DATA MONITORING COMMITTEE (DMC) CHARTER FOR THE EUROTHER3235 TRIAL
VERSION 1.0 27/04/2009

EUROPEAN SOCIETY OF INTENSIVE CARE MEDICINE STUDY OF THERAPEUTIC HYPOTHERMIA (32-35°C) AFTER TRAUMATIC BRAIN INJURY

VERSION 1.1 25.05.2009

1. INTRODUCTION
The trial is funded by the European Society of Intensive Care Medicine. REC approval has been gained in Scotland and England. CAS reference 09/MRE00/34 (Scotland AWI Study) and 09/H1302/44 (England and Wales ALC study)**.**

The trial is registered on the European registry of trials (www.controlledtrials.com, ISRCTN ISRCTN34555414)

1.1. Trial Objectives
The EUROTHERM3235Trial is an international trial in neurological intensive care that will confirm or refute the research question, does therapeutic hypothermia (32-35°C) reduce morbidity and mortality rates at 6 months after TBI assessed by the extended Glasgow Outcome Scale questionnaire?

Other questions that will be answered include:

Does therapeutic hypothermia (32-35°C) reduce intra cranial hypertension? And is therapeutic

hypothermia a cost effective treatment to improve outcome after TBI?

1.2. Scope

The purpose of this document is to describe the roles and responsibilities of the independent DMC for EUROTHERM, including the timing of meetings, methods of providing information to and from the DMC, frequency and format of meetings, statistical issues and relationships with other committees

2. ROLES AND RESPONSIBILITIES
2.1.Aims

To protect and serve EUROTHERM participants, in particular with regard to safety and to assist and advise Principal Investigators so as to protect the validity and credibility of the trial. To safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial, and monitor the overall conduct of the clinical trial.

2.2.Terms of reference

The DMC should receive and review the progress and accruing data of the EUROTHERM trial and provide advice on the conduct of the trial to the Trial Steering Committee. The DMC should inform the Chair of the steering committee if, in their view the results are likely to convince a broad range of clinicians, including those supporting the trial and the general clinical community, that on balance one trial arm is clearly indicated or contraindicated for all participants or a particular category of participants, and there was a reasonable expectation that this new evidence would materially influence patient management.

2.3.Specific roles of DMC

Interim review of the trial's progress including updated figures on recruitment, data quality, and main outcomes and safety data. This review would include, but not be restricted to, the following:

· assess data quality, including completeness (and by so doing encourage collection of high quality data)
· monitor recruitment figures and losses to follow-up
· monitor compliance with the protocol by participants and investigators
· monitor evidence for treatment differences in the main efficacy outcome measures
· monitor evidence for treatment harm (e.g. toxicity data, SAEs, deaths)
· decide whether to recommend that the trial continues to recruit participants or whether recruitment should be terminated either for everyone or for some treatment groups and/or some participant subgroups
· suggest additional data analyses
· monitor planned sample size assumptions
· monitor continuing appropriateness of patient information
· monitor compliance with previous DMC recommendations
· consider the ethical implications of any recommendations made by the DMC
· assess the impact and relevance of external evidence

3. BEFORE OR EARLY IN THE TRIAL

3.1.DMC input into the protocol

All potential DMC members should have sight of the protocol before agreeing to join the committee. Before recruitment began the trial had undergone review by the ESICM and a REC. Therefore, if a potential DMC member has major reservations about the trial (e.g. the protocol or the logistics) they should report these to the Chief Investigator and may decide not to accept the invitation to join. DMC members should be independent and constructively critical of the ongoing trial, but also supportive of aims and methods of the trial.

3.2.Timing of 1st DMC meeting

The 1st meeting of the DMC has been scheduled for early in the course of the trial, to discuss the protocol, the trial, any analysis plan, future meetings, and to have the

opportunity to clarify any aspects with the principal investigators, and to discuss the format of reports to the DMC from the Trial Office (in the Edinburgh Clinical Trials Unit, University of Edinburgh). Subsequent meetings of the DMC will, where possible, be timed to precede a trial Steering Committee meeting by a few weeks.

3.3.DMC member's contracts
Members of a DMC will have indemnity cover from the Sponsor for their work on the DMC.

4. COMPOSITION

4.1.DMC Membership

The DMC members are independent of the trial (that is, they are not involved with the EUROTHERM trial in any other way or have some competing interest that could impact on the EUROTHERM trial). Any competing interests, both real and potential, should be declared. A short competing interest form should be completed and returned by the DMC members to the Chief Investigator, Peter Andrews, at Western General Infirmary Edinburgh. The members of the DMC for the EUROTHERM trial are:
· Professor Peter M. Suter, Président ASSM/SAMW, Centre Médical Universitaire, Université de Genève, Rue Michel-Servet 1, CH-1211 Genève, Switzerland
· Professor Ian Ford, Professor of Statistics, Robertson Centre for Biostatistics, Glasgow
· Professor Peter Sandercock, University of Edinburgh, Edinburgh

4.2.The responsibilities of the DMC statistician

Professor Ian Ford will act as the DMC statistician, guiding the DMC on the statistical interpretation of the reports they receive. Professor Ford will liaise with the trial statistician on the specification of the statistical analyses and reports, which will be produced for him.

4.3.The responsibilities of the trial statistician
The independent statistician (located in ECTU Office) in conjunction with ECTU Senior Trial Coordinator (Bridget Colam) will oversee production of reports to the DMC and if appropriate the independent statistician will participate in DMC meetings, guiding the DMC through the report, participating in DMC discussions and, on some occasions, taking notes.

4.4.The responsibilities of the Trial Office

The Trial Office team comprises:
· Clinical Coordinator [Jonathan Rhodes]
· Trial Manager [Louise Sinclair]
· Data Manager [TBA]
· Senior Trial Manager [Bridget Colam]
· Experienced Trialist [Stuart Ralston]
· Trial Statistician [Gordon Murray]
· Independent Statistician [TBA]
With the exception of the independent statistician, these Trial Office staff will usually only contribute to the production of the non-confidential sections of DMC reports.

4.5.The responsibilities of the Chief Investigator and other members of the EUROTHERM Trial Steering Committee

The Chief Investigator (Peter Andrews), may be asked, and should be available, to attend open sessions of the DMC meeting. Other EUROTHERM Steering Committee members will not usually be expected to attend but can attend open sessions when necessary.

5. RELATIONSHIPS

5.1.Relationships between study teams
The study is guided by a Trial Steering Committee that meets approximately annually. The TSC has an independent chair, additional independent members, the grant holders and principal investigators, and members of the Trials Office. The day to day running of the trial is overseen by the Project Management Group, who meet weekly at the Trial Office and are joined by the Chief Investigator. The Trial Management Team in addition meet face to face approximately every 6-8 weeks.

5.2.Advisory role of DMC

As is customary, the EUROTHERM DMC will not make decisions about the trial, but rather make recommendations to the EUROTHERM Steering Committee from the DMC Chair to the Chief Investigator.

5.3.DMC payments

EUROTHERM DMC members will be reimbursed for travel and accommodation. No other payments or rewards are anticipated.

5.4.DMC members competing interests

Competing interests should be disclosed. These are not restricted to financial matters – involvement in other trials or intellectual investment could be relevant. Although members may well be able to act objectively despite such connections, complete disclosure enhances credibility. (See Annex 1)

DMC members should not use interim results to inform trading in pharmaceutical shares, and careful consideration should be given to trading in stock of companies with competing products.

6. ORGANISATION OF DMC MEETINGS

6.1.Frequency of DMC meetings
It is recommended that the DMC meet at least yearly. If possible the DMC meetings should be arranged to take place just prior to planned meeting of the Trial Steering Committee, so that the DMC report can be considered by the Trial Steering Committee in a timely fashion.

6.2.DMC meetings location and style
It is expected that all the meetings will be face-to-face with teleconferencing if required.

6.3.DMC meetings format
· Open session: Introduction and any "open" parts of the report
· Closed session: DMC discussion of "closed" parts of the report
And, if necessary;
· Further open session: Discussion with other attendees on any matters arising from the previous session(s).
· Further closed session: extra closed session

7. TRIAL DOCUMENTATION AND PROCEDURES TO ENSURE CONFIDENTIALITY AND PROPER COMMUNICATION

7.1.Intended content for open sessions
Accumulating information relating to recruitment and data quality (e.g. data return rates, treatment compliance) will be presented. SAE details based on pooled data will be presented and total numbers of events for the primary outcome measure and other outcome measures may be presented, at the discretion of the DMC.

7.2.Intended content for closed sessions
In addition to all the material available in the open session, the closed session material will include efficacy and safety data by treatment group.

7.3.DMC blinding
DMC will not be blind to treatment allocation. However the randomised groups will be labelled A and B. The identity of A and B will be supplied under separate cover, not in the report.

7.4.Access to accumulating data and interim analysis
No study personnel, with the exception of the independent statistician and his delegates (for example, a junior statistician to perform the analyses under the independent statistician's supervision, or a clerical assistant to format the reports) will be unblinded to any study results during the conduct of the study. DMC members do not have the right to share confidential information with anyone outside the DMC, including the Chief Investigator.

7.5.Responsibility for identifying and circulating external evidence
The Chief Investigator (Peter Andrews) takes responsibility for the identification and circulation of external evidence (e.g. from other trials/ systematic reviews).

7.6.DMC communications
The DMC will report its recommendations in writing to the Trial Steering Committee. This will be copied to the trial statistician and if possible should be sent via the study data centre in time for consideration at a meeting of the Trial Steering Committee (See Annex 2)

7.7.Prior availability of DMC reports
The DMC will receive the independent statistician's report at least 1 week before a DMC meeting.

7.8.Destruction of confidential papers
The DMC members should destroy their reports after each meeting. If requested, fresh copies of previous reports will be circulated with the newest report before each meeting. The Trial Office will take responsibility for keeping all DMC study reports and minutes for inspection at study termination and for subsequent archiving.

8. DECISION MAKING

8.1.Possible DMC decisions/recommendations
Possible recommendations could include:-
· No action needed, trial continues as planned
· Early stopping due, for example, to clear benefit or harm of a treatment, futility, or external evidence
· Stopping recruitment within a subgroup
· Stopping the trial on the basis of futility of recruitment
· Extending recruitment (based on actual control arm response rates being different to predicted rather than on emerging differences) or extending follow-up
· Sanctioning and/or proposing protocol changes

8.2.Statistical guidelines for termination
The DMEC has the responsibility for deciding whether, while randomisation is in progress, the unblinded results (or the unblinded results for a particular subgroup), should be revealed to the TSC. The DMEC terms of reference state that they will do this if, and only if, two conditions are satisfied: (1) the blinded results provide proof beyond reasonable doubt that treatment is on balance either definitely harmful or definitely favourable for all, or for a particular category of patients, in terms of the major outcome; (2) the blinded results would, if revealed, be expected to substantially change the prescribing patterns of doctors who are already familiar with any other trial results that exist. Exact criteria for "proof beyond reasonable doubt" are not, and cannot be, specified by a purely mathematical stopping rule, but they are strongly influenced by such rules. DMEC members have expressed sympathy with the stopping rule proposed in Part I of the 1976 report to the MRC Leukaemia Committee, whereby an interim analysis of major endpoint would generally need to involve a difference between treatment and control of at least three standard errors to justify premature disclosure. An interim subgroup analysis would, of course, have to be even more extreme to justify disclosure. This rule has the advantage that the exact number and timing of interim analyses need not be pre-specified. In summary, the stopping rules as specified in the CRASH trial protocol (as successfully applied in other trials including the MRC International Stroke Trial, which randomised 19,436 acute stroke patients) require extreme differences to justify premature disclosure and involve and appropriate combination of mathematical stopping rules and scientific judgement.

8.3.DMC decision making methods
It is recommended that every effort should be made for the DMC to reach a unanimous decision. If the DMC cannot achieve this, a vote may be taken, although details of the vote should not be routinely included in the report to the TSC as these may inappropriately convey information about the state of the trial data. It is important that the implications (e.g. ethical, statistical, practical, and financial) for the trial be considered before any recommendation is made. The role of the Chair is to summarise discussions and encourage consensus; it may be best for the Chair to give their own opinion last.

8.4.DMC quorum for decision-making
Effort should be made for all members to attend. The trial coordinating office will ensure that a date is chosen to enable this. With only 3 members comprising the DMC, all members will need to be taking part (in person or by teleconference) for any major decision to be taken.

8.5.Non participation
If a member does not attend a meeting, it should be ensured that the member is available for the next meeting. If a member does not attend a second meeting, they should be asked if they wish to remain part of the DMC. If a member does not attend a third meeting, they should be replaced.

9. REPORTING

9.1.Communication of DMC recommendation
By letter to the Chief Investigator (Peter Andrews), within 3 weeks of the DMC meeting, with a copy of the letter to the Trial Office (ECTU, Edinburgh).

9.2.DMC Minutes
The DMC will keep an accurate minute of their discussions. Separate sections will be required for the open and closed sessions. The DMC Chair will sign off any minutes or notes. A sealed copy will be sent to the independent statistician at the Trial Office (ECTU, Edinburgh).

9.3.DMC and Steering Committee conflict resolution
If the DMC has serious problems or concerns with any Trial Steering Committee decisions a meeting of these groups should be held. The information to be shown would depend upon the action proposed and the DMC's concerns. Depending on the reason for the disagreement confidential data may have to be revealed to all those attending such a meeting. The meeting should be chaired by a senior member of the Trials Office or an external expert who is not directly involved with the trial

10.AFTER THE TRIAL
10.1. Publication of results
At the end of the trial there will be a meeting to allow the DMC to discuss the final data with the Chief Investigator and give advice about data interpretation. The Trial Steering Committee members are committed to publishing the results in a correct and timely manner, irrespective of the findings.

10.2. DMC information to be published
DMC members will be named and their affiliations listed in the main report, unless they explicitly request otherwise. A brief summary of the timings and conclusions of DMC meetings will be included in the body of this paper.

10.3. DMC role in publications
The DMC will be given the opportunity to read and comment on major publications before submission.

10.4. DMC confidentiality post study closedown
The DMC members may discuss details of their involvement after permission is agreed with the Trial Steering Committee.

Annex 1: Suggested EUROTHERM competing interests form
Potential competing interests of Data Monitoring Committee members for EUROTHERM

The avoidance of any perception that members of a DMC may be biased in some fashion is important for the credibility of the decisions made by the DMC and for the integrity of the trial.

Possible competing interest should be disclosed via the trials office. In many cases simple disclosure up front should be sufficient. Otherwise, the DMC member should remove the conflict or stop participating in the DMC. Table 1 lists potential competing interests.
Table 1: Potential competing interests
· Stock ownership in any commercial companies involved
· Stock transaction in any commercial company involved (if previously holding stock)
· Consulting arrangements with the Sponsor
· Frequent speaking engagements on behalf of the intervention
· Career tied up in a product or technique assessed by trial
· Hands-on participation in the trial
· Involvement in the running of the trial
· Emotional involvement in the trial
· Intellectual conflict e.g. strong prior belief in the trial's experimental arm
· Involvement in regulatory issues relevant to the trial procedures
· Investment (financial or intellectual) in competing products
· Involvement in the publication

Please complete the following section and return to the trials office.
No, I have no competing interests to declare
Yes, I have competing interests to declare (please detail below)
Please provide details of
any competing interests:
Name: _____

Signed: _____ Date: _____

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Annex 2: Illustrative report from EUROTHERM DMC to
STEERING Committee where recommendation is to continue the
trial according to the protocol
[Insert date]
To: Chair of Trial Steering Committee
Dear [Chair of Trial Steering Committee]
The Data Monitoring Committee (DMC) for the EUROTHERM trial met on [meeting date] to review its progress and interim accumulating data. [List members] attended the meeting and reviewed the report.
The trial question remains important and, on the basis of the data reviewed at this stage, we recommend continuation of the trial according to the current version of the protocol [specify protocol version number and date] with no changes.
We shall next review the progress and data [provide approximate timing]
Yours sincerely,
[Name of meeting Chair]
Chair of Data Monitoring Committee
On behalf of the DMC (all members listed below)
DMC members:
(1) [Insert name and role]
(2) [Insert name and role]
(3) [Insert name and role]