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Guideline on the clinical investigation of medicinal products in the treatment of patients with acute respiratory distress syndrome

Draft

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This guideline replaces the guideline on clinical investigation of medicinal products for the treatment of patients with acute respiratory distress syndrome (EMEA/CPMP/EWP/504/97 Rev1).

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support.

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Executive summary

The aim of the guideline is to provide guidance for the development of medicinal products for the treatment of Acute Respiratory Distress Syndrome (ARDS) and/or preventing disease progression. This is the first revision of the Guidance on clinical investigation of medicinal products in patients with ARDS issued in 2006. Updates of the diagnosis criteria for ARDS in 2012 [D0] and 2023 [D1, P1] has subsequent implications for identifying patients both in clinical and research settings. The key requirements are described in terms of study population, (co)primary and secondary efficacy endpoints. Specific issues, including biomarker and/or (sub)phenotype defined drug development and preparedness are addressed for a potential future pandemic due to a viral pathogen that causes ARDS. Furthermore, relevant published methodological guidance documents for decision making (e.g. estimand(s)) were added. This document should be read in conjunction with other relevant European Medicine Agency (EMA) and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines (see section 3).

1. Introduction (background)

ARDS is a critical condition characterized by a sudden and severe impairment of lung function, primarily marked by the inability of the lungs to adequately oxygenate the blood. This dysfunction stems from various causes, the most frequent being bronchopulmonary viral infection, sepsis, trauma, or aspiration, triggering an inflammatory cascade within the lungs. As a consequence, the alveolar-capillary membrane becomes permeable, leading to the leakage of fluid into the alveolar spaces and impairing gas exchange. Clinically, ARDS manifests with dyspnea, tachypnea, and refractory hypoxemia, often necessitating mechanical ventilation.

The condition carries a high mortality rate, often attributed to complications such as ventilator-induced lung injury, abnormal organ function, and nosocomial infections. The mortality of ARDS is commensurate with the severity of the disease: 27%, 32%, and 45% for mild, moderate, and severe disease, respectively [D3, D0].

Management involves supportive care, which includes various strategies for assisted ventilation. There is some evidence that mechanical ventilation with lower tidal volume maintaining, a plateau pressure as low as possible and a sufficient positive end expiratory pressure (PEEP) significantly reduces mortality. High frequency ventilation, inverse ratio ventilation and the prone position are techniques that may shortly improve gas exchange.

Standards of and approaches to critical care (e.g., pharmacological treatments, supportive care, ventilation) in ARDS may vary between individual physicians, referral centres, and geographical regions. Many aspects of management of critically ill patients often lack a robust evidence base. This adds to the high degree of heterogeneity within the ARDS population.

Most patients who survive ARDS have a remarkable degree of recovery of lung function within the first three to six months, depending on the severity of the initial lung injury. A few patients experience a permanent decrease in lung function. Pre-existing conditions that predispose to ARDS include chronic lung disease, chronic alcohol consumption, and advanced age, although ARDS may occur at any age.

Several “failed” studies have underscored the challenges in all-cause ARDS research, including difficulties in patient selection, variability in disease presentation and progression, and the lack of understanding targeting underlying pathophysiological mechanisms.

The COVID-19 (Corona VIrus Disease 2019) pandemic had a significant impact on ARDS research and treatment developments. Since severe COVID-19 often led to ARDS, it brought increased attention to

the condition, accelerating advancements in understanding, management, and research that are likely to benefit the broader population of ARDS patients in the future.

2. Scope

The current revision concerns the clinical development program of medicinal products intended to treat ARDS and/or prevent disease progression with specific reference to the definition of the study population, choice of clinical endpoints for inference of efficacy, and estimation of treatment effect (estimands) in confirmatory studies.

New treatments of underlying clinical conditions are not within the scope of this document. This accounts in particular to antiviral medicinal products and monoclonal antibodies that targets severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as these require different considerations for evaluating their safety and efficacy.

The present document does not refer to respiratory distress syndrome (RDS) in preterm neonates caused by surfactant deficiency and also not to infectious conditions presenting with a systemic inflammatory response syndrome, e.g., sepsis, which are addressed in a separate document.

3. Legal basis and relevant guidelines

This Guideline should be read in conjunction with the introduction and general principles of Annex I to Directive 2001/83/EC, as amended, and all other relevant EU and ICH guidelines. These include, but are not limited to:

- Guideline for good clinical practice - EMA/CHMP/ICH/135/1995 (ICH E6[R2]);
- ICH Guideline E8 (R1) on general considerations for clinical studies EMA/CHMP/ICH/544570/1998 Corr*;
- Note for Guidance on Studies in Support of Special Populations: Geriatrics - CPMP/ICH/379/95 (ICH E7) and Questions and Answers - EMA/CHMP/ICH/604661/2009 (ICH E7 Q&A);
- ICH M12 Guideline on drug interaction studies (EMA/CHMP/ICH/652460/2022);
- Note for Guidance on Population Exposure: the extent of population exposure to assess clinical safety (CPMP/ICH/375/95 [ICH E1]);
- Note for Guidance on Dose Response Information to Support Drug Registration - CPMP/ICH/378/95 (ICH E4);
- Reflection paper on methodological issues associated with pharmacogenomic biomarkers in relation to clinical development and patient selection (EMA/446337/2011);
- Note for Guidance on Statistical Principles for Clinical Trials - CPMP/ICH/363/96 (ICH E9) and Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials - EMA/CHMP/ICH/436221/2017 (ICH E9[R1]);
- Note for Guidance on Ethnic Factors in the Acceptability of Foreign Clinical Data CPMP/ICH/289/95 (ICH E5) - and Questions and Answers CPMP/ICH/5746/03 (ICH E5[R1]);
- Qualification of novel methodologies for drug development: guidance to applicants, (EMA/CHMP/SAWP/72894/2008);
- Guideline on Clinical Investigation of Medicinal Products in the Paediatric Population EMA/CPMP/ICH/2711/1999 (ICH E11[R1]);

- Guideline on General Principles for Planning and Design of Multi-Regional Clinical Trials (ICH E17).

4. Clinical Pharmacology studies

Studies should be performed to characterise the pharmacokinetics (PK) of the new medicinal product [D6] and where possible this information should be used to study the relationship between dose, exposure and response.

It should be considered, that in critically ill Intensive Care Unit (ICU) patients, PK may be affected by disease-related alterations in serum protein levels, which can impact drug binding. Fluid shifts, single or multiorgan dysfunction, and extracorporeal circulation (e.g., renal replacement therapy (RRT) or extracorporeal membrane oxygenation (ECMO)) may likewise significantly affect drug distribution.

Population PK analyses may be used to investigate relevant covariates e.g., weight, age, sex (gender), healthy vs. patient population, concomitant medications, etc. which could potentially influence the pharmacokinetics of the drug. The dose selection for the clinical programme should be adequately justified.

In general, the ICH guideline M12 on drug interactions [D7] should be followed to investigate possible PK interactions with other drugs. Interactions with relevant compounds used as standard of care (SOC) treatment should be investigated. It is recommended that pharmacodynamic (PD) interactions between the test drug and any other drug that may be given simultaneously in clinical practice are explored and discussed either through dedicated studies or literature data. If appropriate, PK studies in patients with hepatic and /or renal impairment should be performed.

PD endpoints should be product-specific, defined based on the mechanism of action of the investigational medicinal product with the intention to provide a "proof-of-concept" and evidence of the pharmacological activity of the drug, as well as a characterisation of the exposure-response relationships with regard to the PD effect.

5. Assessment of therapeutic efficacy

5.1. Patients' characteristics and selection of patients

The diagnosis criteria for ARDS in clinical studies must be clearly outlined in the study protocol. Two definitions exist: the "Berlin criteria" from 2012 [D0] and the "New Global Definition" from 2023 [D1, D2]. Both definitions are used and define ARDS based on timing of onset, chest imaging, origin of oedema, and oxygenation levels, with severity graded by PaO2/FiO2 ratios (ratio of arterial oxygen partial pressure to fractional inspired oxygen).

Factors	Berlin Criteria	New Criteria
Timing	- Acute onset within 1 week of known clinical insult or new/worsening respiratory symptoms	- Acute onset or worsening of hypoxemic respiratory failure within 1 week of predisposing risk factor or new/worsening respiratory symptoms
Chest Imaging	- Bilateral opacities on chest X-ray or CT not fully explained by effusions, lobar/lung collapse, or nodules	- Bilateral opacities on chest radiography/CT or bilateral B lines and/or consolidations on ultrasound* - Not fully explained by effusions, atelectasis, or nodules/masses

Risk Factors and Origin of Edema	- Respiratory failure not fully explained by cardiac failure or fluid overload	- Precipitated by acute predisposing risk factor (pneumonia, infection, trauma, etc.) - Pulmonary edema not primarily attributable to cardiogenic causes or fluid overload
Oxygenation	- Based on PaO_2/FiO_2 ratio while on PEEP/CPAP ≥ 5 cmH_2O	- PaO_2/FiO_2 or SpO_2/FiO_2 ratio - HFNO (≥ 30 L/min), NIV, or CPAP (≥ 5 cmH_2O) used for non-intubated ARDS.
Mild (Intubated or non-intubated)	**Intubated** PaO_2/FiO_2: 200 < PaO_2/FiO_2 ≤ 300 mmHg - Requires positive end-expiratory pressure (PEEP) or CPAP ≥ 5 cmH_2O	**Non-intubated** PaO2/FiO2 ⩽ 300 mm Hg or SpO2/FiO2 ⩽ 315 (if SpO2 ⩽ 97%) on HFNO with flow of ⩾30 L/min or NIV/CPAP with at least 5 cm H2O end-expiratory pressure; **Intubated** - 200 < PaO2:FiO2 ⩽ 300 mmHg or 235 < SpO2:FiO2 ⩽ 315 (if SpO2 ⩽ 97%) or SpO2:FiO2 ⩽ 315 (if SpO2 ⩽ 97%)) - No PEEP or minimum flow rate required in resource-limited settings
Moderate (Intubated)	PaO_2/FiO_2: 100 < PaO_2/FiO_2 ≤ 200 mmHg - Requires PEEP or CPAP ≥ 5 cmH_2O	- PaO_2/FiO_2: 100< PaO_2/FiO_2 ≤ 200 mmHg - SpO_2/FiO_2: 148 < SpO_2/FiO_2 ≤ 235 (if SpO_2 ≤ 97%)
Severe (Intubated)	- PaO_2/FiO_2 ≤ 100 mmHg - Requires PEEP or CPAP ≥ 5 cmH_2O	- PaO_2/FiO_2 ≤ 100 mmHg - SpO_2/FiO_2 ≤ 148 (if SpO_2 ≤ 97%) - No PEEP or minimum flow rate required in resource-limited settings

PaO2/FiO2 ratio (ratio of arterial oxygen partial pressure to fractional inspired oxygen); PEEP (positive end-expiratory pressure); NIV (Non-invasive Ventilation); HFNO (high-flow nasal oxygen (HFNO); CPAP (continuous positive airway pressure); SpO2/FiO2 (ratio of oxygen saturation as measured by pulse oximetry to fractional inspired oxygen).

The Berlin criteria focus on patients using PEEP, while the new definition accommodates high-flow nasal oxygen (HFNO) and non-invasive methods, addressing resource-limited settings. The Berlin criteria also specify ARDS severity as mild (PaO2/FiO2 ≤300 mmHg), moderate (≤200 mmHg), or severe (≤100 mmHg). The new global definition expands this by including SpO2/FiO2 ratios and different standards for non-intubated and intubated patients, accounting for limited diagnostic resources. Both definitions stress accurate patient selection, as ARDS severity and mortality depend on various factors, including comorbidities and organ failure.

Validated scores like SOFA (Sequential Organ Failure Assessment) or APACHE (Acute physiology and Chronic Health Evaluation) should be also used to assess disease severity and prognosis at baseline. Any significant baseline differences between treatment groups may complicate data interpretation, so proper stratification is recommended.

The risk of disease progression should also carefully be estimated at baseline. Of note, a prevalence of rapidly improving ARDS (PaO_2/FiO_2 > 300 mmHg or extubated within the first 24 h after diagnosis) has been reported > 10% in six ARDS Network trials [D1]. This group of patients need to be accounted for when the size of the study is being calculated.

In addition, it cannot be anticipated that patients with ARDS of different aetiologies would respond to the same therapy to a similar extent. Therefore, generally, stratified randomisation and analysis should be considered. The number of factors should be restricted to the most clinically important and/or strongly prognostic covariates.

For ARDS due to bronchopulmonary viral infection with deviating underlying pathophysiology special recommendations are given in section 8.4.

5.2. Predictive biomarkers and biomarker assays

Biomarkers may help to identify patients at high risk of disease progression or poor outcomes and could also reflect underlying pathogenic mechanisms and thus represent ARDS (sub)phenotypes. Their variability may align with different ARDS phases. However, co-morbidities, age, and gender can affect biomarker levels, complicating their interpretation.

The appropriateness of using predictive biomarker should be justified. A well-founded strategy for biomarker development and validation should be established as early as possible during the drug development, if applicable. Validation studies must confirm the sensitivity, specificity, reproducibility, and clinical utility of biomarkers, with clear justification of cut-offs as early as possible during the drug development.

Co-development of a companion diagnostic (CDx) is anticipated in such cases. At the time of marketing authorisation, the CDx device should be applicable at the point of care with a short turn-around time to allow for prompt treatment initiation in eligible patients.

5.3. Concomitant therapy and standard of care

SOC vary to a certain degree between centre and/or region. Efforts should be made to standardize as much as possible during confirmatory studies in alignment with the most recent European Society of Intensive Care Medicine Taskforce on ARDS (ESICIM) recommendations [D1]. Their use should be prospectively defined in the protocol and documented in the study report. The effects on treatment should be discussed in the dossier.

Conservative fluid management, intermittent prone positioning as well as lung protective ventilator strategies aiming at reduction of ventilator induced lung injury (VILI), including the use of lower inspiratory pressures and lower tidal volumes in ventilated patients, are key elements to be taken into account. Of note, exclusion of these treatment modalities may impact the generalisability of the trial results.

5.4. Efficacy criteria

5.4.1. Mortality

As ARDS is a disease of high mortality, reduction of mortality is the most important treatment goal in patients with ARDS.

There are several mortality endpoints that may be considered in ARDS clinical studies, each offering different insights into the effects of a treatment:

- All-cause mortality is the most commonly used mortality endpoint and refers to death from any cause within a specified period (e.g., 28-day mortality, 90-day mortality). It captures the overall impact of the disease and the intervention, without attributing the cause of death to ARDS specifically. All-cause mortality avoids potential biases in determining the cause of death.
- ARDS-related mortality focuses on deaths specifically attributable to ARDS and its complications. However, differentiating between ARDS-related mortality and mortality due to other causes (such as sepsis, multiple organ failure, or comorbid conditions) can be challenging and subject to interpretation, hence, it less commonly used.

Short-term mortality, such as 28-day mortality, is frequently used in ARDS trials as it captures early deaths that are most likely related to ARDS and the acute effects of the treatment. This timeframe aligns with the critical illness period and intensive care management.

Long-term Mortality (e.g., 90-Day or 180-Day Mortality) provide insights into the longer-term survival benefits or harms of a treatment. These endpoints are valuable for understanding the durability of the treatment effect but may be influenced by factors beyond the acute phase of ARDS.

In-hospital mortality measures deaths that occur during the initial hospital stay. It is practical to measure but may not fully capture deaths occurring after discharge or transfer to another facility.

Mortality should be measured over a well-defined period, such as 28 days, 60 days, and/or 90 days from the start of the treatment. The chosen timeframe should be justified based on the study objectives and the natural history of ARDS. To ensure consistency and reliability, standardized criteria should be used to report deaths. This includes documentation of the date, cause, and circumstances of death. Clear guidelines should also be provided to distinguish ARDS-related deaths from other causes.

Mortality data can be collected through medical records, electronic health records (EHRs), direct contact with healthcare providers, or follow-up with family members. It is important to have a systematic approach to ascertain all deaths and minimize loss to follow-up.

It is essential to blind data collectors and outcome adjudicators (who may occasionally be the same individuals) to prevent bias in determining attributable mortality. Mortality data, particularly when distinguishing between ARDS-related and non-ARDS-related deaths, should be reviewed by an independent committee.

5.4.2. Maintenance of organ function

Maintenance of organ function (including not only lung, but also kidney, liver, cardiovascular) is a clinically relevant treatment goal in ARDS patients.

Endpoints like “Ventilator-free-days” (VFD) have been used in clinical studies on ARDS. However, main challenges for the use of ventilator related endpoints are heterogeneous weaning and extubating criteria among centres and/or regions. In addition, variations in post-extubating treatment and the risk for reintubation may hamper the interpretability of ventilation related endpoints.

On the other hand, prolonged ventilation over weeks is associated with poor prognosis. As it can be expected that patients on successful treatment will be off ventilator within a reasonable timeframe (at least within 2-3 weeks), the number/proportion of patients off ventilator at 28 days are expected to be less dependent from heterogeneous weaning approaches and may be used as an efficacy outcome measure.

Maintaining pulmonary function, e.g., adequate oxygenation is essential for patients with ARDS. Efficacy measures such as Oxygenation index (OI) or Oxygenation ratio (OR) have been proposed, however, being highly dependent on (mechanical) ventilation settings outcomes are difficult to interpret and thus not suitable to demonstrate a treatment effect in confirmatory clinical studies. Nevertheless, these measures, including information on ventilation (e.g., FiO2, PEEP) should be reported supplementary to the clinically relevant endpoints.

Measurements aiming to quantify pulmonary permeability oedema such as extravascular lung water index (EVLWi) or pulmonary vascular permeability index (PVPI) can be used to guide fluid management in ARDS patients and may be useful as exploratory endpoints, however, a predictive value on the overall outcome (i.e., mortality) has not been established.

Due to limited accuracy and reliability chest radiographs are not regarded as appropriate efficacy outcome measures in clinical studies. Nevertheless, radiographs taken routinely should be documented as supplementary information.

The development/resolution of clinically significant organ dysfunction other than pulmonary, in particular renal, hepatic and cardiovascular, should also be documented (e.g., sequential organ failure assessment (SOFA) score, need for renal replacement therapy (RRT), need for extracorporeal membrane oxygenation (ECMO), monitoring of vasoactive medication).

5.4.3. Biomarkers as clinical trial endpoint

Biomarkers are currently not accepted as surrogate endpoint for efficacy in confirmatory studies as they are not proven to predict clinical outcomes reliably. However, incorporating biomarker as exploratory endpoint into clinical development may be useful.

5.4.4. Patient-reported outcomes

ARDS survivors often experience long-term physical, cognitive, and psychological sequelae that extend beyond the acute phase. Patient-Reported Outcomes (PRO) may offer valuable insights into the persistent symptoms, functional impairments, and health-related quality of life (HRQoL) of survivors.

A number of different questionnaires are frequently used in ARDS clinical trials (e.g. Medical Outcomes Study 36-Item Short Form Health Survey (SF-36), EQ-5D, Hospital Anxiety and Depression Scale (HADS), Functional Status Score for the ICU (FSS-ICU)). The adequacy of these PROs, whether existing, modified, or newly developed, as a measure to support a label claim in the Summary of product characteristics (SmPC) Section 5.1 depends on whether its characteristics, conceptual framework, content validity, and other measurement properties are satisfactory.

5.4.5. Long-term outcomes

Survivors of ARDS may experience significant long-term impairments continuing after hospital discharge and increased mortality during the first year. Common morbidities include cognitive and psychological impairment, physical disability with reduced exercise capacity and muscle wasting (ICU acquired weakness (ICUAW)), pulmonary function impairments, as well as poor quality of life (QoL). Long-term follow up visits should monitor these morbidities (e.g., neurocognitive assessments, psychological evaluations, muscle strength testing, exercise tolerance tests, pulmonary function tests, and HRQoL questionnaires).

5.5. Exploratory studies

The primary aim of exploratory studies in ARDS is to gather preliminary data on the safety and potential efficacy of a new medicinal product. Unlike confirmatory studies, which focus on definitive evidence of efficacy and safety, exploratory studies are designed to generate hypotheses and explore mechanisms of action.

Exploratory studies play also a crucial role in the early stages of drug development for ARDS by identifying potential therapeutic targets, biomarkers, and appropriate patient populations. These studies may adopt broader inclusion criteria to capture a wide range of ARDS (sub)phenotypes and patient characteristics. This may help in understanding how different subgroups respond to the treatment and in identifying potential responders. Alternatively, exploratory studies may already focus

on specific (sub)phenotypes of ARDS patients based on clinical characteristics or biomarker profiles, if sufficiently justified.

The choice of endpoints in exploratory studies should be sufficiently justified, as most likely an effect on mortality cannot be demonstrated due to an expected limited number of patients to be included and short study duration. Findings from exploratory studies should inform the design of later studies and allow integration with findings from confirmatory study(ies). This may enable assessing consistency of results.

Exploratory studies also assess the feasibility of administering a new treatment to ARDS patients, including dosing, administration routes, and safety profiles. This stage is crucial for identifying any early safety signals and determining the optimal dosing regimen.

6. Methodological aspects for confirmatory studies

6.1. Study design

Study planning, design, conduct, analysis, and interpretation must be aligned with the estimand of interest and special focus should be on collecting all relevant data for the targeted estimand(s) (primary and supplementary) (see section 6.3).

Confirmatory studies should have an internal controlled, double-blind, randomised, parallel group design. The control arm may include a placebo and/or an active comparator, if prospectively available.

Investigational product and control treatment should be given on top of SoC, which should be defined in the study protocol as appropriate.

The duration of active treatment phase is expected to be adequately justified depending on the nature of the product and mode of action. The double-blind period should generally include at least 28 days.

The cumulative duration of active treatment period and follow-up period should not be less than 3 months. Preferably, follow-up visits should enable assessments at 6 and at 12 months.

6.2. Efficacy endpoints

It is recommended that a disease severity-specific approach (see ARDS definition, section 5.1) is adopted for the choice of the clinical endpoints to be used in confirmatory studies, also depending on the intended indication (treatment of ARDS vs. prevention of disease progression). The chosen endpoints should be clinically meaningful and consistent with the expected drug effect according to its mechanism of action. For specific aspects regarding clinical endpoints, reference is made to the sections 5.

6.2.1. Primary endpoints in confirmatory trials

All-cause mortality at day 28 since randomisation is the most relevant primary endpoint in confirmatory studies for investigation of new medicinal products in the treatment of ARDS.

Sample sizes required to detect meaningful reductions in mortality may, however, be difficult to achieve depending on the selected population of patients (e.g., lower mortality in less severe ARDS). A composite endpoint including 28-day all-cause mortality and the morbidity criterion of prolonged need for invasive mechanical ventilation (defined as invasive mechanical ventilation for 28 days or longer) could be considered instead.

If a composite endpoint is used, separate analyses of the different components of the composite endpoint should be provided to give insights into the relative contributions of each outcome to the overall result. It should be noted that inconsistent results across the components of the primary endpoint may raise concerns.

Since there is limited experience with studies aiming at preventing disease progression in patients with mild ARDS, no specific recommendations regarding study design and primary endpoint can be given. Engaging with regulatory authorities and scientific advice is recommended prior to initiation of confirmatory studies.

6.2.2. Secondary endpoints in confirmatory trials

Secondary endpoints should include the assessment of mortality at different time points (e.g. at day 60, 90 and 1 year), but also at earlier time points (e.g., at day 7) should be considered.

Other secondary endpoints should inform on pulmonary function (e.g., oxygenation index, EVLWi/PVPI, need for ventilatory support) and other organ function (e.g., SOFA score, renal/hepatic/cardiovascular function/measures of support) at early time points but should also be reported at later stages.

Endpoints should include assessments of HRQoL (see Section 5.4.4).

6.3. Statistical considerations

Statistical analysis of study data should be aligned to the estimand (as described below) and generally follow the Intention-To-Treat (ITT) principle. A predefined data analysis plan should be established before data collection commences, and it is expected that statistical methods and estimators for the defined estimands are described unambiguously in the protocol with sufficient detail.

Adequate sample size is crucial to ensure the statistical power of a confirmatory study for detecting clinically meaningful differences between treatment groups in this setting with a considerable number of "failed" studies. Sample size calculations should consider-., the expected effect size, level of significance, power of the study, anticipated dropout rates, and variability in outcome measures.

In a multi-regional study stratification for region is expected according to ICH E17 [D4], unless otherwise justified. Stratifying a study taking into account the SOC in different regions, e.g. between Europe and the United States (US), can be considered and requires careful observation of several factors to ensure the validity, generalizability, and relevance of study findings. Pre-defined relevant stratification factors can be considered for stratified randomisation or stratified analysis. Further, appropriate sensitivity analysis should be implemented to evaluate potential effect modification by region, adherence to local treatment guidelines or ventilation strategies on study outcomes.

6.3.1. Estimation of the treatment effect (estimands)

The scientific question(s) of interest, i.e. what the study seeks to address, and the target(s) of estimation (estimand) should be clearly specified in the study protocol. Study planning, design, conduct, analysis, and interpretation must be aligned with the estimand. Reference is made to ICH E9 (R1) addendum on estimands and sensitivity analysis in studies [D5]. The estimand attributes should be described. In ARDS treatment conditions of interest may consist of individual interventions, but add-on or combination treatments are likely in this complex condition. A disease-specific approach should be adopted for primary and secondary estimands, with the definition of the main clinical endpoints to be driven by the intended use of a medicinal drug and target population, as defined by disease stage. As a general consideration for ARDS patients, the primary outcome should be either all-cause mortality

or composite of mortality and ventilation status. Intercurrent events of general nature and specific to settings of ARDS studies should be considered in the definition of the primary estimand.

Intercurrent events expected to be potential modifiers of treatment effect in the context of ARDS include treatment discontinuation, changes in background therapies with effects on the ventilation status or drug-to-drug interactions, as well as terminal events (i.e. death). The nature of the specific intercurrent events and their probability to occur vary depending on the target population, as defined by disease severity and presence of comorbidities. It is expected that the study protocol identifies and clearly defines relevant strategies to handle pre-specified intercurrent events. Moreover, protocol violations and deviations should be considered. Generally, unless an alternative strategy is duly justified, treatment discontinuation should be handled with a treatment policy strategy addressing the treatment effect regardless of discontinuing treatment. Similarly, a treatment policy strategy is relevant for changes in background therapies, which is equivalent to considering them as part of the treatment regimen of interest. Supplemental estimands may be needed to characterise the treatment effect, e.g., in case of use of effective rescue medication. Composite strategies may be considered for this intercurrent event.

The primary estimand definition should consider recommendations on the primary outcome (see above and section 6.2.1). The estimator should be aligned to the primary estimand and the population level summary should be clearly described. In ARDS studies rate differences from baseline to the fixed maximum follow-up timepoint (e.g. day 90, or another predefined timepoint, e.g., day 28) between the investigational treatment and a control treatment have traditionally been used and landmark analysis should be provided at least as supplemental estimand. Alternative approaches can be considered if appropriately justified. Time to event analysis in a limited timeframe is likely not meaningful.

Generally, efforts should be made to collect all relevant data for the primary and important other estimands to minimize the need to rely on untestable assumptions in the analysis and interpretation of the study results. Data obtained after discontinuation of treatment or other intercurrent events are of principle interest for the treatment-policy strategy. In case data are missing after treatment discontinuation, appropriate methods that do not unfairly favour the active treatment would have to be applied. For handling of missing data methods that accommodate different missing data assumptions for different types of intercurrent events or reasons for missingness should be considered for the targeted estimand. In any case, assumptions underlying the primary analysis should be examined through pre-specified sensitivity analysis (e.g., tipping point analyses) addressing the same estimand.

7. Safety evaluation

Safety evaluation in clinical studies for ARDS is of paramount importance to ensure the well-being of participants and to accurately assess the risks associated with investigational treatments. By implementing comprehensive safety evaluation strategies, researchers can minimize risks to participants, ensure the integrity and reliability of study data, and contribute to the ethical and responsible conduct of clinical studies in ARDS.

In general, the ICH E1 Guideline on the extent of population exposure to assess clinical safety [S1] should be taken into consideration.

All adverse effects occurring during a clinical study should be fully documented. Any groups especially at-risk should be identified. Special efforts should be made to assess potential adverse effects that are characteristic of the class of drug being investigated.

Adverse drug events occurring during the treatment should be carefully recorded throughout all study phases, including data about their nature, frequency, intensity, and relevance.

An overall follow-up of at least 90 days is anticipated. Preferably, follow-up visits should also enable safety assessments at 6 and at 12 months.

7.1. Specific adverse events to be monitored

Adverse events of special interest should be identified and pre-specified in the study design, including but not limited to allergic/immunologic reactions, severe infections and/or specific AEs of Major adverse cardiovascular events (MACE).

All specific events mentioned below are common events/complications on ICU and not necessarily ARDS or treatment specific and thus important to monitor:

- Ventilator-Associated Complications:

Ventilator-Associated Lung Injury (VALI): Monitoring for exacerbation of lung injury due to mechanical ventilation, such as barotrauma (e.g. pneumothorax) or volutrauma (e.g. excessive tidal volumes).

Ventilator-Associated Pneumonia (VAP): Surveillance for new or worsening pneumonia secondary to mechanical ventilation.

- Hemodynamic Instability:

Hypotension: Monitoring for drops in blood pressure, especially during interventions that may affect fluid balance or systemic vascular resistance.

Arrhythmias: Assessing for new-onset or exacerbated cardiac arrhythmias, which can be related to underlying cardiac dysfunction or electrolyte disturbances.

- Infections and Sepsis:

Secondary Infections: Monitoring for new infections, including bloodstream infections or urinary tract infections, which can complicate the course of ARDS and impact outcomes.

Sepsis: Keeping vigilant for signs of systemic inflammatory response syndrome (SIRS) or sepsis, which can occur as a consequence of ARDS or other complications.

- Renal Dysfunction:

Acute Kidney Injury (AKI): Evaluating renal function and monitoring for signs of AKI, which can be exacerbated by fluid management strategies or nephrotoxic medications.

- Coagulation Abnormalities:

Disseminated Intravascular Coagulation (DIC): Assessing for signs of abnormal coagulation parameters or bleeding complications, which may arise in severe cases of ARDS.

- Metabolic Disturbances:

Electrolyte Imbalances: Monitoring electrolyte levels (e.g. sodium, potassium) and correcting abnormalities promptly to prevent cardiac and neuromuscular complications.

Metabolic Acidosis: Assessing for changes in acid-base balance that can occur due to respiratory and metabolic derangements in ARDS.

- Neurological Complications:

Delirium: Evaluating for acute changes in mental status, which can be associated with critical illness and prolonged hospitalization.

Neuromuscular Weakness: Monitoring for development of weakness related to critical illness polyneuropathy or myopathy.

7.2. Long term safety

The impact of ARDS extends beyond the acute phase, with increased mortality and disability for months to years after hospitalization. Thus, it is advisable to have follow-up periods as long as possible (e.g., at least 1 year) in ARDS clinical studies. Furthermore, an appropriate risk management plan is always required to monitor events in the post-marketing phase.

7.3. Mortality

Even if all-cause mortality is included as part of a composite efficacy endpoint, a direct observation of the effect on mortality is important to rule out a harmful safety profile of a new medicinal product. Any detriment or uncertainty would generally be considered to impact negatively on the benefit risk assessment based on all available evidence and uncertainties.

A separate analysis distinguishing pulmonary mortality from other mortality as a safety endpoint is encouraged, even though these outcomes may overlap.

8. Specific considerations for clinical development

An ideal strategy would be the development of a medicinal product that is effective in the whole range of ARDS conditions. However, taking into account the increasing knowledge about diverse mechanisms underlying different ARDS conditions, this aim is not likely to be achievable for new medicinal product developed for the treatment of ARDS and/or prevention of disease progression.

Recommendations on how to address these challenges are outlined in the following chapters. Alternative approaches are acceptable if adequately justified

8.1. Clinical development plan

Sequential clinical studies offer a strategic and efficient framework for drug development, especially in conditions like ARDS where patient variability and complex pathophysiology challenge traditional study designs. Consequently, beginning with exploratory studies to identify appropriate biomarkers and subpopulations, followed by confirmatory trials to validate efficacy in these targeted groups, represents a valuable strategy in ARDS development.

Confirmatory studies in ARDS are designed to confirm the efficacy and safety of interventions and to provide robust evidence to support clinical decision-making.

Randomised clinical trials (RCTs) are required to demonstrate efficacy.

8.2. Biomarker and/or (sub)phenotype defined drug development

Biomarker and/or (sub)phenotype defined drug development involves designing and developing medicinal products tailored to patients based on their unique biomarker and/or phenotype profiles. This approach holds promise in ARDS due to the syndrome's heterogeneity in terms of aetiology, pathophysiology, and patient response to treatments.

Several biomarkers (e.g., inflammatory or coagulation biomarkers) and/or (sub)phenotypes (e.g., hyper- or hypo-inflammatory or fibroproliferative) are currently being investigated for their potential use in defining subgroups for targeted drug development in ARDS.

Tailoring treatment strategies based on biomarkers and/or the predominant (sub)phenotype may potentially optimize study outcomes. For example, anti-inflammatory agents may be more beneficial in hyperinflammatory phenotypes, while agents targeting fibrosis may be relevant for fibroproliferative phenotypes. However, further research is needed to elucidate the mechanisms underlying ARDS (sub)phenotypes and validation of their clinical relevance.

Further, it is not anticipated that a single study will serve both to justify the study population as well as establish the efficacy of the new medicinal product. Thus, sequential clinical studies are expected. A first stage would explore the definition of an appropriate biomarker over a range of expression and/or an appropriate population (sub)phenotype. A broad range of endpoints are foreseen. Subsequently, efficacy in the selected target population would be confirmed in a larger confirmatory study using a clinically relevant endpoint.

New (innovative) approaches regarding the development [D9] / validation of predictive biomarkers and/or corresponding new assay formats (candidate CDx devices) should preferably be confirmed by a CHMP qualification opinion [D8].

8.3. Further enrichment strategies

To address the limitations of conventional study designs, further enrichment strategies have emerged as an approach to optimize patient selection and improve the likelihood of clinical study success, e.g.:

Prognostic Enrichment:

Prognostic enrichment involves selecting patients who are more likely to have a specific outcome, such as disease progression, death, or prolonged mechanical ventilation, regardless of treatment. This strategy helps in detecting a treatment effect by increasing the event rate in the control group. Patients with moderate to severe ARDS (e.g., lower PaO2/FiO2 ratios, higher SOFA scores) are more likely to experience worse outcomes, making it easier to detect a difference between treatment and control groups. Also, tools like the APACHE score can be used to identify patients with a high risk of poor outcomes, thereby enriching the study population.

Time-to-Intervention Enrichment

Since early intervention may have a greater impact on outcomes, clinical studies may also focus on patients who are within a specific time frame (e.g., within 6-12 hours or 24-48 hours of ARDS onset) to increase the likelihood of observing a treatment effect.

8.4. ARDS due to bronchopulmonary viral infection

ARDS caused by bronchopulmonary viral infections (such as SARS-CoV-2) presents unique challenges and considerations for clinical studies. The pathophysiology, clinical presentation, progression, and treatment response differ from non-viral ARDS. Furthermore, the incidence of disease and seasonality is such that the timely conduct of studies of patients with ARDS due to bronchopulmonary viral infection may be challenging, e.g. following the emergence of omicron variants, the incidence of ARDS due to SARS-CoV-2 has declined substantially.

Targeted therapies have been explored, often relying on a single mode of action aimed at specific aspects of the inflammatory or coagulation pathways. While such approaches have shown promise in certain contexts, they may be insufficient to address the multifaceted nature of ARDS. For example, the coagulation patterns observed in ARDS due to COVID-19, characterized by widespread micro thrombosis and endothelial damage, differ significantly from those seen in ARDS caused by other viral

infections or non-infectious triggers. This underscores the risk of relying too heavily on a single therapeutic strategy without considering the underlying cause of ARDS.

Also in such cases, it is anticipated that viral aetiology may remain an important effect modifier. Therefore, strata of patients with SARS-CoV-2, influenza and potentially other pathogens should be sufficiently large to be informative. The differing importance of secondary bacterial infection depending on viral aetiology should be also considered, if combining patients with SARS-CoV-2 and influenza in the same study.

If patients with SARS-CoV-2 are included, safety assessments should also include long-term follow-up for potential sequelae of COVID-19 (e.g., pulmonary fibrosis, cardiovascular complications). This is important for understanding the risk-benefit profile of the medicinal product.

Clinical studies must also account for potential bacterial or fungal co-infections, which are common in ARDS caused by bronchopulmonary viral infections. Patient selection criteria should consider the presence of any co-infections that may affect treatment response and outcomes. Also, immunomodulatory therapies can increase the risk of secondary infections.

8.5. Drug development for pandemic preparedness

There is a medical need to develop medicinal products for ARDS that may be efficacious regardless of the causative infectious agent. However, in the absence of successful examples, sponsors planning the development of e.g. host-targeting medicinal products covering a variety of etiologies that would be supportive of pandemic preparedness are encouraged to seek an early and continued dialogue with the Emergency Task Force (ETF) of the EMA, on the design of the clinical study program.

During emergencies, based on the experience with the COVID-19 pandemic and the large number of simultaneous COVID-19 studies, there is a potential risk of patient overlap or competition for enrolment. Coordination within study networks and registries can help optimize patient recruitment and prevent duplication of efforts.

8.6. Label claims and regulatory considerations

Broad label claims should be supported by robust data from adequately powered clinical study(ies) that account for the heterogeneity of ARDS.

Using any enrichment strategies, which although could increase likelihood of study success, will have implications for external validity of the study results and may lead to restriction of a target population as described in the indication of the medicinal product. Furthermore, the expectations for biomarker thresholds and their practical implementation in clinical practice should be clearly defined prior to the confirmatory study(ies) to ensure that treatment strategies are both effective and feasible.

Specific considerations are also needed when extrapolating from studies conducted in specific subgroups, such as those with ARDS caused by SARS-CoV-2. The unique pathophysiology of ARDS caused by SARS-CoV-2, particularly its distinct immunological and coagulation profiles, presents a significant challenge in extrapolating study results to other types of ARDS. While ARDS caused by SARS-CoV-2 has been extensively studied, the evidence suggests that the mechanisms driving ARDS in this context may not be representative of ARDS caused by other factors. For example, while immunomodulatory therapies have shown efficacy in ARDS caused by SARS-CoV-2, their applicability to ARDS resulting from bacterial infections or trauma remains uncertain. This variability highlights the need for caution in generalizing findings from ARDS caused by SARS-CoV-2 also to other causes of ARDS.

9. Special populations

9.1. Elderly patients

In accordance with ICH and EMA guidelines, it is essential to gather evidence on clinical pharmacology, efficacy, and safety that accurately represents this subgroup as well as the various elderly age categories [E0, E1]. The prevalence and mortality rate for ARDS increases with age though this is not fully reflected in ICU admissions, possibly due to age-related differences in recognition of ARDS and admission criteria [E2, E3]. Thus, new medicinal products should be also studied in elderly patients, for which they will have significant utility.

COVID-19 related ARDS has a higher mortality rate in elderly and high-risk patients (e.g., those with obesity, diabetes, cardiovascular disease, and immunosuppression). Clinical studies need to consider including these patients to generate relevant efficacy and safety data, as they may respond differently to treatments.

9.1.1. Efficacy in elderly patients

If clinical studies are conducted in patients aged 65 years or older additional surrogate measures and endpoints that are age-specific, especially with respect to the mechanism of action of the treatment, i.e. cognitive function, level of independence may be called for [E4, E5].

Age is also embedded in several Intensive Care Unit (ICU) scoring system which may inflict prognostic assessment and decision whether a patient is likely to benefit from intensive care.

9.1.2. Safety in elderly patients

Safety in patients aged 65 years or older should be reported separately, as in other special populations. Cognitive and neurological, pulmonary, renal and hepatic function should be reported as well as adverse events and mortality. It is recommended to report outcome in age intervals in the elderly. It is recommended to collect and report treatment restriction decisions.

9.2. Paediatric patients

Paediatric ARDS (PARDS) is a rare disease. PARDS is recognised as a distinct sub-phenotype of ARDS, due to the maturing lung and immune system. In clinical PARDS studies, ARDS should be defined by the PALICC-2 criteria [P10], while the same endpoints can be used as in adult studies. Subgrouping by stage of development and lung maturation is recommended [P2 and P6].

All patients less than 18 years old without active perinatal lung disease should be diagnosed with PARDS using PALICC-2 criteria [P10].

Long-term pulmonary function, health-related quality of life, physical and neurocognitive function are important long-term outcomes in the paediatric population that should be addressed in the development program. As prolonged observation periods are required to come to robust and meaningful conclusions, it might not be possible to fully address these issues in the initial submission for a marketing authorization but monitoring and assessments should continue in accordance with current guidance documents (e.g. PALICC-2) and results should be reported post approval.

Paediatric patients with COVID-19 can present with different ARDS manifestations or associated conditions (e.g., Multisystem Inflammatory Syndrome in Children (MIS-C)). Studies may require separate cohorts or tailored protocols for paediatric populations.

It is unknown to which extend sub-phenotypes and endotypes of PARDS and ARDS overlap. Therefore, extrapolating data from the adults to the paediatric setting requires considerations on a case-by-case basis.

As experience is limited, scientific advice is recommended.

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Definitions

AKI: Acute Kidney Injury
APACHE : Acute physiology and Chronic Health Evaluation
ARDS : Acute Respiratory Distress Syndrome
CDx: Companion diagnostic
COVID-19 : Corona VIrus Disease 2019
CPAP: Continuous positive airway pressure
DIC: Disseminated Intravascular Coagulation
ECMO : Extracorporeal Membrane Oxygenation
EMA : European Medicines Agency
EVLWi : Extravascular lung water index
FiO2: fractional inspired oxygen
FSS-ICU : Functional Status Score for the ICU
HFNO: High-flow nasal oxygen
HADS: Hospital Anxiety and Depression Scale
HRQoL : Health-related quality of life
ICU : Intensive Care Unit
ICUAW : ICU acquired weakness
ICH: International Collaboration Harmonisation
MACE: Major adverse cardiovascular events
OI: Oxygenation index
OR: Oxygenation ratio
PALICC-2: Pediatric Acute Respiratory Distress Syndrome
PaO2/FiO2 ratio : ratio of arterial oxygen partial pressure to fractional inspired oxygen
PARDS: Paediatric ARDS
PEEP: Positive end expiratory pressure
PD : Pharmacodynamic
PK: Pharmacokinetics
PRO: Patient-Reported Outcomes
PVPI :Pulmonary vascular permeability index
RCT: Randomised clinical trials
QoL: Quality of life
RDS : Respiratory Distress Syndrome

RRT: Renal Replacement Therapy
SF-36: Short Form Health Survey
SOC: standard of care
SOFA: Sequential Organ Failure Assessment
VALI: Ventilator-Associated Lung Injury
VAP: Ventilator-Associated Pneumonia
VFD: Ventilator-free-days