**397**:605–12.
111. Abani O, Abbas A, Abbas F, Abbas M, Abbasi S, Abbass H, *et al.* Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial. *Lancet* 2021;**397**:1637–45.
112. RECOVERY Collaborative Group. Colchicine in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet Respir Med* 2021;**9**:1419–26.
113. RECOVERY Collaborative Group. Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial and updated meta-analysis. *Lancet* 2022;**400**:359–68.
114. Abani O, Abbas A, Abbas F, Abbas M, Abbasi S, Abbass H, *et al.* Aspirin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2022;**399**:143–51.
115. Horby PW, Peto L, Staplin N, Campbell M, Pessoa-Amorim G, *et al.*; RECOVERY Collaborative Group. Dimethyl fumarate in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *medRxiv* 2022;**15**:924.
116. RECOVERY Collaborative Group. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2022;**399**:665–76.
117. Abani O, Abbas A, Abbas F, Abbas J, Abbas K, Abbas M, *et al.* Higher dose corticosteroids in patients admitted to hospital with COVID-19 who are hypoxic but not requiring ventilatory support (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2023;**401**:1499–507.
118. Horby PW, Staplin N, Peto L, Emberson JR, Campbell M, Pessoa-Amorim G, *et al.* Empagliflozin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *medRxiv* 2023;**11**:905–14.
119. Sirkis T, Jones B, Bowden J. Should RECOVERY have used response adaptive randomisation? Evidence from a simulation study. *BMC Med Res Methodol* 2022;**22**:216.
120. Proschan M, Evans S. Resist the temptation of response-adaptive randomization. *Clin Infect Dis* 2020;**71**:3002–4.
121. Dodd LE, Freidlin B, Korn EL. Platform trials: beware the noncomparable control group. *N Engl J Med* 2021;**384**:1572–3.
122. Thall P, Fox P, Wathen J. Statistical controversies in clinical research: scientific and ethical problems with adaptive randomization in comparative clinical trials. *Ann Oncol* 2015;**26**:1621–8.
123. Karrison TG, Huo D, Chappell R. A group sequential, response-adaptive design for randomized clinical trials. *Control Clin Trials* 2003;**24**:506–22.
124. Korn EL, Freidlin B. Outcome-adaptive randomization: is it useful? *J Clin Oncol* 2011;**29**:771–6.
125. Pallmann P, Bedding AW, Choodari-Oskooei B, Dimairo M, Flight L, Hampson LV, *et al.* Adaptive designs in clinical trials: why use them, and how to run and report them. *BMC Med* 2018;**16**:29.
126. Park JW, Liu MC, Yee D, Yau C, van 't Veer LJ, Symmans WF, *et al.* Adaptive randomization of neratinib in early breast cancer. *N Engl J Med* 2016;**375**:11–22.
127. Rugo HS, Olopade OI, DeMichele A, Yau C, van 't Veer LJ, Buxton MB, *et al.* Adaptive randomization of veliparib-carboplatin treatment in breast cancer. *N Engl J Med* 2016;**375**:23–34.
128. Wang H, Yee D. I-SPY 2: a neoadjuvant adaptive clinical trial designed to improve outcomes in high-risk breast cancer. *Curr Breast Cancer Rep* 2019;**11**:303–10.
129. Chien AJ, Tripathy D, Albain KS, Symmans WF, Rugo HS, Melisko ME, *et al.*; I-SPY 2 Consortium. MK-2206 and standard neoadjuvant chemotherapy improves response in patients with human epidermal growth factor receptor 2-positive and/or hormone receptor-negative breast cancers in the I-SPY 2 trial. *J Clin Oncol* 2020;**38**:1059–69.

130. Nanda R, Liu MC, Yau C, Shatsky R, Puzstai L, Wallace A, *et al.* Effect of pembrolizumab plus neoadjuvant chemotherapy on pathologic complete response in women with early-stage breast cancer: an analysis of the ongoing phase 2 adaptively randomized I-SPY2 trial. *JAMA Oncol* 2020;**6**:676–84.
131. Clark AS, Yau C, Wolf DM, Petricoin EF, van 't Veer LJ, Yee D, *et al.* Neoadjuvant T-DM1/pertuzumab and paclitaxel/trastuzumab/pertuzumab for HER2(+) breast cancer in the adaptively randomized I-SPY2 trial. *Nat Commun* 2021;**12**:6428.
132. Puzstai L, Yau C, Wolf DM, Han HS, Du L, Wallace AM, *et al.* Durvalumab with olaparib and paclitaxel for high-risk HER2-negative stage II/III breast cancer: Results from the adaptively randomized I-SPY2 trial. *Cancer Cell* 2021;**39**:989–98.e5.
133. Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, *et al.*; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003;**362**:772–6.
134. McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, *et al.*; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-added trial. *Lancet* 2003;**362**:767–71.
135. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, *et al.*; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-preserved trial. *Lancet* 2003;**362**:777–81.
136. Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, *et al.*; CHARM Investigators and Committees. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-overall programme. *Lancet* 2003;**362**:759–66.
137. Kim ES, Herbst RS, Wistuba II, Lee JJ, Blumenschein GR Jr, Tsao A, *et al.* The BATTLE trial: personalizing therapy for lung cancer. *Cancer Discov* 2011;**1**:44–53.
138. Papadimitrakopoulou V, Lee JJ, Wistuba II, Tsao AS, Fossella FV, Kalhor N, *et al.* The BATTLE-2 study: a biomarker-integrated targeted therapy study in previously treated patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2016;**34**:3638–47.
139. The PANTHER Investigators. *PANTHER: statistical design appendix*. URL: https://panthertrial.org/assets/images/uploads/doc/PANTHER_Statistical_design_appendix_V1.0.docx (accessed 30 June 2025).
141. Park JJH, Siden E, Zoratti MJ, Dron L, Harari O, Singer J, *et al.* Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols. *Trials* 2019;**20**:572.
142. The PANTHER Investigators. *PANTHER Platform Trial*. URL: <https://panthertrial.org/> (accessed 11 November 2024).
143. de Grooth HJ, Cremer OL. Beyond patterns: how to assign biological meaning to ARDS and sepsis phenotypes. *Lancet Respir Med* 2023;**11**:946–7.
144. Acute Respiratory Distress Syndrome Network. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004;**351**:327–36.
145. Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, *et al.*; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006;**354**:2564–75.
146. McAuley DF, Laffey JG, O'Kane CM, Perkins GD, Mullan B, Trinder TJ, *et al.*; HARP-2 Investigators. Simvastatin in the acute respiratory distress syndrome. *N Engl J Med* 2014;**371**:1695–703.
147. Villar J, Ferrando C, Martínez D, Ambrós A, Muñoz T, Soler JA, *et al.*; dexamethasone in ARDS network. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. *Lancet Respir Med* 2020;**8**:267–76.
148. Reddy K, O'Kane C, McAuley D. Corticosteroids in acute respiratory distress syndrome: a step forward, but more evidence is needed. *Lancet Respir Med* 2020;**8**:220–2.
149. The WHO Rapid Evidence Appraisal for COVID-19 Therapies Working Group. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA* 2020;**324**:1330–41.
150. Griffiths MJD, McAuley DF, Perkins GD, Barrett N, Blackwood B, Boyle A, *et al.* Guidelines on the management of acute respiratory distress syndrome. *BMJ Open Respir Res* 2019;**6**:e000420.
151. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, *et al.*; Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013;**41**:580–637.

152. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, *et al.* Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Crit Care Med* 2021;**49**:e1063–143.
153. Horie S, McNicholas B, Rezoagli E, Pham T, Curley G, McAuley D, *et al.* Emerging pharmacological therapies for ARDS: COVID-19 and beyond. *Intensive Care Med* 2020;**46**:2265–83.
154. Jacobson JR, Barnard JW, Grigoryev DN, Ma SF, Tudor RM, Garcia JGN. Simvastatin attenuates vascular leak and inflammation in murine inflammatory lung injury. *Am J Physiol Lung Cell Mol Physiol* 2005;**288**:L1026–32.
155. Shyamsundar M, McKeown ST, O’Kane CM, Craig TR, Brown V, Thickett DR, *et al.* Simvastatin decreases lipopolysaccharide-induced pulmonary inflammation in healthy volunteers. *Am J Respir Crit Care Med* 2009;**179**:1107–14.
156. Craig TR, Duffy MJ, Shyamsundar M, McDowell C, O’Kane CM, Elborn JS, McAuley DF. A randomized clinical trial of hydroxymethylglutaryl-coenzyme a reductase inhibition for acute lung injury (The HARP Study). *Am J Respir Crit Care Med* 2011;**183**:620–6.
157. Hills TE, Lorenzi E, Berry LR, Shyamsundar M, Al-Beidh F, Annane D, *et al.*; REMAP-CAP Investigators. Simvastatin in critically ill patients with covid-19. *N Engl J Med* 2023;**389**:2341–54.
158. U.S. Department of Health and Human Services Food and Drug Administration. *Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs and Biological Products: Guidance for Industry*. URL: www.fda.gov/media/121320/download (accessed 11 November 2024).
159. Damsky W, Peterson D, Ramseier J, Al-Bawardy B, Chun H, Proctor D, *et al.* The emerging role of Janus kinase inhibitors in the treatment of autoimmune and inflammatory diseases. *J Allergy Clin Immunol* 2021;**147**:814–26.
160. Gao Q, Liang X, Shaikh AS, Zang J, Xu W, Zhang Y. JAK/STAT signal transduction: promising attractive targets for immune, inflammatory and hematopoietic diseases. *Curr Drug Targets* 2018;**19**:487–500.
161. Bos LDJ, Ware LB. Acute respiratory distress syndrome: causes, pathophysiology, and phenotypes. *Lancet* 2022;**400**:1145–56.
162. Winthrop KL, Harigai M, Genovese MC, Lindsey S, Takeuchi T, Fleischmann R, *et al.* Infections in baricitinib clinical trials for patients with active rheumatoid arthritis. *Ann Rheum Dis* 2020;**79**:1290–7.
163. Di Gioia M, Zanoni I. Toll-like receptor co-receptors as master regulators of the immune response. *Mol Immunol* 2015;**63**:143–52.
164. Martin TR, Wurfel MM, Zanoni I, Ulevitch R. Targeting innate immunity by blocking CD14: novel approach to control inflammation and organ dysfunction in COVID-19 illness. *EBioMedicine* 2020;**57**:102836.
165. Mabrey FL, Nian H, Yu C, Barnes EM, Malhotra U, Mikacenic C, *et al.* Phase 2, randomized, double-blind, placebo-controlled multi-center trial of the clinical and biological effects of anti-CD14 treatment in hospitalized patients with COVID-19 pneumonia. *eBioMedicine* 2023;**93**:104667.
166. Files DC, Aggarwal N, Albertson T, Auld S, Beitler JR, Berger P, *et al.* Report of the first seven agents in the I-SPY COVID trial: a phase 2, open label, adaptive platform randomised controlled trial. *eClinicalMedicine* 2023;**58**:101889.
167. Mabrey L, Esserman L, Liu K, Files DC, Eklund M, Calfee CS, *et al.* Anti-CD14 treatment and mortality in severe COVID-19: a secondary subgroup analysis by baseline plasma presepsin levels in the I-SPY COVID adaptive platform trial (abstract). *Am J Respir Crit Care Med* 2024;**209**:A1120.
168. Carvelli J, Demaria O, Vély F, Batista L, Chouaki Benmansour N, Fares J, *et al.*; Explore COVID-19 IPH Group. Association of COVID-19 inflammation with activation of the C5a-C5aR1 axis. *Nature* 2020;**588**:146–50.
169. Aiello S, Gastoldi S, Galbusera M, Ruggenenti P, Portalupi V, Rota S, *et al.* C5a and C5aR1 are key drivers of microvascular platelet aggregation in clinical entities spanning from aHUS to COVID-19. *Blood Adv* 2022;**6**:866–81.
170. Vlaar APJ, Witzernath M, van Paassen P, Heunks LMA, Mourvillier B, de Bruin S, *et al.*; PANAMO Study Group. Anti-C5a antibody (vilobelimab) therapy for critically ill, invasively mechanically ventilated patients with COVID-19 (PANAMO): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Respir Med* 2022;**10**:1137–46.
171. U.S. Department of Health and Human Services Food and Drug Administration. *Fact Sheet for Healthcare Providers: Emergency Use Authorization for Gohibic*. URL: www.fda.gov/media/166824/download (accessed 11 November 2024).
172. Zhu J, Pang J, Ji P, Zhong Z, Li H, Li B, Zhang J. Elevated interleukin-6 is associated with severity of COVID-19: a meta-analysis. *J Med Virol* 2021;**93**:35–7.

173. Pairo-Castineira E, Clohisey S, Klaric L, Bretherick AD, Rawlik K, Pasko D, *et al.*; GenOMICC Investigators. Genetic mechanisms of critical illness in COVID-19. *Nature* 2021;**591**:92–8.
174. Parsons PE, Eisner MD, Thompson BT, Matthay MA, Ancukiewicz M, Bernard GR, Wheeler AP; NHLBI Acute Respiratory Distress Syndrome Clinical Trials Network. Lower tidal volume ventilation and plasma cytokine markers of inflammation in patients with acute lung injury. *Crit Care Med* 2005;**33**:1–6; discussion 230; discussion 230–2.
175. Nishimoto N, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, Azuma J. Long-term safety and efficacy of tocilizumab, an anti-IL-6 receptor monoclonal antibody, in monotherapy, in patients with rheumatoid arthritis (the STREAM study): evidence of safety and efficacy in a 5-year extension study. *Ann Rheum Dis* 2009;**68**:1580–4.
176. Pawar A, Desai RJ, Solomon DH, Santiago Ortiz AJ, Gale S, Bao M, *et al.* Risk of serious infections in tocilizumab versus other biologic drugs in patients with rheumatoid arthritis: a multidatabase cohort study. *Ann Rheum Dis* 2019;**78**:456–64.
177. Hermine O, Mariette X, Tharaux PL, Resche-Rigon M, Porcher R, Ravaud P; CORIMUNO-19 Collaborative Group. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: a randomized clinical trial. *JAMA Intern Med* 2021;**181**:32–40.
178. Salama C, Han J, Yau L, Reiss WG, Kramer B, Neidhart JD, *et al.* Tocilizumab in patients hospitalized with COVID-19 pneumonia. *N Engl J Med* 2021;**384**:20–30.
179. Salvarani C, Dolci G, Massari M, Merlo DF, Cavuto S, Savoldi L, *et al.*; RCT-TCZ-COVID-19 Study Group. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: a randomized clinical trial. *JAMA Intern Med* 2021;**181**:24–31.
180. Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, *et al.*; BACC Bay Tocilizumab Trial Investigators. Efficacy of tocilizumab in patients hospitalized with COVID-19. *N Engl J Med* 2020;**383**:2333–44.
181. Veiga VC, Prats J, Farias DLC, Rosa RG, Dourado LK, Zampieri FG, *et al.* Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. *BMJ* 2021;**372**:n84.
182. Tleyjeh IM, Kashour Z, Damlaj M, Riaz M, Tlayjeh H, Altannir M, *et al.* Efficacy and safety of tocilizumab in COVID-19 patients: a living systematic review and meta-analysis. *Clin Microbiol Infect* 2021;**27**:215–27.
183. Michel O, Dinh PHD, Doyen V, Corazza F. Anti-TNF inhibits the airways neutrophilic inflammation induced by inhaled endotoxin in human. *BMC Pharmacol Toxicol* 2014;**15**:60.
184. Martin TR, Rubenfeld GD, Ruzinski JT, Goodman RB, Steinberg KP, Leturcq DJ, *et al.* Relationship between soluble CD14, lipopolysaccharide binding protein, and the alveolar inflammatory response in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1997;**155**:937–44.
185. Qiu P, Cui X, Sun J, Welsh J, Natanson C, Eichacker PQ. Antitumor necrosis factor therapy is associated with improved survival in clinical sepsis trials: a meta-analysis. *Crit Care Med* 2013;**41**:2419–29.
186. O'Halloran JA, Ko ER, Anstrom KJ, Kedar E, McCarthy MW, Panettieri RA Jr, *et al.*; ACTIV-1 IM Study Group Members. Abatacept, cenicriviroc, or infliximab for treatment of adults hospitalized with COVID-19 pneumonia: a randomized clinical trial. *JAMA* 2023;**330**:328–39.
187. Fisher BA, Veenith T, Slade D, Gaskell C, Rowland M, Whitehouse T, *et al.*; CATALYST Investigators. Namilumab or infliximab compared with standard of care in hospitalised patients with COVID-19 (CATALYST): a randomised, multicentre, multi-arm, multistage, open-label, adaptive, phase 2, proof-of-concept trial. *Lancet Respir Med* 2022;**10**:255–66.
188. Fidler H, Schnitzler F, Ferrante M, Noman M, Katsanos K, Segaeert S, *et al.* Long-term safety of infliximab for the treatment of inflammatory bowel disease: a single-centre cohort study. *Gut* 2009;**58**:501–8.
189. Deininger MW, Druker BJ. Specific targeted therapy of chronic myelogenous leukemia with imatinib. *Pharmacol Rev* 2003;**55**:401–23.
190. Dong C, Davis RJ, Flavell RA. MAP kinases in the immune response. *Annu Rev Immunol* 2002;**20**:55–72.
191. Aman J, Bezu J, Damanafshan A, Huveneers S, Eringa EC, Vogel SM, *et al.* Effective treatment of edema and endothelial barrier dysfunction with imatinib. *Circulation* 2012;**126**:2728–38.
192. de Brabander J, Duijvelaar E, Schippers JR, Smeele PJ, Peters-Sengers H, Duitman JW, *et al.* Immunomodulation and endothelial barrier protection mediate the association between oral imatinib and mortality in hospitalised COVID-19 patients. *Eur Respir J* 2022;**60**:2200780.
193. Atmowihardjo LN, Schippers JR, Duijvelaar E, Bartelink IH, Bet PM, Swart NEL, *et al.* Efficacy and safety of intravenous imatinib in COVID-19 ARDS: a randomized, double-blind, placebo-controlled clinical trial. *Crit Care* 2023;**27**:226.

194. Aman J, Duijvelaar E, Botros L, Kianzad A, Schippers JR, Smeele PJ, *et al.* Imatinib in patients with severe COVID-19: a randomised, double-blind, placebo-controlled, clinical trial. *Lancet Respir Med* 2021;**9**:957–68.
195. Gaughan EE, Quinn TM, Mills A, Bruce AM, Antonelli J, MacKinnon A, *et al.* An inhaled galectin-3 inhibitor in COVID-19 pneumonitis (DEFINE): a phase Ib/IIa randomised controlled trial. *Am J Respir Crit Care Med* 2022;**207**:138–49.
196. Díaz-Alvarez L, Ortega E. The many roles of galectin-3, a multifaceted molecule, in innate immune responses against pathogens. *Mediators Inflamm* 2017;**2017**:9247574.
197. Mishra BB, Li Q, Steichen AL, Binstock BJ, Metzger DW, Teale JM, Sharma J. Galectin-3 functions as an alarmin: pathogenic role for sepsis development in murine respiratory tularemia. *PLOS ONE* 2013;**8**:e59616.
198. Garcia-Revilla J, Deierborg T, Venero JL, Boza-Serrano A. Hyperinflammation and fibrosis in severe COVID-19 patients: galectin-3, a target molecule to consider. *Front Immunol* 2020;**11**:2069.
199. Reddy K, Nichol A, McAuley DF. Galectin-3 inhibition in COVID-19. *Am J Respir Crit Care Med* 2022;**207**:118–20.
200. Grasselli G, Calfee CS, Camporota L, Poole D, Amato MBP, Antonelli M, *et al.*; European Society of Intensive Care Medicine Taskforce on ARDS. ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies. *Intensive Care Med* 2023;**49**:727–59.
201. Fan E, Zakhary B, Amaral A, McCannon J, Girard TD, Morris PE, *et al.* Liberation from mechanical ventilation in critically ill adults. An official ATS/ACCP clinical practice guideline. *Ann Am Thorac Soc* 2017;**14**:441–3.
202. Marik PE, Khangoora V, Rivera R, Hooper MH, Catravas J. Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock: a retrospective before-after study. *Chest* 2017;**151**:1229–38.
203. Lamontagne F, Masse MH, Menard J, Sprague S, Pinto R, Heyland DK, *et al.*; LOVIT Investigators and the Canadian Critical Care Trials Group. Intravenous vitamin C in adults with sepsis in the intensive care unit. *N Engl J Med* 2022;**386**:2387–98.
204. The PANTHER Investigators. *PANTHER Trial: Interventions Prioritisation*. URL: <https://panthertrial.netlify.app/docs/home/> (accessed 11 November 2024).
205. Loewa A, Feng JJ, Hedtrich S. Human disease models in drug development. *Nat Rev Bioeng* 2023;**1**:545–59.
206. Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A; Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;**342**:1301–8.
207. The ARDS Network Authors for the ARDS Network. Ketoconazole for early treatment of acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2000;**283**:1995–2002.
208. NHLBI ARDS Clinical Trials Network. Randomized, placebo-controlled clinical trial of an aerosolized beta(2)-agonist for treatment of acute lung injury. *Am J Respir Crit Care Med* 2011;**184**:561–8.
209. The NHLBI Acute Respiratory Distress Syndrome Clinical Trials Network. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. *JAMA* 2012;**307**:795–803.
210. Rice TW, Wheeler AP, Thompson BT, deBoisblanc BP, Steingrub J, Rock P; NIH NHLBI Acute Respiratory Distress Syndrome Network of Investigators. Enteral omega-3 fatty acid, γ -linolenic acid, and antioxidant supplementation in acute lung injury. *JAMA* 2011;**306**:1574–81.
211. The ARDS Clinical Trials Network. Randomized, placebo-controlled trial of lisofylline for early treatment of acute lung injury and acute respiratory distress syndrome. *Crit Care Med* 2002;**30**:1–6.
212. Steinberg KP, Hudson LD, Goodman RB, Hough CL, Lanken PN, Hyzy R, *et al.*; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med* 2006;**354**:1671–84.
213. Truwit JD, Bernard GR, Steingrub J, Matthay MA, Liu KD, Albertson TE, *et al.*; National Heart, Lung, and Blood Institute ARDS Clinical Trials Network. Rosuvastatin for sepsis-associated acute respiratory distress syndrome. *N Engl J Med* 2014;**370**:2191–200.
214. The NHLBI PETAL Clinical Trials Network. Early high-dose vitamin D3 for critically ill, vitamin D-deficient patients. *N Engl J Med* 2019;**381**:2529–40.
215. Blackwood B, Ringrow S, Clarke M, Marshall JC, Connolly B, Rose L, McAuley DF. A core outcome set for critical care ventilation trials. *Crit Care Med* 2019;**47**:1324–31.
216. Yehya N, Harhay MO, Curley MAQ, Schoenfeld DA, Reeder RW. Reappraisal of ventilator-free days in critical care research. *Am J Respir Crit Care Med* 2019;**200**:828–36.

217. U.S. Department of Health and Human Services Food and Drug Administration. *Multiple Endpoints in Clinical Trials: Guidance for Industry*. URL: www.fda.gov/files/drugs/published/Multiple-Endpoints-in-Clinical-Trials-Guidance-for-Industry.pdf (accessed 11 November 2024).
218. European Medicines Agency. *Guideline on Multiplicity Issues in Clinical Trials*. Amsterdam: European Medicines Agency; 2016.
219. Cordoba G, Schwartz L, Woloshin S, Bae H, Gøtzsche PC. Definition, reporting, and interpretation of composite outcomes in clinical trials: systematic review. *BMJ* 2010;**341**:c3920.
220. Novack V, Beitler JR, Yitshak-Sade M, Thompson BT, Schoenfeld DA, Rubenfeld G, *et al.* Alive and ventilator free: a hierarchical, composite outcome for clinical trials in the acute respiratory distress syndrome. *Crit Care Med* 2020;**48**:158–66.
221. Tomazini BM, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG, Veiga VC, *et al.*; COALITION COVID-19 Brazil III Investigators. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. *JAMA* 2020;**324**:1307–16.
222. Villar J, Martínez D, Mosteiro F, Ambrós A, Añón JM, Ferrando C, *et al.*; Stratification and Outcome of Acute Respiratory Distress Syndrome (STANDARDS) Network. Is overall mortality the right composite endpoint in clinical trials of acute respiratory distress syndrome? *Crit Care Med* 2018;**46**:892–9.
223. Boyle AJ, Ferris P, Bradbury I, Conlon J, Shankar-Hari M, Rogers AJ, *et al.* Baseline plasma IL-18 may predict simvastatin treatment response in patients with ARDS: a secondary analysis of the HARP-2 randomised clinical trial. *Crit Care* 2022;**26**:164.
224. Duale N, Brunborg G, Rønningen KS, Briese T, Aarem J, Aas KK, *et al.* Human blood RNA stabilization in samples collected and transported for a large biobank. *BMC Res Notes* 2012;**5**:510.
225. Puleo A, Carroll C, Maecker HT, Gupta R. Isolation of peripheral blood mononuclear cells using vacutainer® cellular preparation tubes (CPT(TM)). *Bio Protoc* 2017;**7**:e2103.
226. Walter JM, Helmin KA, Abdala-Valencia H, Wunderink RG, Singer BD. Multidimensional assessment of alveolar T cells in critically ill patients. *JCI Insight* 2018;**3**:e123287.
227. Mikacenic C, Fussner LA, Bell J, Burnham EL, Chlan LL, Cook SK, *et al.* Research bronchoscopies in critically ill research participants: an official American Thoracic Society workshop report. *Ann Am Thorac Soc* 2023;**20**:621–31.
228. Tasbakan MS, Gurgun A, Basoglu OK, Ekren PK, Pullukcu H, Bacakoglu F. Comparison of bronchoalveolar lavage and mini-bronchoalveolar lavage in the diagnosis of pneumonia in immunocompromised patients. *Respiration* 2011;**81**:229–35.
229. Coppola L, Cianflone A, Grimaldi AM, Inconato M, Bevilacqua P, Messina F, *et al.* Biobanking in health care: evolution and future directions. *J Transl Med* 2019;**17**:172.
230. The PANTHER Investigators. *PANTHER Trial Biospecimen Collection and Processing Guide*. URL: https://panthertrial.org/assets/images/uploads/doc/PANTHER_Sample_Collection_and_Processing_Guide.pdf (accessed 11 November 2024).
231. U.S. Department of Health and Human Services Food and Drug Administration. *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products: Guidance for Industry*. URL: www.regulations.gov/document/FDA-2019-D-4964-0002 (accessed 11 November 2024).
232. The PANTHER Investigators. *Summary Report: 1st Critical Care Academic/Pharmaceutical Industry Symposium*. URL: https://panthertrial.org/assets/images/uploads/doc/Industry_Collaboration_Recommendation_report.pdf (accessed 12 May 2025).
233. The PANTHER Investigators. *PANTHER Trial: International Regulatory Review Document*. URL: https://panthertrial.org/assets/images/uploads/doc/International_Regulatory_Review_Document.pdf (accessed 11 November 2024).
234. Dawson S, Banister K, Biggs K, Cotton S, Devane D, Gardner H, *et al.* Trial Forge Guidance 3: randomised trials and how to recruit and retain individuals from ethnic minority groups – practical guidance to support better practice. *Trials* 2022;**23**:672.
235. NHS Health Research Authority. *HRA and MHRA Draft Inclusion and Diversity Guidance*. URL: www.hra.nhs.uk/about-us/news-updates/hra-mhra-guidance-developing-and-submitting-inclusion-and-diversity-plan/ (accessed 11 November 2024).
236. Schoenberg NC, Barker AF, Bernardo J, Deterding RR, Ellner JJ, Hess DR, *et al.* A comparative analysis of pulmonary and critical care medicine guideline development methodologies. *Am J Respir Crit Care Med* 2017;**196**:621–7.
237. Woodcock J, LaVange LM. Master protocols to study multiple therapies, multiple diseases, or both. *N Engl J Med* 2017;**377**:62–70.