Opportunities for improved clinical trial designs in acute respiratory distress syndrome

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The acute respiratory distress syndrome (ARDS) is a common critical illness syndrome with high morbidity and mortality. There are no proven pharmacological therapies for ARDS. The current definition of ARDS is based on shared clinical characteristics but does not capture the heterogeneity in clinical risk factors, imaging characteristics, physiology, timing of onset and trajectory, and biology of the syndrome. There is increasing interest within the ARDS clinical trialist community to design clinical trials that reduce heterogeneity in the trial population. This effort must be balanced with ongoing work to craft an inclusive, global definition of ARDS, with important implications for trial design. Ultimately, the two aims—to design trials that are applicable to the diverse global ARDS population while also advancing opportunities to identify targetable traits—should coexist. In this Personal View, we recommend two primary strategies to improve future ARDS trials: the development of new methods to target treatable traits in clinical trial populations, and improvements in the representativeness of ARDS trials, with the inclusion of global populations. We emphasise that these two strategies are complementary. We also discuss how a proposed expansion of the definition of ARDS could affect the future of clinical trials.

Introduction

No proven pharmacological therapies exist for the treatment of acute respiratory distress syndrome (ARDS), despite several decades of clinical trials and advances in supportive care.[1] The Berlin definition of ARDS is based on a conceptual model that includes both clinical criteria and morphological characteristics,[2] but less than half of the patients who meet the clinical definition of ARDS have the histological findings of diffuse alveolar damage.[3] Furthermore, there is no unifying biological marker of lung injury in ARDS. Thus, the current definition of ARDS can only approximate the underlying biological mechanisms that probably define the pathophysiology of the syndrome.[4] Although negative trial results could plausibly reflect a truly ineffective treatment, negative results in a heterogeneous population could also mask signals for benefit or harm in a subpopulation of patients who share a biological or physiological phenotype.

Key messages

- ARDS is a clinically defined syndrome that affects diverse populations of critically ill adults and children with a broad range of predisposing risk factors
- Heterogeneity in the aetiology, physiology, imaging characteristics, biology, and timing of onset and trajectory of ARDS is a continuing challenge for successful clinical trials
- Predictive and prognostic enrichment of clinical trial populations facilitates reduced heterogeneity to increase the likelihood of identifying effective interventions in ARDS
- Increasing the representativeness of clinical trial populations in terms of age, sex, race, ethnicity, and geographical region is a priority for ARDS research in adults and children that can be accomplished in consort with enrichment strategies
- An expansion of the definition of the syndrome could increase opportunities to study the full spectrum of ARDS and the impact of early interventions, and facilitate clinical trials in global settings
- The ultimate goal of ARDS clinical trials—and the focus of efforts to improve trial designs—is to identify treatment modalities that can be tailored to meet the individual needs of adults and children with ARDS globally

ARDS=acute respiratory distress syndrome.

One strategy for addressing this challenge is to reduce the heterogeneity of clinical trial populations through prognostic (ie, based on the likelihood of a particular ARDS trajectory or outcome) and predictive (ie, focusing on the likelihood of a response to a particular intervention) enrichment,[5] in which the chance of identifying a therapeutic effect is increased by studying a population with a shared risk factor, injury mechanism, or high risk of observing the trial outcome. However, prognostic and predictive enrichment sometimes limits the generalisability of trial findings. Attempts to reduce the heterogeneity of clinical trial populations must be counterbalanced with equally important efforts to increase the representation of participants from typically underrepresented backgrounds and from global settings, including those with limited access to advanced support modalities.

In July 2021, international experts in ARDS clinical investigation convened for the Critical Care Clinical Trialists (3CT) Workshop to discuss the evolving understanding of ARDS heterogeneity and implications for clinical trial design. The aims of this Personal View are to build on the themes of the 3CT Workshop, considering the challenges of ARDS heterogeneity and the opportunities to harness this heterogeneity for effective clinical trial design. In addition, we describe how future trials might balance this goal with steps to

address ongoing underrepresentation of participants from minoritised populations and resource-variable settings, and how a proposed expansion of the Berlin definition[6] could impact clinical trial design, allowing studies across the full spectrum of ARDS (panel 1).

Heterogeneity in ARDS clinical trials

Experts have understood ARDS as a heterogeneous syndrome since the first description of the syndrome in 1967,[7] in which aetiologies ranged from blunt force trauma through viral pneumonia to acute pancreatitis. Since that time and through the various revisions of the clinical definition of ARDS,[2,8,9] the understanding of what defines ARDS heterogeneity has greatly advanced.[10] For example, direct ARDS (eg, that associated with pneumonia and aspiration) has been shown to have distinct respiratory mechanics[11] and a different biological profile[12] when compared with indirect ARDS (eg, ARDS due to non-pulmonary infection, trauma, transfusion). ARDS characterised by diffuse consolidations on CT differs from ARDS with focal consolidations on CT in terms of baseline respiratory mechanics and response to positive end-expiratory pressure (PEEP),[13,14] as well as biological markers of pulmonary epithelial injury such as RAGE (receptor for advanced glycation end-products), which is expressed with higher levels in the plasma in patients with diffuse radiographic opacities.[15] Other sources of heterogeneity in ARDS that are reflected in clinical outcomes and, in some cases, in biomarker profiles include physiological derangements such as the degree of hypoxaemia, shunt fraction, and dead space;[16,17] timing of onset;[18–20] and trajectory of resolution.[21] Two distinct biological phenotypes of ARDS, termed hyperinflammatory and hypoinflammatory, have been consistently identified through latent class analysis[22] across five randomised clinical trials (RCTs), two observational cohorts, and in a paediatric RCT (figure 1).[23–28] The hyperinflammatory phenotype is defined primarily by higher plasma concentrations of proinflammatory biomarkers and more acidosis,[23] and higher mortality has been consistently observed in hyperinflammatory ARDS compared with the hypoinflammatory phenotype.[23–27] There is also evidence of differential responses to interventions such as simvastatin[26] and fluid management strategy between the two phenotypes.[27] Although these classes have been consistently identified and appear to be stable over the first few days of ARDS,[29] they have yet to be prospectively validated. Nevertheless, they offer the promise of treatable biological traits in ARDS that could be of value to future therapeutic trials.

We recommend that ARDS research prioritise the expansion of methods to minimise heterogeneity in clinical trial populations. Innovative clinical trial design (eg, adaptive and platform trials) is another opportunity for improving ARDS clinical investigation. This strategy was the focus of a previous report from the first 3CT conference[30] and is not the focus of this Personal View.

***Panel 1:* Recommendations for future ARDS clinical trials**

Develop new tools to address heterogeneity

- Artificial intelligence to classify ARDS imaging phenotypes
- Point-of-care biomarker assays for real-time biological phenotyping
- Airspace sampling to identify new biological phenotypes
- Validate hyperinflammatory and hypoinflammatory subphenotypes in prospective clinical trials

Improve representativeness of trial populations

- Identify enrolment targets for underrepresented demographics to reflect the population-specific incidence of ARDS
- Prioritise the conduct of ARDS trials in global settings, including low-income and middle-income countries

Study effects of an expanded definition of ARDS

- Study changes in the estimated prevalence and outcomes of ARDS with an expanded definition
- Identify whether known biomarker-derived or imaging subphenotypes exist in patients managed on HFNO, and whether new phenotypes exist
- Study the impact of non-mortality outcomes such as progression to mechanical ventilation on trial design

ARDS=acute respiratory distress syndrome. HFNO=high-flow nasal oxygen.

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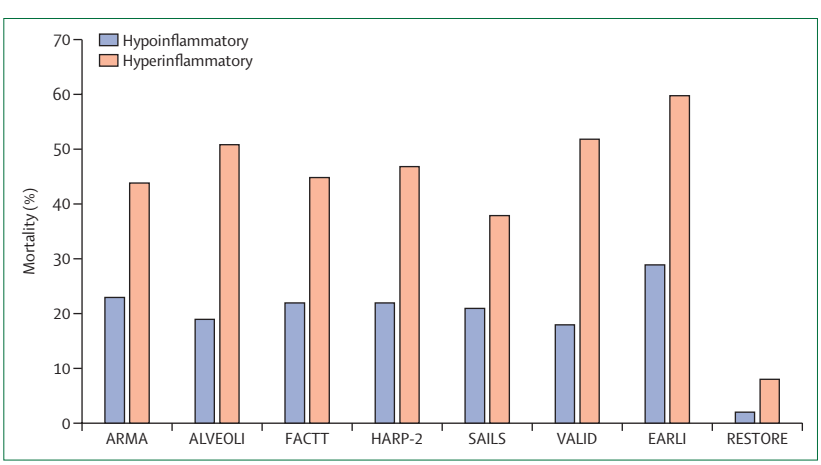

Figure 1: **Mortality by latent class analysis-derived phenotype in seven adult cohorts and one paediatric cohort**

ALVEOLI=Assessment of Low Tidal Volume and Elevated End-Expiratory Volume to Obviate Lung Injury. ARMA=Acute Respiratory Management in ARDS. EARLI=Early Assessment of Renal and Lung Injury. FACTT=Fluids and Catheters Treatment Trial. HARP-2=Hydroxymethylglutaryl-CoA Reductase Inhibition with Simvastatin in Acute Lung Injury to Reduce Pulmonary Dysfunction. RESTORE=Randomised Evaluation of Sedation Titration for Respiratory Failure (paediatric cohort). SAILS=Statins for Acutely Injured Lungs from Sepsis. VALID=Validating Acute Lung Injury Biomarkers for Diagnosis.

Development of tools for prognostic and predictive enrichment

Recognising various clinical and biological classes of ARDS provides an opportunity for prognostic and predictive enrichment in clinical trials.[5,21] Prognostic and predictive enrichment using various domains and

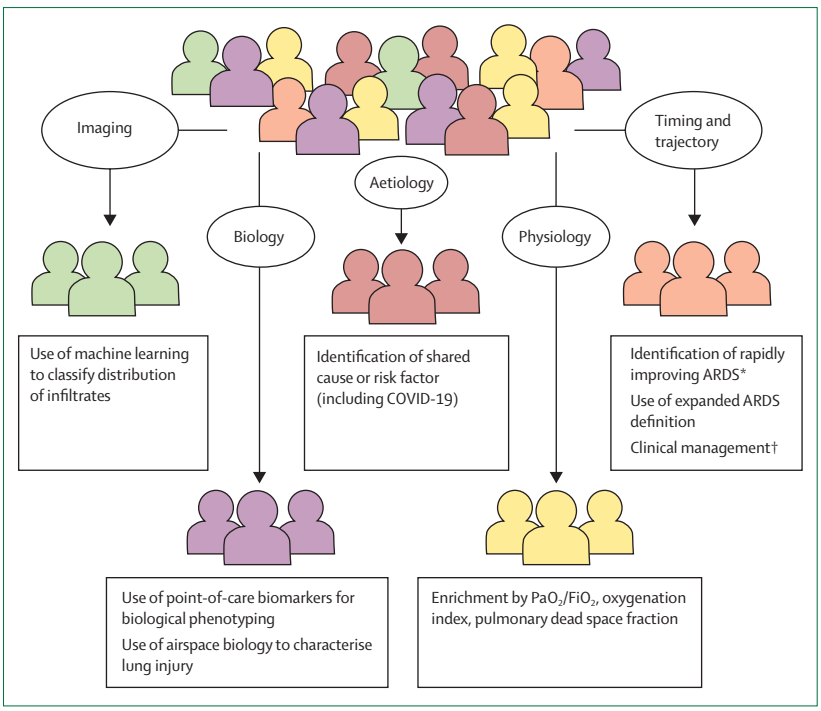

Figure 2: **Enrichment strategies for ARDS clinical trial populations to reduce heterogeneity in various domains**
Prognostic and predictive enrichment using various domains and strategies could increase the likelihood of identifying a signal of benefit or harm in less heterogeneous ARDS subgroups. ARDS=acute respiratory distress syndrome. PaO_2/FiO_2=ratio of partial pressure of arterial oxygen to fraction of inspired oxygen. *Patients with ARDS who have rapidly improved oxygenation in the first 24 h might not be optimal candidates for most clinical trials. †Enrichment by clinical management could include a number of aspects of management, such as prone positioning. An expanded definition of ARDS would allow patients treated with high-flow nasal oxygen to be included in trials of new therapies without the need to wait for intubation and positive-pressure ventilation.

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strategies could increase the likelihood of identifying a signal of benefit or harm in less heterogeneous ARDS subgroups (figure 2) and increase efficiency by reducing the sample size needed to observe an effect. Disadvantages include reduced generalisability, the difficulty of ascertaining enrichment factors, and possible misclassification or misidentification of targetable subgroups.

Artificial intelligence (AI)

Misclassification of imaging phenotypes is a major challenge to enrichment of studies based on imaging characteristics. The Lung Imaging for Ventilator Settings in ARDS (LIVE) trial (NCT02149589)[31] found no benefit of a personalised ventilation strategy based on lung morphology against standard 6 cc/kg, low-PEEP ventilator settings in an intention-to-treat analysis.[32] However, per-protocol analysis based on an a posteriori review in which 21% of images were found to be misclassified showed a benefit of the personalised ventilator strategy and harm for patients who were managed according to the incorrect classification.[31] Use of AI, which has been successful in identifying COVID-19 pneumonia and predicting its severity,[33,34] might in the future mitigate the risk of imaging misclassification. Such algorithms have not yet been tested for the classification of diffuse versus focal ARDS, which has important potential for advancing ARDS trials targeting imaging subphenotypes. Barriers to successful AI implementation include the large up-front investment of resources and the time required to train algorithms. Nevertheless, AI is a promising strategy for ARDS clinical trials, including improving the diagnostic classification of patients with ARDS.

Point-of-care biomarker assays

The lack of validated point-of-care biomarker platforms for prospective biological phenotyping poses another challenge to predictive and prognostic enrichment based on biomarker phenotypes. Strategies to address this challenge include the use of readily available clinical data for phenotyping[35] or the identification of a shared risk factor as a surrogate for a likely shared underlying biological mechanism. The Acetaminophen and Ascorbate in Sepsis: Targeted Therapy to Enhance Recovery (ASTER) trial (NCT04291508), a Prevention and Early Treatment of Acute Lung Injury (PETAL) Network study supported by the US National Heart, Lung, and Blood Institute (NHLBI), uses the shared risk factor of sepsis as a surrogate for the underlying mechanism of oxidative injury from cell-free haemoglobin.[36–38] The ASTER trial is also an example of how predictive enrichment can be combined with innovative trial design[39]—in this case a platform trial for the parallel testing of both ascorbate and acetaminophen. Ultimately, a priority for the continued integration of biological markers and phenotypes into clinical trial design is the development of point-of-care biomarker tests that can be deployed at the bedside for real-time phenotyping. The observational Phenotypes in the Acute Respiratory Distress Syndrome (PHIND) study in the UK (NCT04009330) is currently recruiting participants for the use of point-of-care testing to identify hyperinflammatory and hypoinflammatory phenotypes of ARDS prospectively. The successful development of a point-of-care biomarker platform could be a major advance for the enrichment of future ARDS trials. Point-of-care assays could also be adapted and implemented in resource-variable settings, where biomarker-based strategies for enrichment might otherwise be scarce.

Airspace sampling

There is also increasing interest in acquiring airspace samples for better characterisation of the biology of lung injury. In some cases, airspace samples can provide evidence of biological effects that plasma samples do not, as shown in a secondary analysis of non-bronchoscopic bronchoalveolar lavage samples from the Stem Cells for ARDS Treatment (START) trial of allogeneic mesenchymal stromal cells for moderate-to-severe ARDS.[40] In this study, mini-bronchoalveolar lavage biomarkers of inflammation and tissue damage were significantly lower

in the mesenchymal stromal cell-treated group than in the placebo group—an effect that was not observed in plasma samples. Prioritising the collection of airspace samples in ARDS clinical trials and observational studies could facilitate the identification of new phenotypes of ARDS defined by airspace rather than just plasma biology.[41,42] The routine collection of airspace samples can be challenging because of the relative invasiveness and unknown dilution factor introduced by bronchoalveolar lavage procedures, and short time window in which undiluted pulmonary oedema fluid can be reliably aspirated. However, collecting heat moisture exchange filter fluid, which resembles the protein content and composition of undiluted pulmonary oedema fluid,[43] is a novel approach for non-invasive airspace sample collection.[44] We recommend that future ARDS trials prioritise the collection of airspace samples in settings in which this is feasible, and that a special focus be placed on identifying biological characteristics in the airspaces that differ from those identified on the basis of plasma biomarkers and might increase understanding of the mechanisms of lung injury in ARDS.

Diversity and representation in ARDS clinical trials

To address the global burden of ARDS, steps need to be taken to ensure that study populations are representative of the global ARDS patient population, that evidence is generated in and applicable to both high-resource and low-resource settings, and that any differences between demographic groups in the features, course, and outcomes of ARDS, or in the clinical care received by patients, are understood and recognised in the design of clinical trials.

Representation of marginalised populations

The choice of participants for a clinical trial seeks to maximise the chance of observing an effect, and the study population is often a subgroup of the total patient population for which an intervention might eventually be indicated. As outlined here, this choice is sometimes the result of an a priori trial design strategy; however, there are also cases of inadvertent underrepresentation of marginalised demographic groups. In some fields, such as oncology, the problem of underrepresentation of racially or otherwise minoritised[45] populations is well recognised.[46] Few studies have researched the representation of marginalised communities in ARDS trials. Before COVID-19, a single study of the NHLBI ARDS Network (ARDSNet) showed that racially minoritised patients were not underenrolled relative to the number screened, although White patients were probably slightly over-represented among both the screened (74%) and enrolled (71%) populations (figure 3).[47] The percentages of Black patients among all those screened (16%) and enrolled (19%) were similar to what would be expected given that the baseline US population-adjusted incidence of acute lung injury among Black patients was almost twice that of White patients.[48–50] Hispanic and Asian patients were enrolled at rates below their representation in the population,[49,50] but it is not known how these enrolment rates reflect population-adjusted incidence.

How the racial composition of ARDS clinical trial samples compares with both their national representation and population-adjusted incidence rates has not been studied in the context of more recent non-COVID-19 ARDS trials. In the Reassessment of Systemic Early Neuromuscular Blockade (ROSE) trial (NCT02509078), conducted in 2016–18, White patients were enrolled at a rate proportional to or above their representation in the general population (70·0% White in ROSE *vs* 70·2% of the US population in 2010 and 61·6% in 2020).[50] This might indicate that racially minoritised patients were under-represented relative to their population-adjusted disease burden. In the Vitamin D to Improve Outcomes by Leveraging Early Treatment (VIOLET) trial (NCT03096314), which enriched for vitamin D deficiency, 23% of those enrolled were Black, which is more proportional to the population-adjusted incidence of ARDS and reflects racial differences in vitamin D deficiency.[51] Disparities in trial racial representation relative to disease burden have been evident during the pandemic of COVID-19, which is now the leading cause of ARDS.[52] Black, Hispanic or Latin American, and Native or Indigenous people are disproportionately affected by COVID-19 but have been underrepresented in COVID-19 clinical trials.[53] Other vulnerable populations are also underrepresented in ARDS research. In ARDSNet, elderly patients were less likely to be enrolled in clinical trials relative to their presence in the screened population, often because of severe comorbidities, terminal illness, or desires to limit interventions.[47] There is currently no evidence that sex disparities exist in ARDS trials,[47,54] although the data are scarce, but pregnant people are usually excluded. Of note, recognition of ARDS and the application of evidence-based care, particularly low tidal volume, can differ by sex.[55]

Racial and ethnic enrolment disparities also exist in investigations of paediatric ARDS.[56,57] In the Randomised Evaluation of Sedation Titration for Respiratory Failure (RESTORE) study (NCT00814099),[58] conducted in 2009–13, parents of non-Hispanic Black children (19·5%) were more frequently not offered consent compared with parents of either non-Hispanic White (11·7%) or Hispanic (13·2%) paediatric patients. In addition, declining participation was significantly more common among parents of non-Hispanic Black (29·5%) and Hispanic (25·9%) than among non-Hispanic White (18·2%) children.[56] Investigators of paediatric ARDS in the Prone and Oscillation Paediatric Clinical Trial (PROSpect; NCT03896763), a factorial design study of supine versus prone positioning and high-frequency oscillatory ventilation versus low tidal volume ventilation is currently enrolling a paediatric ARDS cohort worldwide with varying operational definitions of race and ethnicity by continent. This trial will provide an opportunity in

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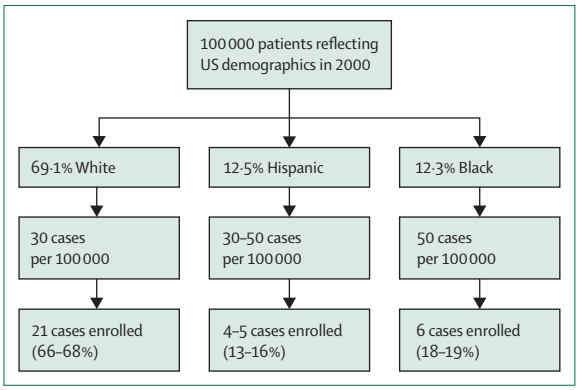

Figure 3: **Estimates of representative proportions of enrolled participants in ARDSNet**

Data are presented by race and ethnicity for White, Black, and Hispanic patients based on population-adjusted incidence estimates and census data in the year 2000, assuming that the population-adjusted incidence of ARDS for Hispanic patients falls between that for White and Black patients. ARDS=acute respiratory distress syndrome. ARDSNet=ARDS Network.

paediatric ARDS to study to what extent critical care trials outside the USA represent the racial, ethnic, and demographic makeup of the affected population.

It is crucial that clinical trial results are applicable to the patient populations most likely to be affected by ARDS, which are often also at higher risk of adverse outcomes.[59–61] Increased representation can and should coexist with strategies to enrich ARDS clinical trials based on biological, clinical, physiological, and imaging characteristics. Enrichment strategies can be implemented hand-in-hand with efforts to enrol patients representative of the general ARDS population. For example, race, sex, and age do not differ substantially between the hyperinflammatory and hypoinflammatory subtypes of ARDS (figure 1),[23,25,27] although race data with more granularity than White versus non-White are absent. Risk factors for and physiological characteristics of ARDS differ slightly but not substantially by race and sex.[55,59] On the basis of available evidence, enrichment strategies should generally not be in conflict with steps to ensure a diverse and representative study population.

We recommend that ARDS trials set specific enrolment targets by age, sex, and race that reflect the population-adjusted incidence of ARDS. We also recommend a renewed focus on the investigation of outcome disparities among minoritised communities and the question of how such disparities might affect clinical trial design. Outreach to and involvement of surrogate decision makers in research design is likely to be an important step in reaching these enrolment targets. Finally, we recommend that ongoing investigational work on subphenotypes of ARDS specifically ask how subphenotype assignment is affected by demographic factors.

Conduct of trials in resource-variable settings

Internationally representative trials are necessary to adequately address the global burden of ARDS.[62] ARDS trials are currently overwhelmingly conducted in high-income countries with ample resources—primarily in North America and Europe, including the UK—although low-income and middle-income countries (LMIC) also have a high burden of ARDS and ARDS risk factors including pneumonia and trauma.[63,64] Evidence generated in high-resource settings is not always directly applicable to settings with variable resources.[65] Patients with ARDS in LMICs are affected by risk factors and management options that differ from those in high-income countries,[55,66] which might mean that enrichment strategies in LMICs need to differ from those in higher-resource settings. For example, on-site extracorporeal membrane oxygenation is a requirement for site participation in the PROSpect study. Of note, latent class analysis-derived phenotypes using clinical data were shown to be valid in the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG-SAFE) observational cohort,[67] which included participants from intensive care units in several LMICs.[62] These results indicate that biological enrichment strategies based on latent class analysis-derived phenotypes might be applicable globally. Ongoing investigation of the epidemiology and impact of ARDS in LMICs is needed in order to generate and translate relevant evidence.[65]

Expansion of the Berlin definition of ARDS

In 2015, a landmark trial of high-flow nasal oxygen (HFNO) in acute hypoxaemic respiratory failure showed that participants randomised to HFNO had a significantly lower rate of intubation at 28 days and a significantly lower risk of mortality.[68] Since that time, there has been a major expansion of the use of HFNO to manage patients with critical acute hypoxaemic respiratory failure. In the past, these patients would most likely have been managed with positive-pressure ventilation, which raises the question of whether these patients have ARDS. Previous studies have shown that patients who otherwise meet the criteria for ARDS but who are initially managed without positive pressure have clinical outcomes and biological characteristics similar to those who meet the formal Berlin definition.[69–71] An expansion of the definition of ARDS has now been proposed, to include patients who meet other diagnostic criteria and are managed with HFNO at a to-be-determined minimum flow rate.[6] Such an expansion could have a major effect not only on the global epidemiology of ARDS, but also on the design and conduct of clinical trials.

What are the possible benefits and drawbacks of expanding the definition of ARDS (panel 2)? Expanding the definition of ARDS could increase power to detect an effect in trials testing preventive therapies or early interventions. For example, the currently enrolling NHLBI-supported double-blind Arrest Respiratory Failure due to Pneumonia (ARREST-Pneumonia) trial (NCT04193878) is testing the effectiveness of inhaled budesonide and formoterol versus placebo in hypoxaemic

patients with pneumonia in reducing progression to acute respiratory failure. The acute respiratory failure endpoint includes need for HFNO as well as non-invasive and invasive positive-pressure ventilation, which will improve the power to detect a benefit as compared with a limited endpoint of the development of ARDS as it is currently defined. Another benefit is the ability to focus on the patient-centred non-mortality outcome of progression to mechanical ventilation in ARDS. Mortality is a notoriously challenging endpoint in critical care trials,[72] and testing non-mortality endpoints such as progression to mechanical ventilation increases power to detect important benefits. Formally designating patients on HFNO as having ARDS would probably increase investigator opportunities to study a key population of patients who have been excluded from past ARDS trials. Expanding the definition of ARDS would also increase opportunities for ARDS investigation in global settings, including LMICs, especially if the Kigali modification of the Berlin definition is formally adopted.[73]

There are also potential drawbacks to expanding the definition of ARDS. It is possible that expanding the definition would introduce yet more heterogeneity into the ARDS population. There is some concern that expanding the definition to include patients on HFNO would reduce power to detect important therapeutic effects, since the mortality rates of patients managed exclusively with HFNO are lower compared with those requiring invasive ventilation. However, this is also true of patients managed exclusively with non-invasive ventilation.[74] Lower rates of mortality among patients who progress to intubation from HFNO could reflect a benefit of HFNO in patients with ARDS rather than fundamental differences in baseline severity.[68,74] Additionally, as noted, mortality is only one metric of benefit in trials including this population. It can be difficult to accurately estimate the fraction of inspired oxygen (FiO_2) in open oxygen delivery systems, including HFNO, although this is less of a concern at higher flow rates. Thus, there is a risk of severity or diagnostic misclassification for patients on HFNO. Inclusion and exclusion criteria for each trial can be customised depending upon whether capturing patients in the earliest stages of their respiratory failure or accurate classification is more important for a specific trial.

We recommend that, if an expansion of the Berlin definition is adopted, key questions about the effect of this change on clinical trials be prospectively studied. First, how will an expanded definition change the estimated prevalence and outcomes of ARDS, and how will these changes impact the design of individual studies in terms of their power to detect effects? Second, do biological and imaging subphenotypes that have been identified in ARDS[23] extend to patients managed on HFNO, and will new subphenotypes be identified? At least one study has found a pattern of elevation of peripheral biomarkers among patients on HFNO similar to that observed in patients with ARDS,[71] but further characterisation of these biomarker patterns has not been reported. Specific patterns of infiltrates in patients on HFNO have also not been extensively studied. Further characterisation of imaging phenotypes before the initiation of mechanical ventilation also provides an opportunity to study potential differential effects of the timing of intubation and the putative phenomenon of patient self-inflicted lung injury,[75,76] for example. And third, what effect will the prospect of non-mortality outcomes such as progression to mechanical ventilation have on study design?

Panel 2: **Benefits and drawbacks of expanding the definition of ARDS to include patients managed on HFNO**

Benefits of an expanded definition

- ARDS population more representative of current clinical practice in many settings
- Earlier identification of eligible patients for clinical trials
- Increased understanding of the natural history of ARDS, including opportunities to study progression to mechanical ventilation
- The study findings potentially more applicable to resource-limited or resource-variable settings
- Opportunity to study patients who decline non-invasive or invasive mechanical ventilation
- Less reliance on surrogate consent

Drawbacks of an expanded definition

- Possible increase in physiological and biological heterogeneity
- Reduced power in clinical trials with mortality as a primary endpoint
- Reduced accuracy in estimating FiO_2 at low flow rates, which might result in severity of ARDS or diagnostic misclassification
- Substantial changes in epidemiological estimates of ARDS incidence and mortality
- Variation by institution and provider in the use of HFNO and criteria for intubation

ARDS=acute respiratory distress syndrome. FiO_2=fraction of inspired oxygen. HFNO=high-flow nasal oxygen.

Priorities and opportunities in future ARDS trials

Major funding for ARDS trials in the USA began in 1994 with ARDSNet, leading to several landmark trials that still guide the fundamental supportive management of ARDS patients.[32,77,78] The PETAL Network then prioritised the identification of early interventions for patients at risk of ARDS or with early disease, and has been pivotal to the research effort during the COVID-19 pandemic. On March 17, 2021, the US National Institutes of Health (NIH) announced a research initiative to comprehensively, prospectively phenotype patients with ARDS, pneumonia, and sepsis (the APS Consortium), supported by NHLBI

Search strategy and selection criteria

References included in relevant presentations regarding acute respiratory distress syndrome (ARDS) heterogeneity, clinical trial design, imaging interpretation, patient engagement, and regulatory priorities presented during the 2021 Critical Care Clinical Trialists Workshop section on ARDS were included in this Personal View. In addition, we searched PubMed from database inception to May 31, 2022, using combinations of the terms "ARDS", "clinical trials", "phenotypes", "HFNO", "imaging", "race AND ethnicity", "age", "representation", "patient engagement", and "survivorship." The authors' personal collections of articles were also used to supplement the search strategy. Articles published in English were selected on the basis of the authors' assessment of their relevance to the topic and the aims of the paper.

and the National Institute for General Medical Sciences.[79] The focus of this funding initiative is to comprehensively characterise the biological, imaging, and clinical characteristics of 5000 patients with critical illness syndromes, with 1 year of follow-up to allow study of longer-term health consequences of ARDS. This initiative will be valuable in achieving better understanding of enrichment opportunities for future trials and in identifying meaningful endpoints beyond mortality.

It is also crucial that enrichment strategies be paired with efforts from national agencies such as NIH and the UK National Institute for Health and Care Research to increase diversity and equity in clinical research.[80–83] Efforts to increase representation among critical care trial participants, in particular, will also require an emphasis on building trusting relationships with designated surrogates, as critical care research relies heavily on informed consent from surrogates.[84–86] Patient representation in ARDS working groups and conferences, including during the 2021 3CT Workshop, is a crucial component in effectively moving ARDS investigation forward.

In conclusion, the future of clinical trials in ARDS will rely on further characterising heterogeneity among a truly representative population of patients, including a globally representative population, and harnessing this heterogeneity for intelligent trial design. Although challenges remain, there are rich opportunities to target new interventions while simultaneously increasing the inclusiveness of ARDS investigations.

Contributors

All authors contributed to the foundational content of this manuscript through their presentations and discussions at the 3CT conference, including literature relevant to their presentations. KDW performed the additional literature search, drafted the initial manuscript, and created the figures. KDW and PS created the panels. All authors critically reviewed and edited the manuscript and approved the final version.

Declaration of interests

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References

1 Matthay MA, McAuley DF, Ware LB. Clinical trials in acute respiratory distress syndrome: challenges and opportunities. *Lancet Respir Med* 2017; **5:** 524–34.
2 Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012; **307:** 2526–33.
3 Thille AW, Esteban A, Fernández-Segoviano P, et al. Comparison of the Berlin definition for acute respiratory distress syndrome with autopsy. *Am J Respir Crit Care Med* 2013; **187:** 761–67.
4 Matthay MA, Zemans RL, Zimmerman GA, et al. Acute respiratory distress syndrome. *Nat Rev Dis Primers* 2019; **5:** 18.
5 Ware LB, Matthay MA, Mebazaa A. Designing an ARDS trial for 2020 and beyond: focus on enrichment strategies. *Intensive Care Med* 2020; **46:** 2153–56.
6 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:** 933–36.
7 Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. *Lancet* 1967; **2:** 319–23.
8 Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis* 1988; **138:** 720–23.
9 Bernard GR, Artigas A, Brigham KL, et al. Report of the American-European consensus conference on ARDS: definitions, mechanisms, relevant outcomes and clinical trial coordination. *Intensive Care Med* 1994; **20:** 225–32.
10 Reilly JP, Calfee CS, Christie JD. Acute respiratory distress syndrome phenotypes. *Semin Respir Crit Care Med* 2019; **40:** 19–30.
11 Gattinoni L, Pelosi P, Suter PM, Pedoto A, Vercesi P, Lissoni A. Acute respiratory distress syndrome caused by pulmonary and extrapulmonary disease. Different syndromes? *Am J Respir Crit Care Med* 1998; **158:** 3–11.
12 Calfee CS, Janz DR, Bernard GR, et al. Distinct molecular phenotypes of direct vs indirect ARDS in single-center and multicenter studies. *Chest* 2015; **147:** 1539–48.

13 Puybasset L, Gusman P, Muller JC, et al. Regional distribution of gas and tissue in acute respiratory distress syndrome. III. Consequences for the effects of positive end-expiratory pressure. CT scan ARDS study group. Adult respiratory distress syndrome. *Intensive Care Med* 2000; **26:** 1215–27.

14 Coppola S, Pozzi T, Gurgitano M, et al. Radiological pattern in ARDS patients: partitioned respiratory mechanics, gas exchange and lung recruitability. *Ann Intensive Care* 2021; **11:** 78.

15 Mrozek S, Jabaudon M, Jaber S, et al. Elevated plasma levels of sRAGE are associated with nonfocal CT-based lung imaging in patients with ARDS: a prospective multicenter study. *Chest* 2016; **150:** 998–1007.

16 Nuckton TJ, Alonso JA, Kallet RH, et al. Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. *N Engl J Med* 2002; **346:** 1281–86.

17 Lucangelo U, Bernabè F, Vatua S, et al. Prognostic value of different dead space indices in mechanically ventilated patients with acute lung injury and ARDS. *Chest* 2008; **133:** 62–71.

18 Zhang R, Wang Z, Tejera P, et al. Late-onset moderate to severe acute respiratory distress syndrome is associated with shorter survival and higher mortality: a two-stage association study. *Intensive Care Med* 2017; **43:** 399–407.

19 Liao KM, Chen CW, Hsiue TR, Lin WC. Timing of acute respiratory distress syndrome onset is related to patient outcome. *J Formos Med Assoc* 2009; **108:** 694–703.

20 Reilly JP, Bellamy S, Shashaty MG, et al. Heterogeneous phenotypes of acute respiratory distress syndrome after major trauma. *Ann Am Thorac Soc* 2014; **11:** 728–36.

21 Schenck EJ, Oromendia C, Torres LK, Berlin DA, Choi AMK, Siempos II. Rapidly improving ARDS in therapeutic randomized controlled trials. *Chest* 2019; **155:** 474–82.

22 Rindskopf D, Rindskopf W. The value of latent class analysis in medical diagnosis. *Stat Med* 1986; **5:** 21–27.

23 Calfee CS, Delucchi K, Parsons PE, Thompson BT, Ware LB, Matthay MA. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. *Lancet Respir Med* 2014; **2:** 611–20.

24 Sinha P, Delucchi KL, Thompson BT, McAuley DF, Matthay MA, Calfee CS. 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.

25 Sinha P, Delucchi KL, Chen Y, et al. Latent class analysis-derived subphenotypes are generalisable to observational cohorts of acute respiratory distress syndrome: a prospective study. *Thorax* 2021; **77:** 13–21.

26 Calfee CS, Delucchi KL, Sinha P, et al. Acute respiratory distress syndrome subphenotypes and differential response to simvastatin: secondary analysis of a randomised controlled trial. *Lancet Respir Med* 2018; **6:** 691–98.

27 Famous KR, Delucchi K, Ware LB, et al. Acute respiratory distress syndrome subphenotypes respond differently to randomized fluid management strategy. *Am J Respir Crit Care Med* 2017; **195:** 331–38.

28 Dahmer MK, Yang G, Zhang M, et al. Identification of phenotypes in paediatric patients with acute respiratory distress syndrome: a latent class analysis. *Lancet Respir Med* 2021.

29 Delucchi K, Famous KR, Ware LB, Parsons PE, Thompson BT, Calfee CS. Stability of ARDS subphenotypes over time in two randomised controlled trials. *Thorax* 2018; **73:** 439–45.

30 Harhay MO, Casey JD, Clement M, et al. Contemporary strategies to improve clinical trial design for critical care research: insights from the first Critical Care Clinical Trialists workshop. *Intensive Care Med* 2020; **46:** 930–42.

31 Constantin JM, Jabaudon M, Lefrant JY, et al. 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.

32 Brower RG, Lanken PN, MacIntyre N, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004; **351:** 327–36.

33 Lassau N, Ammari S, Chouzenoux E, et al. Integrating deep learning CT-scan model, biological and clinical variables to predict severity of COVID-19 patients. *Nat Commun* 2021; **12:** 634.

34 Li L, Qin L, Xu Z, et al. Using artificial intelligence to detect COVID-19 and community-acquired pneumonia based on pulmonary CT: evaluation of the diagnostic accuracy. *Radiology* 2020; **296:** E65–71.

35 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.

36 Piagnerelli M, Boudjeltia KZ, Vanhaeverbeek M, Vincent JL. Red blood cell rheology in sepsis. *Intensive Care Med* 2003; **29:** 1052–61.

37 Janz DR, Ware LB. The role of red blood cells and cell-free hemoglobin in the pathogenesis of ARDS. *J Intensive Care* 2015; **3:** 20.

38 Shaver CM, Upchurch CP, Janz DR, et al. Cell-free hemoglobin: a novel mediator of acute lung injury *Am J Physiol Lung Cell Mol Physiol* 2016; **310:** L532–41.

39 Berry SM, Connor JT, Lewis RJ. The platform trial: an efficient strategy for evaluating multiple treatments. *JAMA* 2015; **313:** 1619–20.

40 Matthay MA, Calfee CS, Zhuo H, et al. Treatment with allogeneic mesenchymal stromal cells for moderate to severe acute respiratory distress syndrome (START study): a randomised phase 2a safety trial. *Lancet Respir Med* 2019; **7:** 154–62.

41 Rogers AJ, Contrepois K, Wu M, et al. Profiling of ARDS pulmonary edema fluid identifies a metabolically distinct subset. *Am J Physiol Lung Cell Mol Physiol* 2017; **312:** L703–09.

42 Morrell ED, Bhatraju PK, Mikacenic CR, et al. Alveolar macrophage transcriptional programs are associated with outcomes in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2019; **200:** 732–41.

43 McNeil JB, Shaver CM, Kerchberger VE, et al. Novel method for noninvasive sampling of the distal airspace in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2018; **197:** 1027–35.

44 Bastarache JA, McNeil JB, Plosa EJ, et al. Standardization of methods for sampling the distal airspace in mechanically ventilated patients using heat moisture exchange filter fluid. *Am J Physiol Lung Cell Mol Physiol* 2021; **320:** L785–90.

45 Milner A, Jumbe S. Using the right words to address racial disparities in COVID-19. *Lancet Public Health* 2020; **5:** e419–20.

46 Loree JM, Anand S, Dasari A, et al. Disparity of race reporting and representation in clinical trials leading to cancer drug approvals from 2008 to 2018. *JAMA Oncol* 2019; **5:** e191870.

47 Cooke CR, Erickson SE, Watkins TR, Matthay MA, Hudson LD, Rubenfeld GD. Age-, sex-, and race-based differences among patients enrolled versus not enrolled in acute lung injury clinical trials. *Crit Care Med* 2010; **38:** 1450–57.

48 Erickson S, Cooke C, Eisner M, Martin G. Effect of race on the incidence of acute lung injury. C92 ALI/ARDS: outcomes and predictors of failure. *Am J Thor Soc* 2009; **179:** A5096 (abstr).

49 Brewer C, Suchan T. Mapping Census 2000: the geography of US diversity. Washington, DC: US Census Bureau, 2001.

50 US Census Bureau. Race and Ethnicity in the United States: 2010 Census and 2020 Census. 2021. https://www.census.gov/library/visualizations/interactive/race-and-ethnicity-in-the-united-state-2010-and-2020-census.html (accessed Feb 1, 2022).

51 Weishaar T, Rajan S, Keller B. Probability of vitamin D deficiency by body weight and race/ethnicity. *J Am Board Fam Med* 2016; **29:** 226–32.

52 Matthay MA, Leligdowicz A, Liu KD. Biological mechanisms of COVID-19 ARDS. *Am J Respir Crit Care Med* 2020. https://doi.org/10·1164/rccm.202009–3629ED.

53 Chastain DB, Osae SP, Henao-Martínez AF, Franco-Paredes C, Chastain JS, Young HN. Racial disproportionality in COVID clinical trials. *N Engl J Med* 2020; **383:** e59.

54 Lat TI, McGraw MK, White HD. Gender differences in critical illness and critical care research. *Clin Chest Med* 2021; **42:** 543–55.

55 McNicholas BA, Madotto F, Pham T, et al. Demographics, management and outcome of females and males with acute respiratory distress syndrome in the LUNG SAFE prospective cohort study. *Eur Respir J* 2019; **54:** 1900609.

56 Natale JE, Lebet R, Joseph JG, et al. Racial and ethnic disparities in parental refusal of consent in a large, multisite pediatric critical care clinical trial. *J Pediatr* 2017; **184:** 204–208.e1.

57 Paquette E, Shukla A, Davidson J, Rychlik K, Davis M. Burden or Opportunity? Parent Experiences When Approached for Research in a Pediatric Intensive Care Unit. *Ethics Hum Res* 2019; **41:** 2–12.

58 Curley MA, Wypij D, Watson RS, et al. Protocolized sedation vs usual care in pediatric patients mechanically ventilated for acute respiratory failure: a randomized clinical trial. *JAMA* 2015; **313:** 379–89.

59 Erickson SE, Shlipak MG, Martin GS, et al. Racial and ethnic disparities in mortality from acute lung injury. *Crit Care Med* 2009; **37:** 1–6.

60 TenHoor T, Mannino DM, Moss M. Risk factors for ARDS in the United States: analysis of the 1993 national mortality followback study. *Chest* 2001; **119:** 1179–84.

61 Parcha V, Kalra R, Bhatt SP, Berra L, Arora G, Arora P. Trends and geographic variation in acute respiratory failure and ARDS mortality in the United States. *Chest* 2021; **159:** 1460–72.

62 Bellani G, Laffey JG, Pham T, et al. 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.

63 Riviello ED, Kiviri W, Twagirumugabe T, 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:** 52–59.

64 Fleischmann C, Scherag A, Adhikari NK, et al. Assessment of global incidence and mortality of hospital-treated sepsis. Current estimates and limitations. *Am J Respir Crit Care Med* 2016; **193:** 259–72.

65 Chowdhury S, Laux T, Morse M, Jenks A, Stonington S, Jain Y. Democratizing evidence production—a 51-year-old man with sudden onset of dense hemiparesis. *N Engl J Med* 2019; **381:** 1501–05.

66 Graça L, Abreu IG, Santos AS, Graça L, Dias PF, Santos ML. Descriptive acute respiratory distress syndrome (ARDS) in adults with imported severe plasmodium falciparum malaria: a 10 year-study in a Portuguese tertiary care hospital. *PLoS One* 2020; **15:** e0235437.

67 Maddali MV, Churpek M, Pham T, et al. 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.

68 Frat JP, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med* 2015; **372:** 2185–96.

69 Coudroy R, Frat JP, Boissier F, Contou D, Robert R, Thille AW. Early identification of acute respiratory distress syndrome in the absence of positive pressure ventilation: implications for revision of the berlin criteria for acute respiratory distress syndrome. *Crit Care Med* 2018; **46:** 540–46.

70 Kangelaris KN, Ware LB, Wang CY, et al. Timing of intubation and clinical outcomes in adults with acute respiratory distress syndrome. *Crit Care Med* 2016; **44:** 120–29.

71 García-de-Acilu M, Marin-Corral J, Vázquez A, et al. Hypoxemic patients with bilateral infiltrates treated with high-flow nasal cannula present a similar pattern of biomarkers of inflammation and injury to acute respiratory distress syndrome patients. *Crit Care Med* 2017; **45:** 1845–53.

72 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.

73 Vercesi V, Pisani L, van Tongeren PSI, et al. Correction to: external confirmation and exploration of the Kigali modification for diagnosing moderate or severe ARDS. *Intensive Care Med* 2018; **44:** 403–04.

74 Ranieri VM, Tonetti T, Navalesi P, et al. High flow nasal oxygen for severe hypoxemia: oxygenation response and outcome in COVID-19 patients. *Am J Respir Crit Care Med* 2021; **205:** 431–39.

75 Grieco DL, Menga LS, Eleuteri D, Antonelli M. Patient self-inflicted lung injury: implications for acute hypoxemic respiratory failure and ARDS patients on non-invasive support. *Minerva Anestesiol* 2019; **85:** 1014–23.

76 Carteaux G, Parfait M, Combet M, Haudebourg AF, Tuffet S, Mekontso Dessap A. Patient-self inflicted lung injury: a practical review. *J Clin Med* 2021; **10:** 2738.

77 Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. 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:** 1301–08.

78 Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006; **354:** 2564–75.

79 National Institutes of Health. Notice of Intent to Publish a Funding Opportunity Announcement for the ARDS, Pneumonia, and Sepsis Phenotyping Consortium Clinical Centers—U01 Clinical Trial Not Allowed. 2021. https://grants.nih.gov/grants/guide/notice-files/NOT-HL-21-002.html (accessed Feb 7, 2022)

80 Witham MD, Anderson E, Carroll CB, et al. Ensuring that COVID-19 research is inclusive: guidance from the NIHR INCLUDE project. *BMJ Open* 2020; **10:** e043634.

81 Witham MD, Anderson E, Carroll C, et al. Developing a roadmap to improve trial delivery for under-served groups: results from a UK multi-stakeholder process. *Trials* 2020; **21:** 694.

82 National Institutes of Health. Inclusion of women and minorities as participants in research involving human subjects. 2022. https://grants.nih.gov/policy/inclusion/women-and-minorities.htm (accessed Feb 7, 2022).

83 National Institutes of Health. Inclusion Across the Lifespan. Bethesda, MD: National Institutes of Health, 2020.

84 Krutsinger DC, Courtright KR, Estabrooks PA. Historic abuses, present disparities, and systemic racism: threats to surrogate decision-making for critical care research enrollment. *Ann Am Thorac Soc* 2021; **18:** 1118–20.

85 Burns KE, Prats CJ, Maione M, et al. The Experience of Surrogate Decision Makers on Being Approached for Consent for Patient Participation in Research. A multicenter study. *Ann Am Thorac Soc* 2017; **14:** 238–45.

86 Lane T, Brereton E, Nowels C, McKeehan J, Moss M, Matlock DD. Surrogate informed consent: a qualitative analysis of surrogate decision makers' perspectives. *Ann Am Thorac Soc* 2021; **18:** 1185–90.

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