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Dr Les Gelling, Chair
East of England – Cambridge South Research Ethics Committee
The Old Chapel
Royal Standard Place
NG1 6FS

05 May 2021

Dear Dr Gelling

**Study title:** **Protocolised Evaluation of permiSSive blood pressure targets versus Usual care (PRESSURE)**
**REC reference:** **21/EE/0084**
**IRAS number:** **289545**

On behalf of the PRESSURE Trial Management Group, I would like to thank the Cambridge South REC members for their thoughtful views of our application which you reviewed on 25 March 2021.

Further to your email on 12 April 2021 we have amended and resubmitted the study documentation in response to the Committee's conditions, as detailed below:

| | Ethical Review - Further Information required | Response from the applicant |
|---|---|---|
| 1 | *The Committee reviewed A6-2 o the IRAS form.*<br><br>*Members noted there was a statement of "As the study will use identifiable and health data, there is a small risk that data could be lost or breached. Robust measures will be in place to prevent this from occurring"*<br><br>*The Committee asked what robust measures would be used and what the percentage of 'small risk' of lost or breached data could be.* | ICNARC have a suite of measures – organisational, technical and contractual - to mitigate the risk of data loss.<br><br>Organisational<br><br>• An overarching information security framework containing a suite of policies covering data protection, information governance and confidentiality<br><br>• A 'Standards Met' rating for the DSP Toolkit<br><br>• Valid certification with the Cyber Essentials scheme<br><br>• Written processes for restricting privilege access to accounts<br><br>• Comprehensive staff training on cyber security and data protection<br><br>Technical<br><br>• High grade encryption by default on our laptops<br><br>• Blocks on USB use to prevent data |

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| | | exfiltration<br>• DLP (Data Loss Prevention) policy enabled via Office 365<br>• Antivirus and email scanning to prevent data loss through malware<br>• Controls on databases to prevent downloads of data on devices<br>Contractual<br>• Clauses in employment contracts to ensure confidentiality<br>• UK GDPRcompliant contracts in place with suppliers and processors<br>• Terms with ISO 27001accredited third-party storage providers<br>• Use of approved data sharing agreements for NHS health data, such as the DSFC |
| 2 | The Committee noted further information would be collected from participants after 12 months.<br><br>Members asked what mechanism was in place for this collection and how it would be collected. if it would be by questionnaire, this should be submitted for review.<br><br>The Committee also asked for clarity how the applicants would ensure the information collection would not be sent to the parents of the children that had died in the past 12 months. | The information will be collected by a postal / email questionnaire sent by ICNARC. These would be sent after 12 months if the parents/legal guardians had consented to this follow up. These questionnaires were submitted within the IRAS application (PedsQL for various age groups)<br><br>Questionnaires will only be sent to the parents/legal guardians who have consented to receiving it (question 7 of the consent form). ICNARC are collecting survival data at 30 days, 90 days and 12 months following PICU discharge (sites will provide this information e.g. through NHS Spine). This information will be reviewed by the ICNARC team before any parents/legal guardians are contacted to ensure questionnaires are only sent to surviving children. |
| 3 | The Committee reviewed A35 of the IRAS form<br><br>Members agreed this section had been completed incorrectly and should be revised. | Original text - "Consent for patient's participation will be gained from parents who are not expected to have fluctuations in capacity."<br><br>Revised text now reads – “As participants are children and not giving informed consent, their parents / legal guardians will be approached. Child participants who are not expected to have capacity due to (1) age and (2) sedation drugs – will have consent sought from an individual with parental / legal guardian responsibility.<br><br>Assent will be obtained by participants as soon practically possible.” |
| 4 | The following changes are requested to the information leaflet:<br>a) Revise the word order of column one, | a)<br>Original text - "We are doing this study to find out more about at how low blood pressure (also known as hypotension) is managed and |

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| | paragraph one regarding hypotension. Members commented that hypotension was the condition, not its management and treatment.<br>b) Column three, paragraph two: reference to the care received by the parent (and the parent's ability to withdraw) are inappropriate. | treated, which is a common condition in children in the intensive care unit."<br><br>Revised text now reads - "We are doing this study to find out more about at how low blood pressure (also known as hypotension), a common condition in children in intensive care, is managed and treated."<br><br>b)<br>Original text – "If your child is eligible, joining the study is entirely voluntary. You are free to leave the study at any time and this will not affect the standard of care you or your child receives."<br><br>Revised text now reads – "If your child is eligible, joining the study is entirely voluntary. You are free to withdraw your child from the study at any time."<br><br>Updated information leaflet V1.1, 19 April 2021 (tracked and clean) available. |
| 5 | The following changes are requested to the main Participant Information Sheet:<br>a) Review page one, column one, bullet point two: "If they do not take part, this will not affect the care your child receives" Members commented this was not strictly true and should be revised.<br>b) Page one, column one; the Committee agreed it would be helpful a bullet along the lines of "Both the lower and standard target blood pressures are within the approved range given in current guidelines".<br>c) Page two, column one, paragraph four; revise the sentence to "lower blood pressure targets, still within the normal range" rather than "lower blood pressure targets"<br>d) Page four, column two; there has been multiple references to "you" and "your information" that should be "your child" and "your child's information". | a) Original text – "You are free to decide whether your child's information is included in the research. If they do not take part, this will not affect the care your child receives".<br><br>Revised text now reads – "You are free to decide whether your child's information is included in the research".<br><br>b) Thank you for the comment. The below text has been added as a bullet point, though we felt it is better situated in paragraph 2 "Important things you need to know".<br><br>Revised text now reads - 'Both the lower and usual target blood pressure targets are within the normal range for your child.'<br><br>c) Thank you for the comment. We have added the suggested text.<br><br>d) Thank you for the comment, the text has been adjusted as suggested. |
| 6 | Review all study documents for typographical errors. | completed |

We also respond to the HRA/HRCW assessment queries, as follows:

| HRA and HCRW assessment - Further Information Required | Response from the applicant |
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| PISs (Parents or Guardians) - to be updated if a link list will be available as the data will not be pseudonymised instead. | Comment 1 – The PIS ensures that the explanation of data flow, including the use of identifiable or anonymised data is made clear. We have updated the PIS to explain any reference to child's data will use a code number |

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|---|---|
| □PIS (Parents or Guardians) - to be updated to show that if they consent to contact about future research then their identifiable data will be kept for 5 years.<br><br>□Consent form (Parents or Guardians) - clause 4 refers to 'full anonymised dataset' sent to ICNARC but this will be identifiable data that will be sent. This needs to be clarified and updated.<br><br>□Bereaved Consent form (Parents or Guardians) - clause 3 refers to 'full anonymised dataset' sent to ICNARC but this will be identifiable data that will be sent. This needs to be clarified and updated. | (participant ID). Although there is no link list, the participant ID will be linked to patient identifiable data in the CTU study database in the event that consent is obtained to collect this information. If consent is not obtained to collect identifiable data, only the participant ID will remain in the database. ICNARC will keep the identifiable data for no longer than one year after the study has finished (unless agreed otherwise), as specified in the PIS.<br><br>Comment 2 – This is present under 'future research'- 'if you agree to this option, we will keep your contact details for up to five years after the end of the study'.<br><br>Comment 3 – We have ensured the consent form and PIS have clear separation between identifiable and anonymised data.<br><br>Identifiable data of the child (child name, DOB, postcode, NHS number) will only be sent to ICNARC if clause 5 is agreed to, this will be for NHS digital / NHS Wales Informatic Services. This is reflected in section 9 of the PIS.<br><br>Agreeing to clause 4 means anonymised datasets would be sent to ICNARC via trial ID, therefore non identifiable.<br><br>Comment 4 – We have ensured that the PIS and consent form are clear in detailing that only anonymised data will be sent to ICNARC. No identifiable data of the child will be collected as NHS digital / NHS Wales Informatic Services will not be used.<br><br>Agreeing to clause 3 means anonymised datasets would be sent to ICNARC via trial ID, therefore non identifiable. |

We have also taken this opportunity to make a minor change to the protocol in Appendix 1 – PRESSSURE Permissive MAP Targets.

This is due to a recent detailed review of the MAP 5th centile data derived from our previous observational work, we found that preterm babies had erroneously not been excluded from the dataset. The consequence of this was that the observed MAP 5th centile between 6 months – less than 1 year is slightly lower than previously reported. When preterm babies are excluded from the analysis, the MAP 5th centile in this age group is 39mmHg rather than 36mmHg. This finding has been discussed within the study team, and in view of it we split the under 1 age band into two bands: under 6 months (0 – 5 months, in completed months) and 6 months – less than 1 year (6 – 11 months, in completed months). The permissive MAP target was increased from 35 – 40 to 38 – 43 in the older group. Exclusion of preterm babies did not result in the observed MAP 5th centile changing in any other age bracket and hence no other changes in the permissive target ranges were required.

Please do let me know if there is any further information or clarification that you or the Committee require.

I look forward to hearing from you.

Yours sincerely

Miss Alanna Brown
Trial Manager

Copy to: Dr David Inwald, Chief Investigator
Stephen Kelleher, Sponsor Contact
Beverley Mashegede, Health Research Authority

**Enc.**
PRESSURE Participant Information Leaflet (Parents or Guardians), v1.1, 19 April 2021_tracked changes
PRESSURE Participant Information Leaflet (Parents or Guardians), v1.1, 19 April 2021
PRESSURE Study Bereaved-Participant Information Sheet (Parents or Guardians) v1.1, 28 April 2021_tracked changes
PRESSURE Study Bereaved-Participant Information Sheet (Parents or Guardians) v1.1, 28 April 2021
PRESSURE Study Participant Information Sheet (Parents or Guardians) v1.1, 28 April 2021_tracked changes
PRESSURE Study Participant Information Sheet (Parents or Guardians) v1.1, 28 April 2021
PRESSURE Protocol v2.0, 28 April 2021_tracked changes
PRESSURE Protocol v2.0, 28 April 2021