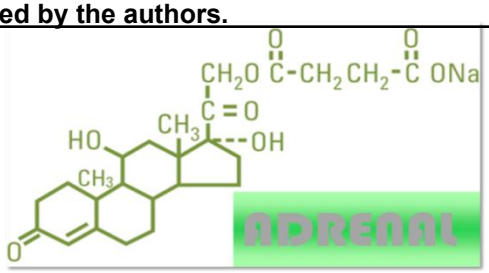

DATA MONITORING COMMITTEE CHARTER

Full Title	A randomised blinded placebo controlled trial of Hydrocortisone in critically ill patients with septic shock
Short Title	ADRENAL Study ADjunctive coRticosteroid trEatment iN criticAlly ilL patients with septic shock
Acronym	ADRENAL
Protocol No.	GI-CCT372273
Version No.	4
Protocol Date	25 September 2012
ANZCTR registration No.	ACTRN12611001042932
ClinicalTrials.gov Identifier	NCT01448109

1. INTRODUCTION

Objectives of the trial, including interventions being investigated

Primary Objective:
The proposed study is a multi-centre blinded randomised-controlled trial. Critically ill patients with septic shock will be randomised to receive 200 mg of hydrocortisone or placebo in addition to conventional treatment. The primary end point will be 90 day all-cause mortality.
Secondary objectives:

Secondary endpoints will include shock resolution, recurrence of shock, 28 day, 6mth mortality, length of ICU and hospital stay, duration of ventilation, duration of renal replacement therapy, development of bacteraemia (2-14 days post randomisation), bleeding requiring blood transfusions while in ICU and index of functional survival (defined as Quality Adjusted Life years [QALY] at 6 months.

Outline of scope of charter

The purpose of this document is to describe the roles and responsibilities of the independent DMC for the ADRENAL study, 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

A broad statement of the aims of the committee

The DMC helps to safeguard the rights, safety and well-being of research participants. It does this by examining the data accumulated during the trial and other relevant information and advising the Trial Steering Committee (TSC) if there is proof beyond reasonable doubt that the

treatment is either definitely harmful or definitely beneficial for all, or a particular subcategory of patients.

The DMC has access to un-blinded data from the trial and will review interim analyses of the outcome data. It will consider these data and other relevant information when recommending to the TSC whether the study needs to continue, be changed, or be terminated.

Specific roles of DMC

The DMC will review the progress of the trial, including updated figures on recruitment, data quality, main outcomes and safety data.

A selection of specific aspects may be compiled from the following list:

- Monitoring evidence for treatment differences in the main efficacy outcome measures.
- Monitor evidence for treatment harm (e.g. unexpected serious ADRs, superinfections, duration of ventilation, reintubation rates, duration of ICU and hospital stay).
- 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.
- Assess data quality, including completeness.
- Review recruitment figures and monitor losses to follow-up.
- Monitor compliance with the protocol by participants and investigators.
- Monitor compliance with previous DMC recommendations considering the ethical implications of any recommendations made by the DMC.

3. PRE TRIAL COMMENCEMENT OR EARLY IN THE TRIAL

DMC input into the protocol

All potential DMC members will have sight of the protocol before finalising their agreeing to join the committee. Before recruitment begins the trial will have undergone review by a research ethics committee. 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 Study Management Committee (SMC) 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.

DMC first meeting

The DMC will meet early in the course of the trial to discuss the protocol, the trial progress, any analysis plan, future meetings, and to have the opportunity to clarify any aspects with the Study Management Committee (SMC). The DMC should meet within 6 months of recruitment commencing.

An initial “dummy” report, including tables, to familiarise the DMC members with the format that will be used in the reports. The DMC will review the “dummy” report at the first meeting and confirm the final format of the report to be provided at subsequent meetings. Alterations to the report can be made at subsequent meetings to reflect the requirements of the DMC.

Issues specific to the disease under study

In accordance with the Protocol, the DMC has the responsibility for deciding whether, while randomisation is in progress, the un-blinded results (or the un-blinded results for a particular subgroup), should be revealed to the SMC.

Stopping rules

The DMC will reveal the un-blinded results to the SMC if, taking into account both statistical and clinical issues and exercising their best clinical and statistical judgement, the un-blinded results provide sufficient evidence that the trial treatment is on balance beneficial or harmful for all, or for a particular category of patients. Stopping rules will be based on the following:

- A responsibility to inform investigators if at any time the randomised comparisons provided evidence "beyond reasonable doubt" of a difference between randomised groups in total (all causes) mortality
- OR evidence that is likely to lead many clinicians conversant with the available evidence to change their practice with regard to the choice to use or not to use steroids.
- A three standard deviation difference in mortality (p-value < 0.00135) would constitute such evidence, unless the Data Monitoring Committee should itself decide in the circumstances of the trial that other evidence constitutes evidence beyond reasonable doubt.
- Additionally, while the primary focus of the committee should be on all cause mortality, this would not preclude the committee recommending termination of the study (or some modification to its design) if there emerged evidence of an important difference in some other major outcome (such as cause specific mortality).

Specific regulatory issues

All serious adverse drug reactions (expected and unexpected) are reported to the Trial Coordinating Centre (TCC). The TCC will provide all safety reports to the DMC for their consideration as part of their safety assessment.

Other issues specific to the treatment under study

The DMC will also consider information from other clinical trials of the same or similar compound and should be provided with any such information by the TCC.

DMC membership and their obligations

Members of a DMC are required to:

- Confirm their agreement to take on the responsibilities of membership as outlined in this Charter
- Agree to maintain the confidentiality of the data provided and the deliberations of the Committee
- Have no conflict of interest which will prejudice their role as a DMC member

By agreeing to adopt this Charter, all members confirm the above.

4. COMPOSITION

Membership and size of the DMC

Membership is international and includes previous expertise in trials of investigational medicinal products, the clinical setting of critical care medicine and previous DMC membership.

The members of the DMC for this trial are:

Dr Duncan Young (Chair)

Director of Research, UK Intensive Care Society
Consultant, Intensive care Medicine and Anaesthetics, John Radcliffe Hospital, Oxford, UK
Clinical Director for Critical Care Services at the Oxford Radcliffe Hospitals NHS Trust

Professor Ian Roberts
Director, Clinical trials unit.
Professor of Epidemiology and Public Health
London school of Hygiene & Tropical Medicine, Nutrition and Public Health
Intervention Research Unit, Keppel St, London WC1E 7HT, UK

Professor John Marshall
Director of Research
Critical Care Medicine,
St Michael's Hospital, 30 Bond St Toronto, Ontario M5B 1W8, Canada

Selection of the Chair

The Chair should have previous experience of serving on a DMC and experience of chairing meetings, and should be able to facilitate and summarise the DMC discussions. The Chair is expected to facilitate and summarise discussions.

The responsibilities of the DMC statistician

An independent statistician (i.e. independent of the trial team), Laurent Billot or designee from TGI is responsible for producing the report to the DMC. This is to ensure all trial related staff remain blind to the interim analysis. Laurent Billot will prepare the reports in accordance with the DMC reporting requirements and disseminate the required reports in a timely fashion to the DMC members. Laurent Billot may participate in DMC meetings if required for the purpose of guiding the DMC through the reports. DMC discussions will remain confidential and will not be communicated to the TCC

The responsibilities of the Chief Investigator (CI), other members of the TCC, members of the SMC

The CI is Prof Bala Venkatesh. He will be available to attend open sessions of the DMC meeting. Other TCC members may attend open sessions when necessary.

The ADRENAL Project Manager will provide inputs to the production of the non-confidential sections of the DMC report. The TCC are all George Institute (GI) employees and are comprised of:

Dorrilyn Rajbhandari
Project Manager with overall study responsibility

Meg Harward
Clinical Research Associate with responsibility for Queensland, Northern Territory and South Australian sites

Kelly Thompson
Clinical Research Associate with responsibilities for New Zealand, Western Australia, New South Wales, International sites and safety reporting

Ann Gould
Clinical Research Associate with responsibility for New South Wales, Tasmania and Victorian sites

The Study Management Committee is comprised of:

Bala Venkatesh	Chief Investigator, Principal Investigator (PI) Princess Alexandra & Wesley Hospitals, QLD

John Myburgh	PI St George's Hospital, NSW
Simon Finfer	PI Royal North Shore Hospital, NSW
Steve Webb	Chair ANZICS Clinical Trials Group
Jeremy Cohen	PI Royal Brisbane & Women's Hospital, QLD
Rinaldo Bellomo	PI Austin Hospital, VIC
Chris Joyce	PI Princess Alexandra Hospital, QLD
Colin McArthur	PI Auckland City Hospital, New Zealand
Dorrilyn Rajbhandari	Project Manager, Critical Care & Trauma Division, GI
Meg Harward	Clinical Research Associate, Critical Care & Trauma Division, GI
Parisa Glass	Deputy Director, Critical Care & Trauma Division, GI

5. RELATIONSHIP

Clarification of whether the DMC are advisory or executive

The DMC does not make decisions about the trial, but rather makes recommendations to the SMC.

Payments to DMC members

Members will be reimbursed for any travel and accommodation for DMC duties. All claims will be made to the TCC. The cost of telephone conferences will be the responsibility of the TCC.

The need for DMC members to disclose information about any competing interests

All competing interests should be disclosed prior to agreeing this Charter. 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 helps to enhance credibility.

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

Expected frequency of DMC meetings

The DMC will determine the frequency of their meeting. A minimum of one interim analysis will be performed after 1900 patients have been recruited and reached the 90 day follow up period.

Whether meetings will be face-to-face or by teleconference

The DMC will decide on the type of meeting required (face-to-face and/or teleconference). The TCC will make arrangements accordingly.

How DMC meetings will be organised - regarding open and closed sessions, including who will be present in each session

Only DMC members and others whom they specifically invite (e.g. independent Statistician) are present in closed sessions.

In open sessions, all those attending the closed session are joined by the CI and/or the other TCC/SMC members as required.

The format of the meetings will be as follows:

- Open session: Introduction and any "open" parts of the report
- Closed session: DMC discussion of "closed" parts of the report and, if necessary,
- Open session (if required by DMC): to address further questions to the CI/SPM.

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

Intended content of material to be available in open sessions

Open sessions: Accumulating information relating to recruitment and data quality (e.g. data return rates, treatment compliance) will be presented.

Intended content of material to be available in closed sessions

Closed sessions: In addition to all the material available in the open session, the closed session material will include safety and efficacy data by treatment group.

Will the DMC be blinded to the treatment allocation?

The DMC will be provided with full un-blinded data by Laurent Billot.

Who will see the accumulating data and interim analysis?

DMC members do not have the right to share confidential information with anyone outside the DMC, including the CI, TCC or SMC.

To whom the DMC will communicate the decisions / recommendations that are reached

The DMC will report its recommendations in writing to the SMC. This should be copied to the CI and, if possible, sent in time for consideration at a SMC meeting. If the trial is to continue largely unchanged the DMC may be asked to include a summary paragraph suitable for HREC reporting.

Whether reports to the DMC will be available before the meeting or only during the meeting

The DMC will receive all documents and reports for consideration at least 1 week before any meetings unless urgency prevails. Newest reports will be circulated by Laurent Billot before each meeting.

What will happen to the confidential papers after the meeting?

The DMC members must ensure the safety and confidentiality of unblinded data reports after each meeting. If in doubt, these may be destroyed and copies subsequently requested from the Independent Statistician with the newest report.

8. DECISION MAKING

What decisions / recommendations will be open to the DMC?

Possible recommendations could include:

- No action needed, trial continues as planned.
- Stopping recruitment within a subgroup or for the whole trial.
- 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.

How decisions or recommendations will be reached within the DMC

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 SMC as these may inappropriately convey information about the state of the trial data.

It is important that the implications (e.g. ethical, statistical, practical, regulatory) 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.

When the DMC is quorate for decision-making

Effort should be made for all members to attend. The TCC will try to ensure that a date is chosen to enable this. Members who cannot attend in person at face-to-face meetings can attend by teleconference. If, at short notice, any DMC members cannot attend at all then the DMC may still meet if the Chair and one other member is present. If the DMC is considering recommending major action after such a meeting the DMC Chair should talk with the absent member as soon after the meeting as possible to check they agree. If they do not, a further teleconference should be arranged with the full DMC.

Can DMC members who cannot attend the meeting input?

If the report is circulated before the meeting, DMC members who will not be able to attend the meeting may pass comments to the DMC Chair for consideration during the discussions.

Whether different weight will be given to different endpoints (e.g. safety/efficacy)

The DMC will reveal the un-blinded results to the SMC if, taking into account both statistical and clinical issues and exercising their best clinical and statistical judgement, the un-blinded results provide compelling evidence that the trial treatment is on balance beneficial or harmful for all, or for a particular category of patients.

The DMC terms of reference state that they will do this if, and only if, two conditions are satisfied: (1) the 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 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.

9. REPORTING

DMC reporting of their recommendations / decisions

This will be a letter sent to the CI within 3 weeks of the meeting. A copy of the letter should be sent to the TCC for the Trial Master File.

Disagreement between the DMC and the body to which it reports

If the DMC has serious problems or concerns with the SMC's decision, 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.

10. POST TRIAL

Publication of results

The SMC undertakes to publish the primary results within 1 year of the end of trial. The SMC will provide draft reports on these results to the DMC for their consideration prior to submission. The DMC may provide comments to the SMC on the draft reports, and give advice about data interpretation.

The information about the DMC included in published trial reports

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 may be included if appropriate in the body of this paper.

Any constraints on DMC members divulging information about their deliberations after the trial has been published

The DMC may discuss issues from their involvement in the trial 12 months after the primary trial results have been published. If a DMC needs to discuss their involvement any earlier, permission is required from the SMC.

This Charter was agreed by all members of the DMC:

Name	Agreement (signature)	Date
Professor Duncan Young		
Ian Roberts		
John Marshall		