Subphenotype Appendix:

ARDS

PANTHER:-

Precision medicine Adaptive Network platform Trial in Hypoxaemic acutE respiratory failuRe

Subphenotype Appendix ARDS Version V1.0 dated 06 FEB 2025

This Subphenotype Appendix applies to the following:-

Subphenotypes of ARDS	Hyperinflammatory	Hypoinflammatory

** This appendix covers the subphenotypes of ARDS .*

ABBREVIATIONS

ARDS	Acute Respiratory Distress Syndrome
EC	Ethics Committee
IL-6	Interleukin 6
sTNFR1	Soluble tumour necrosis factor 1

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1. APPENDIX STRUCTURE

The structure of this protocol differs to that of a conventional trial due to the trial's adaptive nature. These adaptations are specified using a modular protocol structure. For further details on the structure of protocol, please see section 1 of the master protocol.

The master protocol contains information about the general conduct of the platform irrespective of the regional location in which the study is conducted and the interventions being studied.

The master protocol omits information specific to subphenotyping as the groups are expected to change over time. Information specific to subphenotyping can be found in this sub-phenotyping appendix. The subphenotyping appendix should be submitted to the relevant Ethics Committee (EC).

2. BACKGROUND

Multiple approaches to identify subphenotypes of clinical syndromes in critically ill patients have been proposed. These subphenotypes may also determine differential treatment effect. In order to assess treatment response by subphenotype in this platform trial, subphenotype will be determined prior to randomisation.

3. SUBPHENOTYPES

Initial subphenotypes will be the hyper- and hypo-inflammatory subphenotypes initially described in ARDS (2).

3.1 Identification of hyper- and hypo-inflammatory subphenotypes

The subphenotypes will be defined by using a ≥0.5 probability cut off to assign the hyperinflammatory phenotype. The data will be analysed using the Youden index (1) for a sensitivity analysis.

Subphenotyping should be undertaken as quickly as possible after trial inclusion. Although the trial inclusion period is within 48hrs of the patient first meeting the criteria for inclusion in the trial, it is imperative that the subphenotyping is completed as soon as possible. Appropriate consent (which may include waiver of immediate consent in the emergency situation) must be obtained before the subphenotyping can be undertaken. Measurement of the biomarkers to determine subphenotype will take place in real time, prior to randomisation. Hyper and hypoinflammatory phenotyping will be determined using validated assays for IL-6 and sTNFR1 (please see the device manual for further details). These measurements will be combined with measurement of the worst bicarbonate level within the proceeding 24hrs from a plasma or an arterial blood gas and the data used to determine phenotype in real time at the bedside using a validated algorithm.

The algorithm, (a logistic regression equation which incorporates IL-6 and sTNFR1 values with a measurement of bicarbonate from plasma or an arterial blood gas measurement) determines the patient's subphenotype. The device used to measure

bicarbonate must have the relevant approved marking/certification from the relevant competent authority for the country in which the machine is being used, and used in clinical practice for this purpose.

The equation is:-

$$P = \frac{e^{-11.9593+1.0138ln(IL6+1)+1.1903ln(STNFR1+1)-0.2436HCO3}}{1+e^{-11.9593+1.0138ln(IL6+1)+1.1903ln(STNFR1+1)-0.2436HCO3}}$$

Where P = the probability of allocation to the hyperinflammatory subphenotype, *e* = Euler's number (base of the natural logarithm), IL6 = plasma concentration of interleukin-6 in pg/mL, sTNFR1 = plasma concentration of soluble tumour necrosis factor receptor 1 in pg/mL, and HCO3 = bicarbonate concentration mmol/L (1).

Over time different approaches to phenotyping may be added.

4. DEVICE

The device used to determine the allocation of hyper- and hypo-inflammatory subphenotypes is described below.

4.1 Randox Device

The Randox device is compiled of two separate elements. The competent authority in each region may consider the multiSTAT device and assay as one device. The regulator should be approached to clarify prior to submission. The separate elements of this device are listed below:-

(i) Randox multiSTAT device

The multiSTAT device is a fully automated immunoanalyser that enables on-site simultaneous detection of analytes from a single sample of blood. It requires a sample of approximately 200µl of blood which is centrifuged and diluted 4-fold prior to analysis. The results are generated typically within 60 minutes. The device is CE marked for use with a toxicology assay.

(ii) ARDS biomarker Assay

The ARDS biomarker assay is loaded into the Randox multiSTAT device and measures IL-6 and sTNFR1.

Relevant data and risk management files for the multiSTAT device and the ARDS biomarker assay provided by Randox are included in the appendix.

4.2 Other Devices

Other devices to identify the phenotypes may be added during the trial, these may also vary by region as the availability of such devices may also vary. Before a device is added to the trial a risk assessment will be completed to ensure the device is suitable for the allocation of the subphenotype. As a minimum the device must measure the biomarkers used for

phenotyping with acceptable reliability as determined by the appropriate regulatory requirements.

5. TREATMENT

The treatment for each subphenotype group will be described in the Intervention specific appendix.

6. REFERENCE DOCUMENTS

1. Randox Array Risk Management Report_A 01May24
2. Risk management file for the multiSTAT device and the ARDS biomarker assay

7. REFERENCES

1. Sinha P, Delucchi KL, McAuley DF, et al. Development and validation of parsimonious algorithms to classify acute respiratory distress syndrome phenotypes: a secondary analysis of randomised controlled trials. Lancet Respir Med. 2020;8(3):247-57. https://doi.org/10.1016/s2213-2600(19)30369-8.

2. Reddy K, Sinha P, O'Kane CM, et al. Subphenotypes in critical care: translation into clinical practice. Lancet Respir Med. 2020;8(6):631-43. https://doi.org/10.1016/s2213-2600(20)30124-7.

8. REVISION HISTORY

Version	Date	Summary of changes
1.0	06 Feb 2025	First version