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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: NIHR128895: Evaluating the clinical and cost effectiveness of using a more permissive blood pressure target to guide careful titration of vasoactive agents in critically ill children with hypotension: PRotocolised Evaluation of permiSSive blood pressure targets versus Usual caRE (PRESSURE)

Thank you for your email of 16 October 2019, please find - set out below - our responses to the feedback, as requested.

Funding Committee Feedback

- The applicants should monitor fidelity and separation between the groups throughout the trial and not just in the pilot.

Apologies that this was not clear in the proposal. Fidelity to the protocol and separation will be monitored closely by the Trial Management Group and reported to the Trial Steering committee throughout the course of the trial. We have added further detail in on monitoring adherence in section 5.4 (as below). We have also taken the opportunity to make the process and responsibility for monitoring adherence and separation clearer in sections 5.11, 8.1 and 8.2 in the detailed research plan.

'Failure to discontinue vasoactives or reduce their dose once MAP is above the 5th centile for at least three hours in the intervention group will be defined as a potential protocol deviation (i.e. there can be no treatment protocol deviation in the usual care group). Potential protocol deviations, identified from the trial data, will trigger a query to the participating site who will have the opportunity to provide a justification. In some cases (for example, MAP values may have been above range only transiently on the hour but within range between the hourly recordings in the trial data), the Trial Management Group may determine that the event did not constitute a protocol deviation. Adherence will be monitored throughout the who duration of the recruitment period.
'

- This should involve monitoring and targets for both mean arterial pressure and vasoactive medication, as specified in the proposal, and not just medication, as suggested in the response to reviewers.

We agree that it is vital to monitor actively both mean arterial pressures and exposure (dose and duration) to vasoactive agents. As stated above, as mean arterial pressures are being used as a lever to reduce the exposure of vasopressor agents to critically ill children, our process for monitoring adherence to the intervention will be based on adjustment of vasoactive agents in relation to the mean arterial pressure of the patient (i.e. if the mean arterial pressure is above the target, we will expect a reduction of dose or discontinuation of vasoactive agents). Drift in usual care will be monitored throughout the trial. Separation between the groups in mean arterial pressure and exposure to vasopressor agents will be monitored throughout the internal pilot phase (key progression criteria) and the whole trial period. This has been made clearer in the detailed research plan.

- The applicants should provide the recruitment rate by site per week for the pilot. Specifying stop/go criteria as 100% achievement as 'Green', with a target of 1 participant per site, per week. Amber to be 0.5-1.0 participant per site, per week.

This has been updated as requested.

- The applicants propose both adjusted and unadjusted analyses. The primary analysis should be an adjusted analysis which accounts for the variables included in the randomisation scheme.

We have updated the detailed research plan (section 5.12) to specify that the primary analysis method will account for stratification by age. As the primary endpoint is a rank-based outcome measure, which will be analysed using non-parametric methods, adjusting for both age and site in the primary analysis is not feasible due to the expected small numbers of patient in the resulting strata. The trial will be run in highly specialised units based in a relatively small number of major hospitals (n=17) in the UK, so we do not expect to see major variation in effect size across sites, however we will report this as a secondary descriptive analysis.

- The Committee would like clarification around the use of CHU-9D as this measure is not recommended for use in younger children.

For the economic evaluation we aim to estimate Quality-adjusted life years (QALY) based on preference-based measure of health-related quality of life (QOL). However, there is currently no validated generic preference-based measure of QOL that covers the entire spectrum of paediatric population. This is a challenge not only for this study, but a common issue/challenge for capturing QOL in children.

We have selected CHU-9D because it is widely used paediatric generic preference-based measure of QOL for children and has age appropriate versions covering the wide range included in the study. While CHU-9D is suitable to use in children age 7-17 years, it also has a proxy version for younger children age <7 years which we will use for PRESSURE. To complement the preference-based measure of QOL, we will also use PedsQL, the most widely used non-preference-based generic QOL measure for children.

Finance Feedback

- It is our usual preference for the contractor to be the substantive employer of the chief investigator; please therefore provide justification for the proposed contractual arrangement.

The contractual arrangements are identical to those that have been successful in other NIHR HTA programme PICU studies (e.g. FEVER, Oxy-PICU). This model ensures a close working relationship between the Chief Investigator and the Clinical Trials Unit and has proven to be successful.

- In the posts and salaries - details section there has been no geographical weightings included for any staff salaries. Please can you confirm that this is correct?

Geographical weighting has now been detailed for staff salaries, where applicable.

- In the posts and salaries - details section, D Inwald and J Manning have been allocated as employed by a HEI e.g Imperial College London and Nottingham University. However the cost in the annual salary details section has been allocated as an NHS cost. Please could this be corrected so that both sections detail the same type of cost? If the salary costs should be allocated to HEI, the associated Indirect cost values will also need to be added to the application for both Universities.

Thank you for seeing these errors. The employing organisation for D Inwald was written as 'Imperial College Healthcare', this has been updated in full to 'Imperial College Healthcare NHS Trust'. For J Manning, his University affiliation was used incorrectly, this has been corrected to his NHS employing organisation.

- Please check the salary calculations for M Peters and Research Assistant (LSHTM). These appear to be lower than expected.

Annual salary and on-cost details have been amended on the form for M Peters. National Insurance/Superannuation for Research Assistant (LSHTM) have been amended. Actual costs requested for both confirmed.

- Please check the salary calculations for P Mouncey, K Thomas, CTU Manager and Trial Manager. These appear to be higher than expected.

For P Mouncey, K Thomas and CTU Manager the National Insurance/Superannuation values have been amended. Trial Manager values are correct

- Please could you provide further information and detail about what the cost within Other Direct Costs totalling 3 x £4,150 for collaborators meeting at start, follow up and end of the project is for.

Costs are based on attendance and costs at previous collaborators meetings for similar studies. We would expect 45 attendees across the 17 sites and PRESSURE trial team at a £70 delegate rate with an additional £1000 for hire of audio-visual equipment.

- Please could you provide a breakdown of how the site research nurse cost has been calculated, detailing the number of hours/cost per hour or FTE and breakdown of annual salary between Basic, Geographical, Superannuation and National Insurance.

The costs used for site research nurses are those outlined in the summary page of the SOECAT with this been used to generate the costs for the site research nurse cost.

- The SOECAT is missing standard care costs and the treatment costs for treating patients. Please could these be added in, even though the cost may be the same for both arms of the trial.

These have been based on the interventional (vasoactive agents) costs within an economic evaluation of a similar study in adults and scaled for children.

- Once the standard care and treatment costs have been added to the SOECAT, the SOECAT will require approval from the LCRN.

This has now been approved and uploaded. The review process slightly altered the site research nurse costs and NHS support costs.

Please note we have added one further cost under 'Dissemination'. Recently we have worked with clinical staff, patients and family members to maximise the impact of our dissemination. This feedback has led to an additional cost of £2,500 to create infographics (for all audiences), and a simple video that can be hosted online.

Intellectual Property (IP) Feedback

- Please clarify what third party rights exist in relation to background IP. If there are none then please inform us as this means there will be no requirement for schedule C in the contract. If third party rights exist in relation to background IP please provide your proposed wording in the Intellectual Property Feedback document that was attached to the email, so it can be reviewed and, if approved, will replace the standard wording to Schedule C.

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:
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- It appears that the CI's employing organisation and the contracting organisation are different. The ownership of any foreground IP will need to be clarified.

The foreground IP will be owned by the contracting organisation, but utilised by the trial team through dissemination to ensure patient benefit will be maximised.

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

Yours faithfully

David Inwald
Chief Investigator, PRESSURE