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Rheumatology/Immunology Working Party (RIWP)
Committee for Medicinal Products for Human Use (CHMP)

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

Agreed by Rheumatology/Immunology Working Party	24 February 2023
Adopted by CHMP for release for consultation	26 April 2023
Start of public consultation	4 May 2023
End of consultation (deadline for comments)	31 July 2023

The proposed guideline will replace the Guideline on clinical investigation of medicinal products in the treatment of patients with acute respiratory distress syndrome (EMEA/CPMP/EWP/504/97 Rev 1).

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

Keywords	Acute Respiratory Distress syndrome (ARDS), Acute Lung Injury (ALI), Systemic Inflammatory Response Syndrome (SIRS)

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1. Introduction

Acute lung injury (ALI) is the clinical syndrome of acute respiratory failure with bilateral pulmonary infiltrates of non-cardiac origin. When it is accompanied by severe hypoxemia, the condition meets criteria for acute respiratory distress syndrome (ARDS). ALI is typically a consequence of Systemic Inflammatory Response Syndrome (SIRS). Despite the progress in critical care medicine, severe ARDS is still associated with a high incidence and mortality rate. Moreover, patients who survive with ARDS are at high risk for neurological/psychiatric and respiratory disorders leading to decreased quality of life. Hence, new potential approaches are needed to enhance the drug development for ARDS in order to minimize the ARDS-associated mortalities and to improve the quality of life of ARDS survivors.

2. Problem statement

In view of the considerable heterogeneity of the patient population generally included in ARDS studies it is important to accurately define baseline characteristics. The European Society of Intensive Care Medicine (ESICM) with endorsement from the American Thoracic Society (ATS) and the Society of Critical Care Medicine (SCCM) convened an international expert panel to revise the ARDS definition focusing on feasibility, reliability, validity, and objective evaluation of its performance. The panel met in 2011 in Berlin and the definition was formally agreed by the ARDS Network at the American Thoracic Meeting to be held in May 2012[1]. There are a few key modifications (oxygenation, timing of acute onset, Chest X-ray, and wedge pressure criterion) in the "Berlin" definition as compared with the previous definition. Based on the new definition for adult ARDS, the Paediatric Acute Lung Injury Consensus Conference (PALICC) Group published in 2015 also a new definition of paediatric ARDS (PARDS)[2]. Both new definitions need to be included in the revised guideline.

There are currently no authorised medicinal products for ARDS, neither in the adult nor paediatric populations. Thus, supportive therapies remain the mainstay of treatment. To reduce the degree of heterogeneity confirmatory studies should be planned and conducted with standardised best practice concomitant treatment and care. In view of the changed definition for ARDS, the previous proposal for standardisation of care needs to be modified.

This concept paper concerns the guideline that is intended to provide guidance for the evaluation of new medicinal products for prevention and treatment of ARDS. The guideline came into effect in April 2007. There are several new agents in development for the treatment of ARDS. In recent requests for CHMP scientific advice on the development of new agents intended for the treatment of ARDS, several issues have emerged as being central to development programmes. So, there is a need to re-consider the EU regulatory expectations with regard to the data that should be generated to support the approval of novel agents, like e.g. (co)primary and secondary endpoints, time of assessment, stratification and functional assessment indices recorded in confirmatory studies. The principles that were agreed by CHMP need to be included in the revised version.

The COVID-19 pandemic has also seen many agents tested for prevention or treatment of ARDS after infection with SARS-COv2. The experienced gained in these studies and the impact on future studies needs to be considered.

Furthermore, recently published methodological guidance documents relevant for decision making should be added.

3. Discussion (on the problem statement)

The following items have been identified and would need to be addressed in the revised guideline:

- The most recent ARDS definition[1], also called as "Berlin" definition, as well as the new definition of paediatric ARDS[2] should be included in the revised guideline.
- In view of the changed definition for ARDS, the previous proposal for standardisation of care needs to be modified. In addition, the standard of care procedures in terms of the use of ECMO (extracorporeal membrane oxygenation) should be defined as far as possible.
- As stated in the current guideline, all-cause mortality is the most relevant primary endpoint in confirmatory studies for investigation of new medicinal products in the treatment and prevention of ARDS particularly because of the heterogeneity of the disease. Mortality remains an important parameter for the regulatory decision and effects on mortality should be quantified with due precision. However, taking into account the prognostic impact of long term-ventilation, also a composite endpoint "Alive at Day 28 and no more need for invasive mechanical ventilation" may be appropriate. This would be acceptable under the prerequisite that the study is randomised and placebo-controlled because the decision to discontinue mechanical ventilation has some subjective elements even if driven by an explicit protocol. The current recommendation should be revised accordingly.
- The list of secondary endpoints needs to be revised. For example, the current guideline recommends to evaluate barotrauma as short-term secondary endpoint. However, barotrauma is extremely rare due to the almost universal adoption of lung protective strategies in routine clinical practice in the intensive care units. Thus, barotrauma should be deleted from the list of secondary endpoints. Instead, any evidence of barotrauma should be collected as safety data.
- The opinions of the clinical community[3] focusing also on day 60 and/or 90 mortality should be taken into account because substantial proportion of late deaths occur after day 28.
- The current guideline recommends stratification by site. However, it is acknowledged that in most cases there will not be sufficient numbers of patients at the site level to make stratification at this level meaningful. Thus, stratification at the country level rather than the individual site level seems to be more appropriate. The current guideline should be revised accordingly.
- Several functional assessment indices to describe the severity of the disease and the estimated prognosis are mentioned in the current guideline. Considering the fact that these assessments are time-consuming, the number of the indices recorded should be reduced.
- The actual population recruited may cover a large proportion of patients with underlying viral infections. Similarities and differences between COVID-19 and other aetiologies will be discussed in the guideline[6]. The possibility to extrapolate across patient populations with or at risk of ARDS requires clarification.
- A reference to the ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials (CHMP/ICH/436221/2017) should be added.

4. Recommendation

The Rheumatology/Immunology Working Party recommends revising the current Guideline on clinical investigation of medicinal products in the treatment of patients with acute respiratory distress

syndrome taking into account the issues identified above. The guideline will be developed in coordination with the Emergency Task Force (ETF).

5. Proposed timetable

Released for consultation on 4 May 2023, deadline for comments 31 July 2023.

6. Resource requirements for preparation

The update of the guideline will involve representatives of Member States from the Rheumatology/Immunology Working Party including the ARDS drafting Group. It should be discussed in their meetings and in ETF meetings.

7. Impact assessment (anticipated)

The document is intended to provide guidance on how to evaluate new medicinal products for prevention and treatment of Acute Respiratory Distress syndrome (ARDS).

8. Interested parties

The pharmaceutical industry, European learned societies and scientific organisations (e.g. the European Respiratory Society). Consultation with other working parties or committees (e.g. PDCO, COMP) will be initiated as appropriate.

9. References to literature, guidelines, etc.

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