

## Reviewer 1 Comments

NIHR 158714

My first observation is that the two PPI are on 0.0% FTE where I would normally expect see 0.2% or 0.5%, whereas the PPI lead is on 2.5%, being the question what will the 2.5% PPI Lead member of the team be doing that the PPI members won't.

I recognise that there has been PPI involvement in this study, and reading between the lines it becomes clear that their contribution has shaped aspects of the study.

The recruitment target is ambitious, 70 sites worldwide, the ambition becomes more squeaky when it is borne in mind that these sites may also be recruited to participate in other clinical trials creating competition between units and consultants over which patients get enrolled in which trials. I recognise the point about this study being timely for pharmacological study into ARDS, but how do studies compete for patients in critical care where the topics are not ARDS? Could this create recruitment difficulties elsewhere in the chain? I swing between wondering if 70 sites is too few or too many.

Considering now the follow up EQ-5D at 3/12, has there been sufficient reflection that patients might between being enrolled for this study and then have had subsequent cardiovascular critical events, and how does that affect the trial? If they have survived the ITU intervention but have gone on to experience other events, does that inform the study or does it mean that is an inconsequential and unfortunate outcome for the data? How will they know if the intervention of the study drugs have had a consequence to critical events alongside-morbidities, and whether the interventional study drugs have had no impact and the critical events are simply a consequence of comorbidities that would have occurred in any case?

Turning now to the international aspect of the study, will there be PPI representation in each of the recruited countries? If not, how will those patients consented to the study be represented? How will the PPI group reasonably represent patients and their NoK, unless of course, they hold meetings with clinicians in those centres, and if so, how is the matter of translation dealt with? This all goes back to the puzzle of how and why the PPI representatives are on 0% FTE. I would be greatly comforted to know there is PPI representation in each country recruited, not least because I would want to be satisfied that patient and NoK facing documents have not only been accurately translated but have also echoed cultural concerns particular to those centres. This point is recognised by the team in their application (P.14) but I would be happier if resolution of these points were more advanced than they are at this late stage of the application. How will international participants and NoK receive lay summaries of the study outcomes? How will the study convey to international participants and NoK the value the study places on their consent? The dissemination plan as far as the public goes, is unambitious. The dissemination plan as far as the international public goes, is non-existent. This is a serious point; what does this say to the international community about how science values the public? Each study that recruits patients and involves those who love them has the potential to influence the next request made to them to participate in a study. If they don't feel valued, when asked to take part in the next study they may well think, 'why should I? I wasn't valued the last time'.

If there are sites in many countries, why is there mention only of one patient tab on the

website, and that presumably being in English? Why isn't there sites that are language specific for all international participants and their NoK?

I'm unclear at what point treatment is withdrawn. Is treatment withdrawn when biomarkers are absent, when the patient is extubated, on transfer to a general ward, or when they are discharged, or once prescribed does the prescription become added to the GP budget?

What is the threshold of success? Absence of ARDS or successful management of ARDS?

Will the data distinguish the impact of other supporting therapies, such as steroids in case there is an impact and whether other drugs are adjuvants to the intervention drugs, or will this not be captured?

Will the data filter PMHx and FMHx to understand if there are influences present that may explain the development ARDS?

Reference is made to ethnicity and socioeconomically disadvantages regarding inclusivity, but the falls short of the Gold Standard. True EDI should embrace not just colour and culture but all gross never seen in the research conversation, such as shift workers, single parents, those with dysphasia and aphasia, those working and living in remote populations such as agriculture and fisheries. The EDI aspect here could be more ambitious.

In summary, I am satisfied this study has the potential to demonstrate that the international drugs do or do not have a beneficial impact on patients who develop ARDS. That there is an international component adds the potential benefit that the outcomes could change protocols for patients worldwide. The study appears feasible, albeit the recruitments targets are ambitious, and while it could be delivered, I do not wish to diminish the points made above.

## **Reviewer 2 Comments**

This stage two application aims to address an important clinical question and the research as described has the potential to lead to impactful change. Identification of pharmacological interventions based on phenotyping of ARDS will have clear benefits for patients and the public with reducing duration of organ support and improving survival.

The project aims to establish an international phase 2 precision medicine adaptive platform trial, applying for just under £6000K over a period of 5 years. During this period, it will assess the efficacy and futility of two potential immune modulating agents Simvastatin or Baricitinib in addition to usual care compared to usual care alone.

The research plan seems feasible and project delivery is supported by prior work by members of the group in platform trials and other aspects of ARDS research. The selected primary and secondary outcomes are patient focused and there is embedded PPI involvement.

Overall, the proposal is clearly written and detailed, with consideration given for potential

project risks. There is evidence that the applicants have responded comprehensively to feedback from the Board at Stage 1. I would like to raise the following points below which I feel could benefit from further clarification.

The proposal aims to recruit patients from a minimum of 70 sites across at least 10 countries but with 50% of trial sites based in the UK. How will the study equal sufficient representation across countries and sites accounting for the need to reduce potential biases from differences in patient population characteristics, definitions of usual care.

More detail on the methodology with respect to the use of 'a range of strategies to protect against bias.' would be helpful. For example, selection bias, the proposal states that the study will evaluate screening logs and examine reasons why patients have not been enrolled into the study to ensure clinicians have equipoise. However, how will this be implemented on a practical level, what will the project team do if there is evidence of lack of equipoise at a site? Will the site be excluded and/or patients be retrospectively excluded?

The proposal also mentions plans to work with the PPI group to develop strategies to improve inclusivity and access underserved groups but there is a lack of detail on what this will involve. The study will report on included patients based on the NIHR INCLUDE guidance and but how will the study consider this in terms of patient recruitment? What will they do if they find differential retainment across certain groups, for example.

### **Reviewer 3 Comments**

This study is expected, as it is a logical step in the management of ARDS.

The interventions proposed are the ones we have high in our list and the protocol is straightforward. The platform design is now well accepted.

I see two issues

1-there is no good analysis of organ function over time - yet this is the most important outcome (it is very difficult to show a reduction in mortality in such a heterogeneous group of patients and event-free survival is often not sufficient to show a benefit. There is nothing on SOFA scores over time.

2-the possibility to use other drug therapy is unclear. Of course high doses of corticosteroids is not allowed in the baricitinib group, but what about moderate doses of corticosteroids started in the context of ARDS itself?

### **Reviewer 4 Comments**

Research question is "In patients with ARDS with hyper and hypoinflammatory phenotypes, do pharmacological interventions in addition to usual care, compared to usual care alone, reduce the risk of death or the duration of organ support?"

Study design is a Bayesian Adaptive Multi-Arm Trial design with pre-defined triggers for efficacy and futility (compared to usual care).

Primary Outcome is 28-day organ support-free days, incorporating mortality.

The research plan seems feasible and project delivery is supported by prior work by members of the group in platform trials and other aspects of ARDS research.

Randomisation approach is reasonable, stratified by phenotype and site.

Very detailed SS calculation simulation, and seem appropriate.

Detailed analysis plan and nice to see use of estimands framework. Looks well through through and appropriate.

### **Reviewer 5 Comments**

The investigators propose a clinical trial using a Bayesian adaptive multi-arm design to examine whether simvastatin or baricitinib improve outcomes in patients with ARDS, with the ultimate goal of establishing a clinical trials network (PANTHER) which will sequentially test these and other interventions using a platform trial design. The Principal Investigator is highly accomplished and amply qualified to lead such a endeavor. The research team of co-applicants consists of an array of highly skilled individuals whose proposed contributions to the work to be undertaken are complimentary to one another.

The investigator has responded to an earlier iteration of the proposal by adding long term outcomes. Modeling for enrollment examining varying rates of recruitment or alterations in ARDS mortality and/or incidence of the hyper-inflammatory phenotype are important of the front end in helping to insure the proposed research questions will be addressed and not thrown off by these variables.

Patient and public involvement has been utilized during protocol development to validate the importance of the proposed research as well as it's relevancy. The investigator acknowledged that the proposed trials network will be international in scope while the public surveyed for the proposal was only from the UK and Ireland. A plan to access underserved groups received only cursory mention and could have been further delineated.

The selection of the initial two agents for investigation are justified by earlier work in ARDS patients who where retroactively analyzed according to inflammatory sub-phenotypes (simvastatin) or work done in COVID-19 patients (baricitinib). Trial design is sound and reflects current thinking as regards to how to be most efficient in testing new interventions. Additionally, the presence of a usual care arm will be important to mitigate a criticism which has been frequently made of other trials. I would have preferred additional detail regarding sample size and statistical power been included in the proposal.

Overall, my criticisms of this proposal are exceedingly minor and I receive this with great enthusiasm.

### **Reviewer 6 Comments**

Considerable morbidity and mortality is attributed to ARDS in the critically ill. The use of ability of platform trials to quickly identify and evaluate multiple new treatments is established an as such are efficient and very cost effective. As such this trial has great potential to identify both effective and ineffective new treatments and improve the clinical outcomes of patients with ARDS. This may also reduce both immediate and longer term healthcare costs.

The proposed study team has extensive expertise in clinical research design and methodology and further many of the team members have been involved in the design and the very successful delivery of previous platform trials. The planning and design of this study is detailed and extensive. The study excels in its adaptability in that it has potential to i) introduce new diagnostic techniques enabling development and improvement in the investigation and delivery of precision medicine, ii) identify new therapeutic interventions and iii) with engagement of industry evaluate new technologies to support precision medicine. The study team have previously delivered platform trials with success and it seems likely that this study will be delivered as described.

A minor concern is in the usual care arm it is proposed that treatment will be directed by international guidelines. Although often widely acknowledge and accepted implementation is also recognised to be very variable. How will this be monitored and what deviation /variance from the guidelines will be accepted

Suggestions for consideration. It is noted that all cause mortality and health related quality of life assessments are proposed at 3 months which could be considered early in the reported long term recovery trajectory and suggest that this may be more informative at 6 or 12 months. Further has physical disability assessment been considered at the same time - e.g 12 item WHODAS 2. With the broader adverse outcomes of ARDS (interterms of disability, cognition mental ill health). Although possible beyond the immediate scope of this study, construction of a patient registry could be considered which would give rise to access of a large cohort in whom these outcomes could be assess at a future timepoint.