Meeting Minutes – PANTHER: Discussion with the MHRA

21st July 2023, 1400–1600
Online via Microsoft Teams

Present:

Study team

Imperial College London: Daphne Babalis (DB); Keith Boland (KB; Sponsor representative); Eloise Britten (EB); Jonathan Dao (JD – minutes); Anthony Gordon (AG).
Queen's University Belfast: Danny McAuley (DM – Chief Investigator), Kiran Reddy (KR).
University of California San Francisco: Michael Matthay (MM)

MHRA: Khadija Rerhou Rantell (KRR – MHRA); Joseph Burt (JB – MHRA).

Background

DM presented slides on the study proposal. Acute respiratory distress syndrome (ARDS) is the target disease and there are few therapies currently available. Hypoinflammatory and hyperinflammatory subphenotypes have been identified. The PANTHER platform trial will investigate a series of interventions using a Bayesian Adaptive platform phase 2 trial design.

All patients enrolled will receive the same treatment; phenotyping (hypoinflammatory or hyperinflammatory) is required for implementing the trial design, notably for the interim analyses required for the Bayesian adaptive design.

The Investigators propose to use the multiSTAT device (which is CE-marked for use with a toxicology assay) in combination with an ARDS biomarker assay measuring IL-6 and sTNFR1 (not CE/CA marked) and a calculation (logistic regression equation) incorporating IL-6 and sTNFR1 values with a measurement of serum bicarbonate from an arterial blood gas measurement to determine the patient's subphenotype. This calculation was noted to be analogous to an equation used to determine body mass index and would undergo testing and validation within the clinical trial database. It was emphasised that this was not being developed as a companion diagnostic. The MHRA were approached to seek advice on whether the device/assay/equation combination can be used in the setting of a trial of a clinical investigation of a medicinal product (CTIMP), without the need for a CE/CA mark. Questions submitted to the MHRA in advance of the meeting were reviewed during the discussion.

Discussion and Questions submitted to the MHRA

Question 1: Could subphenotyping in PANTHER be done under a CTA without CE/CA mark?
Question 2: Was there a need for CE/CA marking for the:

- **multiSTAT device**
- **ARDS biomarker assay**
- **Equation to allocate phenotype**

DM asked whether any further approvals over and above a CTA (MHRA Medicines) would be required. JB answered that a single combined application can be submitted to MHRA to cover approvals for both medicines and devices, provided that it is clearly stated that the device is included.

In the absence of UKCA/CE marking for a device or assay for the target disease, the MHRA would ask for evidence of the analytical performance and scientific validity of the each aspect to be demonstrated. Tables to show the evidence of this for the biomarkers to be analysed must be included in the submission. The investigators noted that the required information on the analytical performance of the ARDS biomarker assay for IL-6 and sTNFR1 would be available and would be submitted as part of the MHRA application.

Regarding the equation, JB noted that it would be necessary to go through the standard conformance route for assessing the performance of an equation or algorithm. It was clarified that these data are already available and were submitted as part of Annex 3 and 4 prior to the meeting. JB confirmed that this would be sufficient.

JB confirmed that the bicarbonate value could be obtained from an arterial blood gas machine and used in the planned clinical trial, as long as the arterial blood gas machine was UKCA or CE marked and used in routine clinical practice for this purpose. On this basis information about the arterial blood gas machine bicarbonate measurement was not required for the MHRA application.
It was noted that the MHRA could assess confirmation of this as part of a regulatory inspection.

Action: JB to send table of requirements of data to be provided in application.

JB confirmed that the risk management file for the multiSTAT device and the ARDS biomarker assay would also be required by the supplier (Randox) on behalf of the applicant.

DB asked for clarification about the 3 elements of the device and which would be considered regulated by MHRA Devices, to understand how to approach the application in future and also understand regulatory and safety reporting requirements.

JB recommended that the multiSTAT device and assay be combined as one device for consideration, and the equation as a separate device. All 3 could be considered as one device but hardware, software and equation combined would be much harder to review, performance assess and certify, so is not the recommended approach.

Question 3: Mechanism for harmonising international regulatory approvals?

The trial will be international, starting in the UK in the first instance. Communications with regulators in EU member states as well as in the US is anticipated. The study would need to work to UK, EU and US regulations. The plan is to do the study at sites in the US, Canada, the UK and a few European countries at minimum.

MM enquired about the possibility of taking a harmonised approach to regulatory submissions and conduct of the trial. JB and KRR noted that regulatory harmonisation is not their area, but currently there is no option for a harmonised approach; separate submissions to each regulatory authority would be required, and the trial would need to be conducted in accordance with all applicable regulations in all regions and countries.

Question 4: Streamlined approach to protocol amendments for platform trials?

For the proposed platform trial, a change in arm, e.g. addition of treatment arms or stopping an arm, would be a substantial protocol change and require an amendment to be submitted for approval. DB asked whether there was any scope for these types of complex, innovative trials to use a streamlined approach for review of substantial amendments. The fast-track/streamlined approach implemented during the COVID-19 pandemic was referenced as an example where trials could obtain approvals for amendments rapidly and implement them without delay. This would be

important for the proposed platform trial since decisions following interim analyses could have implications for patient safety or benefit and delaying implementation is not ideal.

JB and KRR confirmed that a fast-track approach cannot be supported for this or any other trial at present. The usual process and timelines must be followed. The accelerated pathway implemented during the Covid-19 pandemic was an exception and the MRHA does not have the resources to support this anymore.

Trial design feedback
KRR provided feedback and advice on the proposed trial design based on the dossier that had been submitted, noting that many of the comments referred to a phase 3 trial or a trial submitted for licencing purposes which were not relevant to the planned trial.

- The level of patient/public involvement was complimented.
- A Bayesian adaptive approach would be acceptable for a phase 2 trial. If the group intended to conduct a trial for marketing authorisation / licensing in future there are additional considerations to have in mind, particularly in relation to the control of Type I error and seeking specific MHRA advice for this is encouraged.
- For the combined MHRA application, the study team were advised that information about simulations performed and the Bayesian approach should be presented in a format and style that is accessible to data assessors. Applicants should explain the design steps to show the working of the trial and be transparent about all assumptions made.
- KRR recommended the Clinical Trial Facilitation Group guidance on complex trials was a useful resource for reference
- It was recommended that the protocol should cover as many potential future adaptations as possible up-front to simplify trial conduct and potential need for amendments as much as possible. It was recommended to pre-specify as much as possible in the protocol, including referencing potential additional medicinal products to be introduced – even if the drug is not confirmed for inclusion at the time of submission.
- It is recommended to use the estimand framework to define the primary endpoint.
- The primary endpoint of 28-organ free support days was suitable for a phase 2 trial but may not be suitable for a future marketing authorisation application. There was a suggestion to consider collecting additional data/endpoints in this trial to inform a future phase 3 trial and potential for licensing in future.

Action: KRR to provide CTFG reference for complex trials (link included above but to be confirmed by MHRA if this is correct).

Northern Ireland regulations & considerations
Northern Ireland is following the EU regulations for devices, so EU Medical Devices and IVD regulations apply. This was enforced as part of the EU exit protocol via the MHRA. This would require a named contact in Northern Ireland.
Ethics approval will need to be obtained first. Invasive techniques to capture sample have an additional requirement in Article 58 – this does not apply for this study. Doing performance evaluations in Northern Ireland is free.
The rest of the UK does not have the option to opt out of the UK Medical Device Regulations (as outlined above).

Study team confirmed that the trial would commence with Prof McAuley as the Chief Investigator (based in NI) but with sites in Great Britain initially. Sites in NI would join at a later stage to coincide with EU sites.