Author's response to reviews

Title: Study of therapeutic hypothermia (32-35 degrees C) for intracranial pressure reduction after traumatic brain injury (the Eurotherm3235 Trial). Outcome of the Pilot phase of the trial

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Author's response to reviews: see over
Author's covering letter for initial submission

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

Authors:

Version: 1 Date: 30 July 2013

Comments: see over
To, the editor,
BMC Trials

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.

**Reviewer: Robert Stevens**

In this manuscript, Andrews et al. relate on feasibility based on the pilot phase of the Eurotherm 3235 Trial. The investigators are to be congratulated on their implementation of this large scale study in multiple sites across the world.

We thank the reviewer for recognising the challenge that this trial represents.

Several limitations need to be addressed.

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”, on 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?
SAEs were:

<table>
<thead>
<tr>
<th>Event</th>
<th>Description</th>
<th>Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalisation</td>
<td>Bleeding - defined as a new haemorrhage requiring 2 units of packed red cells</td>
<td>Unrelated</td>
</tr>
<tr>
<td>Hospitalisation</td>
<td>Bleeding - defined as a new haemorrhage requiring 2 units of packed red cells</td>
<td>Unrelated</td>
</tr>
<tr>
<td>Life threatening</td>
<td>Cerebral perfusion pressure &lt;50mmHg for 15mins</td>
<td>Unrelated</td>
</tr>
<tr>
<td>Death</td>
<td>Cardiovascular instability - systolic BP &lt;90mmHg for ≥50mins</td>
<td>Unrelated</td>
</tr>
<tr>
<td>Life threatening and persistent or</td>
<td>Cerebral perfusion pressure &lt;50mmHg for 15mins</td>
<td>Unrelated</td>
</tr>
<tr>
<td>significant disability or Incapacity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>Cerebral perfusion pressure &lt;50mmHg for 15mins</td>
<td>Unrelated</td>
</tr>
<tr>
<td>Life threatening</td>
<td>Cerebral perfusion pressure &lt;50mmHg for 15mins</td>
<td>Unrelated</td>
</tr>
</tbody>
</table>

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.*

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.

*The category other is a “mixed bag” that includes: decompressive craniotomy (largest group), enrolled in another trial, no research staff available, multiple trauma, no relatives available, no permanent address, severe burns.*

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

*Please see final paragraph, page 11.*

“Two of the most frequent reasons for exclusion from the trial were age over 65 years and more than 72 hours from injury (Table 2). As a result of this analysis, recruiting sites and all database users were surveyed and asked if they would be prepared to randomise older patients and those more than 72 hours from injury. Following a majority positive response, we submitted a protocol amendment to every ethics committee involved in the trial to remove the upper age limit for inclusion (allowing the clinician at each site to triage patients) and increase the time from injury from 72 hours to 10 days. This change was implemented in January 2012.”
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.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: None.

Thank you.

Reviewer: Felix Schlachetzki
Traumatic brain injury is a devastating condition with little evidence based therapies. Implementation of an easy study protocol is therefore crucial for recruitment of patients for experimental therapies such as hypothermia.

The abstract is well written and probably the best information there is in the paper.

We thank the reviewer for these observations.

Introduction: Written well and precise, yet a fundamental sentence as to why hypothermia would be a rational therapy in TBI would help especially the non-trauma-neurosurgeon reader.

The focus of this paper is not the rationale for the use of hypothermia as this is covered extensively elsewhere, but the challenges and outcome of a pilot phase of a multi-centre, international trial. The protocol for the trial is published and quoted in this paper and is available, free in full text format on-line.


Page 6: either the authors should give a brief description of the specific aim of the study, or discuss every point in detail, but not a mixture ("patient eligibility - previous observational studies had predicted that 50% of all TBI patients would be eligible[11]").

The specific aims are described on page 5 & 6 of the manuscript:

“In this report we evaluate data collected during the internal pilot phase (January 2009 to August 2011) to assess the following criteria:
• design and implementation of an online electronic case report form (eCRF) for screening, randomisation and data collection;
• feasibility of recruitment (sites and patients);
• patient eligibility - previous observational studies had predicted that 50% of all TBI patients would be eligible[11]
• feasibility of the protocol, in particular the effectiveness of delivery of the cooling protocol.”

Design&Methods: This chapter mainly describes how hypothermia should be induced in this trial. Yet, I would envision a thorough description of the aim of this paper – mainly what is described in Pilot Findings/Results.

Please see the answer to the question above for specific aims, which all relate to feasibility of delivering this trial, namely:
• design and implementation of an online electronic case report form (eCRF) for screening, randomisation and data collection;
• feasibility of recruitment (sites and patients);
• patient eligibility - previous observational studies had predicted that 50% of all TBI patients would be eligible[11]
• feasibility of the protocol, in particular the effectiveness of delivery of the cooling protocol.”

Pilot Findings/Results:
This is quite unstructured and without sometimes any confounding data, i.e. “The Eurotherm3235Trial inclusion criteria are tighter than most previous trials and the pilot shows they have been effective at recruitment of a homogenous group of TBI patients with brain swelling.” What I also miss is a general table what patients were included, i.e. with epidural hematomas, with/without intraventricular drainage, intracerebral hemorrhage.

In this trial we have used the Marshall classification for abnormalities seen of CT scan of brain.
In the pilot phase this comprised:

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Number of</td>
<td>67</td>
<td>100</td>
</tr>
<tr>
<td>Patients randomised</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>1.4</td>
</tr>
<tr>
<td>Diffuse I</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Diffuse II</td>
<td>10</td>
<td>14.9</td>
</tr>
<tr>
<td>Diffuse III</td>
<td>12</td>
<td>17.9</td>
</tr>
<tr>
<td>Diffuse IV</td>
<td>5</td>
<td>7.4</td>
</tr>
<tr>
<td>Evacuated Mass Lesion</td>
<td>21</td>
<td>31.3</td>
</tr>
<tr>
<td>Non- evacuated Mass Lesion</td>
<td>18</td>
<td>29</td>
</tr>
</tbody>
</table>

This has been added to the text as table 3.
Discussion: Very difficult to read, and sometimes rather a description of what has been done after the pilot phase i.e. page 10 “based on the invaluable experience obtained from the pilot a significant number of measures have been put in place to ensure compliance with the trial protocol through improved support of the trial sites. Study site initiation, access to support and feedback have all been refined.” I cannot follow these thoughts nor are they really supported by the data given in the paper. The next paragraphs are also more a project description how it is done now than a discussion of the work.

*I understand that the reviewer is not clear why this information is important, however, for readers wishing to design and run an Intensive Care based trial in patients with traumatic brain injury, these information are invaluable. Much of the output of the pilot phase report are qualitative and descriptive as we cannot compromise the main trial by giving any of the outcomes that will be included in our end of trial report.*

The paragraphs “patient eligibility” and “trial size” are better as they discuss relevant literature and consequences for the project.

*Thank you.*

Reviewer's report:
see attached file
Level of interest: Reject as not of sufficient priority to merit publishing in this Journal –

*Clearly we disagree!*

Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I have no competing interests as described above.

Yours sincerely,

Peter JD Andrews