Author's response to reviews

Title: Study of therapeutic hypothermia (32-35°C) for intracranial pressure reduction after traumatic brain injury (the Eurotherm3235Trial). Outcome of the Pilot phase of the trial

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Version: 5 Date: 12 August 2013

Author's response to reviews:

To, the editor,
BMC Trials
August 12, 2013

Dear Editor(s),

Study of therapeutic hypothermia (32-35°C) for intracranial pressure reduction after traumatic brain injury (the Eurotherm3235Trial): Outcome of the Pilot phase of the trial

Thank you for giving us the opportunity to respond to your reviewer's comments. Please see our responses below.

Version: 4 Date: 6 August 2013
Reviewer: Robert Stevens
Reviewer's report:
In their response letter, the authors have responded satisfactorily to the Reviewer comments.
We thank the reviewer for these positive comments.

It is essential that the content of these responses is explicitly integrated into the revised manuscript.
With the exception of the SAE table, all the other information is available in this text or the published protocol, which is publicly available. However, I have included the text from my previous response into this latest version of the paper.
From previous reviewer comments

1. What are the targeted and actual patient accrual rates? Is this study on target for enrolment or are they running behind? If the target is not being met, can the authors explain why?

The original recruitment plan, submitted and accepted by the funder of the pilot phase of the trial, was for 1800 participants. This was based upon previous published work suggesting 50% of ICP monitored TBI patients would be eligible with ICP >50%. However, the recruitment feasibility we report show that only 16% of such patients are eligible. But, those that are eligible are less heterogeneous.

Please see section “Feasibility of recruitment“, (Already in the text, PAGE 8).

2. Can the authors provide more details on safety? They state “There were seven serious or severe adverse events (SAEs), all unrelated to the intervention.” What were these events?

SAE Table (4) now included in the text.

3. Is there a data safety monitoring board? How are they exercising their oversight?

There is an independent DSMB who work according to a charter (based upon DAMOCLES principles) signed by all three members (Peter Suter, Ian Ford, Kathy Rowan). They report to an independent steering committee and recommend whether the trial should continue recruiting.

4. Is there a plan for interim analysis to determine efficacy, harm, futility?

The DSMB charter allows for stopping if there is overwhelming evidence of benefit or harm (this or another trial) but no other interim analysis is planned.

Response to 3 and 4 combined and included in the text.

5. A large number of patients (46) were excluded for “other reason” (table 2). Can the authors provide a breakdown of these reasons? This is important information for this and other trials.

These information were included at the foot of table 2.

6. Many other patients were excluded because they were > 72 hours from injury – would it be worthwhile considering a wider enrolment window?

The response to this query is already in the text - Please see final paragraph, page 11.

7. Could the authors clarify the funding source? It appears that the study was initially funded by the ESICM, but now is being funded by the NHS. How and why did this change occur?
Initial funding was by the ESICM. One of the objectives set out in the research contract between ESICM and the University of Edinburgh was to seek funding from another source. We are grateful to the National Institute for Health Research, Health Technology Assessment (NIHR HTA) Programme for funding the full trial. The new funder is a UK statutory funding agency.

This paragraph is now included in the text.

Date: 4 August 2013
Reviewer: Felix Schlachetzki

Reviewer's report: The manuscript has been significantly improved. However, I still think that the discussion includes data that should be mentioned in the results part, and commented on in the discussion part (i.e. trial management: second to last paragraph – suggestion: split results and comments).

The paragraph second to last and starting “With a conventional dichotomous analysis of the GOSE, comparing the proportions of patients with an unfavourable outcome in the two groups, a 600 patient trial has 81% power at the 5% significance level (2-sided) to detect an absolute reduction………” These are not results of the pilot phase of this trial but a discussion and only a discussion of an alternative method of analysis of the Glasgow Outcome Scale. This should stay in the discussion section.

Please comment on the differences of the POLAR-RCT trial to the Eurotherm3235Trial – why does it answer a different but complementary research question?

This is the only concurrent large trial of hypothermia in TBI, which will answer a different but complementary research question, does prophylactic early hypothermia improve outcome after traumatic brain injury, compared with the Eurotherm3235Trial, which is testing titrated hypothermia to reduce intracranial pressure and the effect that may have on outcome.

I have included some text for clarification.

Yours sincerely

Peter Andrews