icnarc intensive care national audit & research centre

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National Institute for Health Research
Evaluation, Trials and Studies Coordinating Centre
University of Southampton
Alpha House
Enterprise Road
Southampton
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Dear Madam/Sir

Re: NIHR130508: Evaluating the clinical and cost-effectiveness of a conservative approach to oxygen therapy for invasively ventilated adults in intensive care (UK-ROX)

Thank you for your letter of 28 April 2020, we are really pleased the HTA Funding Committee has recommended our application for funding. Please find - set out below - our responses to the feedback, as requested.

Funding Committee Feedback

- The applicants should define what successful data linkage would mean (Section 11 of the detailed research plan). Is there variation in the availability of data within the time frames proposed that might lead to bias?

Successful data linkage would consist of linkage to:

- the case mix programme (the national clinical audit of adult general critical care, conducted by ICNARC) at the start of recruitment (month 6);
- civil death registrations (NHS Digital) for the two interim analyses (months 18 and 26)
- HES and civil registrations at NHS Digital for the final 90-day and one-year follow-up (month 34 onwards).

Our team has extensive prior experience of completing similar data-enabled trials in critical care settings and linkage to routine databases and these timeframes are all well-within previously delivered timeframes.

There should be no variation in the availability of data, either between data fields or between arms during the time frame of the study, so there is no reason this would have the potential to lead to any bias.

- The applicants should explain how refusal of consent for data linkage, withdrawals and loss to follow up have been considered in the sample size calculation.

As outlined in the application, we have allowed for a 6% refusal of consent, withdrawal and loss to follow-up within the sample size calculation. This figure this was based on our data from the 65 Trial (Lamontagne et al. JAMA 2020), which was a similar data-enabled trial, using the same consent model and linkage to identical routine data sources.

- The applicants should monitor the range of practice in terms of oxygen therapy / SpO_2 targets within the usual care group during the trial.

Our proposed plan is to monitor oxygen concentration and SpO_2 in both the intervention and usual care groups in-depth during the course the six-month pilot study. At the end of the pilot study we will analyse the data to ensure adequate group separation in terms of oxygenation. Following the successful completion of this phase of the study, we will monitor oxygen concentration and SpO_2 in a total of 15% of participants. This will include the first 10 patients at each of the 100 planned sites and then randomly selected participants from all sites. These data will be regularly reviewed as time progresses by the Trial Steering Committee and the Data Monitoring and Ethics Committee. With a trial of this magnitude and an efficient design approach, it is not possible to collect comprehensive oxygenation data on all participants.

- We have now had an opportunity to scrutinise the two NEJM studies. You described the Barrot study as a single centre study whereas it was multicentre. Please make sure your study protocol is updated given the new study results.

Many thanks for pointing out this error. When we submitted our original application, the study led by Dr Barrot which we mentioned (NCT02713451) was still in progress, it has now been published (March 12th 2020). We have updated the research plan to reflect it is multicentre and will include up-to-date results in our trial protocol.

- Given the safety concern of lower oxygen for patients with ARDS in the Barrot study and the fact that you are planning to start your study on July1st 2020 i.e. during intense ICU activity from the COVID-19 pandemic, we are interested in your views on whether it would be wise to start the study now given the high likely prevalence of ARDS patients with COVID-19 or whether it would be wiser to start recruitment at a later date so that a more typical spectrum of patients are included. If you do suggest starting as soon as possible, please explain how you would mitigate the risk of adverse outcomes in those with ARDS as a result of COVID-19.

Barrot et al.'s study was stopped early by the data and safety monitoring board because of safety concerns and a low likelihood of a significant difference between the two intervention groups. The data that were analysed showed no difference in 28-day survival between conservative and liberal oxygen therapy and groups. The findings of this study reinforce the need for a very large, multi-centre randomised controlled trial to address the question of optimal oxygenation targets in mechanically ventilated critically ill patients.

The recent COVID-19 pandemic affected intensive care units throughout the UK. We intend to allow the National Health Service to recover from this unprecedented disruption to its usual programme of healthcare delivery before we commence recruitment of participants into this trial. Our original plan was to commence the setup phase of the study on 1st July 2020 and recruitment of patients into the pilot phase of the study on 1st January 2021. We feel it would be prudent to delay this by one month (contract start date 1st August 2020) to allow recruitment to commence recruitment in February 2021. This will allow adequate time to understand the course of the pandemic over the next six months if there is a potential second wave.

In terms of recruiting patients with COVID-19, we would not specifically exclude these patients as this is an emerging disease that we wish to understand more about. If we exclude them from this study, the results of it may not be generalisable to patients with future novel respiratory infectious diseases that require mechanical ventilation. However, if there is a large and sustained increase in COVID-19 admissions to ICUs in the UK we would considering suspending the trial until numbers subsided again. ICNARC are already monitoring all admissions of patients with COVID-19 to ICUs in the UK so have a unique overview of the national situation.

Finance Feedback

- We note that the host institution is ICNARC but the CI organisation is UCL. We prefer the host institution and the CI to be based at the same institution. Please provide justification and reassurance for this not being the case.

The contractual arrangements are identical to those that have been successful in other NIHR HTA programme studies. This model ensures a close working relationship between the Chief Investigator and the Clinical Trials Unit and has proven to be successful. In addition to these benefits, it is the institution of the joint Chief Investigator. We would also like to take the opportunity to inform the committee that Professor Daniel Martin has moved institution, to the University of Plymouth (from 1st May 2020).

- Please provide complete annual salary costings for O'Driscoll.

Ronan O'Driscoll has retired from the NHS so does not require a salary.

- Please provide a breakdown of the collaborator meeting costs.

Costs are based on attendance and costs at previous collaborators meetings for similar studies. We would expect 150 attendees across the 100 sites at a £75 delegate rate with an additional £1000 for hire of audio-visual equipment, an average of £50 travel in included per patient**.** For this study, we have limited to a sole collaborators' meeting to present and discuss the results, which is always appreciated by the participating sites.

- Please provide a quote for NHS digital.

Thank you for identifying this. Our initial costs had been based on historical costs from NHS Digital. We have now been through the advertised costs, as these have changed since our last application. The detail has been provided below, and our costs have been updated in the application and scheduled across the grant.

Service component	**Unit cost (£)**	**Occurrences**	**Cost per component (£)**
Application	1030	1	1030
Extension	820	1	820
Annual review	500	5	2500
Data volumes	320	9	2880
Dissemination	930	4	3720
Service required	2060	7	14420
Total (£)			**25370**

- Please provide more information on the £10K included for preparing data for future research, because this is not a cost we would normally expect to see.

In line with NIHR advice, we are committed to sharing an anonymised dataset to other researchers to allow maximum benefit from the data accrued on the study. At the end of the trial, data will be made ready for future re-use through anonymisation (generation of random patient and site IDs, conversion of all dates into lengths of time from relative time points, and grouping or coarsening of continuous and categorical variables with containing rare values) and preparation of detailed metadata documentation to guide future researchers. In addition, data will be made available in-line with data-sharing agreements, including those requirements of NHS Digital. The costs will cover staff costs (statistician/data management) at the end of the grant period.

- We expect indirects to be based on fte and the Indirects included for Paul Young are much higher than we would expect to see.

The indirects for Paul Young have been checked and are based upon 75% of the actual staff costs. These have now been removed from the application.

- Please confirm that the cost of the oxygen in both arms will be the same.

Medical oxygen and air are piped into a standard ICU ventilator and blended to generate the selected oxygen concentration. The cost difference between oxygen and air is negligible.

Intellectual Property (IP) Feedback

- If any third party owns or controls rights in the Background IP for the Research (for example if the Background is being used under licence), please consider the warranty given at clause 23.1.5(a) and the opportunity to list exclusions form this warranty at Schedule C of the research contract. If necessary, please complete Schedule C for our review and approval. Please note the Contractor need only complete Schedule C where it cannot warrant that it has an 'unrestricted and free right to use' the Contractor Background IP for the purposes of the Research.

No third party rights exist in relation to background IP.

- It is NIHR's starting position that all arising foreground IP shall vest with the contractor. If you wish NIHR to consider alternative ownership arrangements then please provide your proposed wording so it can be reviewed and, if approved, will replace the standard wording to Schedule D.

We are happy with this position.

- If you have not already done so, I would strongly encourage you to discuss the above points with the appropriate department at your University/ Trust e.g. Research Office, Technology Transfer Office, Contracts Office etc. Please provide me with the contact details for your contact(s) in these departments so that I can copy them in to future correspondence when appropriate.

Please use the following details:
Keji Dalemo
Clinical Trials Unit Manager
Intensive Care National Audit & Research Centre

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- You should clearly explain the arrangements which have been or will be made relating to the terms of access to the datasets.

As outlined previously, we are fully committed to allowing access to datasets generated as part of all of our research studies, with data prepared in such a format to allow analysis and interpretation by external researchers. Researchers will submit requests for access to the ICNARC CTU for access to the data, specifying the objectives, data fields required, who requires access to the data, and details of controllership/hosting of the data. This will be reviewed and approved by the Chief Investigators (and other members of the trial management group, if required) – all reasonable requests will be reviewed. Datasets are usually made available to the participating sites/investigators in the first instance, with wider accessibility soon after. We are also in the process of building an online data library on our website, which will allow publication of metadata from research studies.

Please do not hesitate to contact us if you require any further clarification.

Yours faithfully

Daniel Martin
Chief Investigator, UK-ROX