Trial Title: Real Time Continuous Glucose Monitoring in Neonatal Intensive Care (RCT)

Trial Sponsor: Cambridge University Hospitals NHS Foundation Trust & University of Cambridge

Independent Data Monitoring Ethics Committee DMEC Charter

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(Developed from DAMOCLES DMEC Charter Template v1. February 2005)

Authorised by:

Name: Dr Kathryn Beardsall | Role: Chief Investigator

Signature: | Date: 10 March 2015

Prepared by:

Name: Catherine Guy | Role: Trial coordinator

Signature: | Date: 10 March 2015

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1. INTRODUCTION	
Name of trial	Real Time Continuous Glucose Monitoring in Neonatal Intensive Care (REACT RCT)
Sponsor name	Cambridge University Hospitals NHS Foundation Trust and University of Cambridge
Objectives of trial, including interventions being investigated	Randomised Controlled Trial 200 babies will be randomised 1:1 ratio between 1. Real time continuous glucose monitoring (rCGM) with paper based algorithm (Intervention) and 2. Standard clinical management with continuous glucose monitoring data blinded to the clinical team (Control) Purpose To evaluate efficacy, safety and utility of real time continuous glucose monitoring (rCGM) in Neonatal Intensive Care (NICU) Primary Objective ▪ To evaluate the efficacy of rCGM in helping control levels of glucose in the preterm infant ▪ To evaluate clinical acceptability in the preterm infant ▪ To assess safety in terms of risk for hypoglycaemia in the preterm infant Secondary Objective ▪ To evaluate the cost-effectiveness and NHS importance of such an intervention
Outline of scope of charter	The purpose of this document is to describe the membership, terms of reference, roles, responsibilities, authority and decision-making of the independent DMEC for the REACT RCT, including the timing of meetings, methods of providing information to and from the DMEC, frequency and format of meetings, statistical issues and relationships with other committees.

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2. ROLES AND RESPONSIBILITIES	
A broad statement of the aims of the committee	To protect and serve REACT Trial patients (especially re: safety) and to assist and advise Chief Investigator and Trial Management Group (TMG) so as to protect the validity and credibility of the REACT Trial. To safeguard the interests of REACT Trial participants, assess the safety and efficacy of the interventions during the trial, and monitor the overall conduct of the REACT Trial.
Terms of reference	The DMEC should receive and review the progress and accruing data of the REACT Trial and provide advice on the conduct of the trial to the Trial Steering Committee (TSC). The DMEC should inform the Chair of the TSC 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 one trial arm, or a subset of trial population, is clearly indicated or contraindicated, and there was a reasonable expectation that this new evidence would materially influence patient management
Specific roles of DMEC	Interim review of the trial's progress including updated figures on recruitment, data quality, and main endpoints including safety data. • assess data quality, including completeness • monitor recruitment figures and losses to follow-up • monitor evidence for treatment differences in the main efficacy endpoints • monitor evidence for treatment harm (eg Serious Adverse Device Effects (SADEs), Adverse Device Effects (ADEs), Serious Adverse Events • review the report of suspected unexpected serious adverse reaction (SUSAR) and Unexpected Serious Adverse Device Effects (USADEs) provided by the trial team whenever occurs • decide whether to recommend that the trial continues to recruit participants or whether recruitment should be terminated • suggest additional data analyses • advise on protocol modifications suggested by the TMG • monitor continuing appropriateness of patient information • monitor compliance with previous DMEC recommendations

CONTENT	CHARTER DETAILS
	• consider the ethical implications of any recommendations made by the DMEC • assess the impact and relevance of external evidence • maintain confidentiality of all trial information that is not in the public domain • protect validity and scientific credibility of the trial
3. BACKGROUND	
Protocol Input	All potential DMEC members should have sight of the protocol/outline before agreeing to join the committee. Before recruitment begins the trial will have undergone review by the funder/sponsor (e.g. a research ethics committee and Medicines and Healthcare products Regulatory Agency (MHRA). Therefore, if a potential DMEC member has major reservations about the trial (eg the protocol or the logistics) they should report these to the CI or trial coordinating team and may decide not to accept the invitation to join. DMEC members should be independent and constructively critical of the ongoing trial, but also supportive of aims and methods of the trial.
Meeting prior to Trial starting	The DMEC will meet before the trial starts to discuss the protocol, the trial, any analysis plan, future meetings, and to have the opportunity to clarify any aspects with the CI(s) and coordinating team. The DMEC should meet within one year of recruitment commencing. A dummy report will be provided to the DMEC members prior to their first meeting after recruitment commences to enable them to become familiar with the format data will be presented.
Safety Issues	All hypoglycaemic episodes will be recorded and reported if BG ≤2.2mmols/l. In addition the CI will notify DMEC of all safety events (SUSARs, USADEs and SADEs) when they occur.
Regulatory issues	MHRA and UK ethics approval will need to be obtained prior to recruiting UK participants and regulatory and ethics approval will be obtained prior to recruiting from each country.
DMEC contracts	DMEC members will not formally sign a contract but should formally register their assent to join the group by confirming (1) that they agree to be on the DMEC and (2) that they agree with the contents of this Charter. Any competing interests should be declared at the same time. Members should complete and return the form in Annexe 1. Observers attending any part of the meeting should sign a confidentiality agreement on the first occasion they attend all or part of a meeting (Annexe 2).

CONTENT	CHARTER DETAILS
4. COMPOSITION	
DMEC Membership	Membership should consist of a small number of members, who include at least one clinician experienced in the clinical area and at least one statistician. Additional members experienced in clinical trials should reflect the other specialities involved in the trial. The members should not be involved with the trial in any other way or have some competing interest that could impact on the trial. Any competing interests, both real and potential, should be declared. Although members may well be able to act objectively despite such connections, complete disclosure enhances credibility. A short competing interest form should be completed and returned by the DMEC members to the trial coordinating team (Annexe 1). **The independent members of the DMEC for this trial are:** • Professor David Field - Professor of Neonatal Medicine - University of Leicester • Professor Diana Elbourne - Professor of Health Care Evaluation - London School of Hygiene and Tropical Medicine • Dr Jane Hawdon - Consultant Neonatologist - Barts Health NHS Trust
The Chair and the Chair's role	Professor David Field has agreed to be the Chair and is an internationally respected and experienced neonatologist with a breadth and depth of experience of serving on Clinical Trial DMECs.
The responsibilities of the DMEC statistician	Professor Diana Elbourne is the DMEC statistician who will provide independent statistical expertise. **Trial Statistician for this trial is:** • Dr Simon Bond - Senior Trial Statistician
The responsibilities of the trial statistician	The trial statistician will have the overall responsibility for producing the report to the DMEC and will participate in DMEC meetings, guiding the DMEC through the report, participating in DMEC discussions and, on some occasions, taking notes.
The responsibilities of the trial coordinating team	The trial coordinator/or project manager of trial will help the trial statistician to produce the non-confidential sections of the DMEC report. The trial coordinator/or project manager may attend open sessions of the meeting.
The responsibilities of the CI and other members of the TMG	The CI may be asked, and should be available, to attend open sessions of the DMEC meeting. The other TMG members will not usually be expected to attend but can attend open sessions when necessary (See Section 6. Organisation of DMEC Meetings).

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5. RELATIONSHIPS	
Relationships with CI(s), other trial committees (TSC, TMG), sponsor and regulatory bodies	The DMEC will report directly to the TSC and submit regular reports to the TSC Chair. The DMEC will have access to data by trial arm and be responsible for monitoring these data and making recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue. The DMEC will be responsible for providing recommendations to the TSC regarding early termination of the trial for safety but decisions regarding early termination lie with the TSC.
Clarification of whether the DMEC are advisory (make recommendations) or executive (make decisions)	The TSC is oversight body of the trial and is delegated this role by the sponsor. The DMEC does not make decisions about the trial, but rather makes recommendations to the TSC.
Payments to DMEC members	Members will be reimbursed for travel and accommodation where required. No other payments or rewards are given. DMEC members should not use interim results to inform trading in pharmaceutical shares, shares in companies making and marketing devices and careful consideration should be given to trading in stock of companies with competing products.
6. ORGANISATION OF DMEC MEETINGS	
Expected frequency of DMEC meetings	DMEC will review safety on a patient number basis and plans to meet following recruitment of the first 50 patients and then again following recruitment of a total of 125 patients. However, the exact frequency of meetings will depend on trial events. The wishes of the DMEC and needs of the trial coordinating team will be considered when planning each meeting. An unplanned DMEC meeting may be called by the Chair or requested by the TMG if there is an emergency concern on the safety of participants.
Meeting Format	The first meeting should ideally be face-to-face to facilitate full discussion and allow members to get to know each other. It is recommended that all subsequent meetings should be face-to-face if possible, with teleconference as a second option.
Organization of Meeting	The format of the REACT DMEC meetings will be:

CONTENT	CHARTER DETAILS
	1. Open session: Introduction and any "open" parts of the report that need to be discussed between DMEC and CI or other members of the trial coordinating team and if necessary representatives of the sponsor, funder or regulator. 2. Closed session: Discussion of "closed" parts of the report by DMEC and Trial Statistician if requested or others specifically invited by DMEC
7. TRIAL DOCUMENTATION AND PROCEDURES TO ENSURE CONFIDENTIALITY AND PROPER COMMUNICATION	
Content of material to be available in open sessions	Open sessions: Accumulating information relating to recruitment and data quality including data return rates will be presented. Safety event details and compliance of using paper based algorithm will be presented.
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 efficacy and safety data by treatment group.
Blinding to treatment allocation	The DMEC will not be blinded to the treatment allocation.
The people who will see the accumulating data and interim analysis	The confidential accumulating data and interim analysis by treatment allocation will be seen by the DMEC members and the trial statistician(s). DMEC members do **not** have the right to share confidential information with anyone outside the DMEC, including the CI.
Responsibility for identifying and circulating external evidence (eg from other trials/ systematic reviews)	The CI, TMG and the trial coordinating team will collate any such information for the presentation in an open session. Other Trial DMECs may pass information to REACT DMEC for consideration.
To whom the DMEC will communicate the decisions/ recommendations that are reached	The DMEC will report its recommendations in writing to the TSC. This will be copied to the trial statistician (or trial coordinator) and if possible, should be sent via the trial statistician and trial coordinator in time for consideration at a TSC meeting. If the trial is to continue the report will be sent to the TSC from the DMEC to include a summary paragraph suitable for trial promotion purposes. (See Annexe 3.) In its communications, the DMEC should be careful not to relay any unnecessary information to the TSC: the TSC membership might have members of TMG. The DMEC should take care to protect the CI from interim trial results where possible.
Timing of Reports	The DMEC will receive the trial report at least 2 weeks before any meetings.

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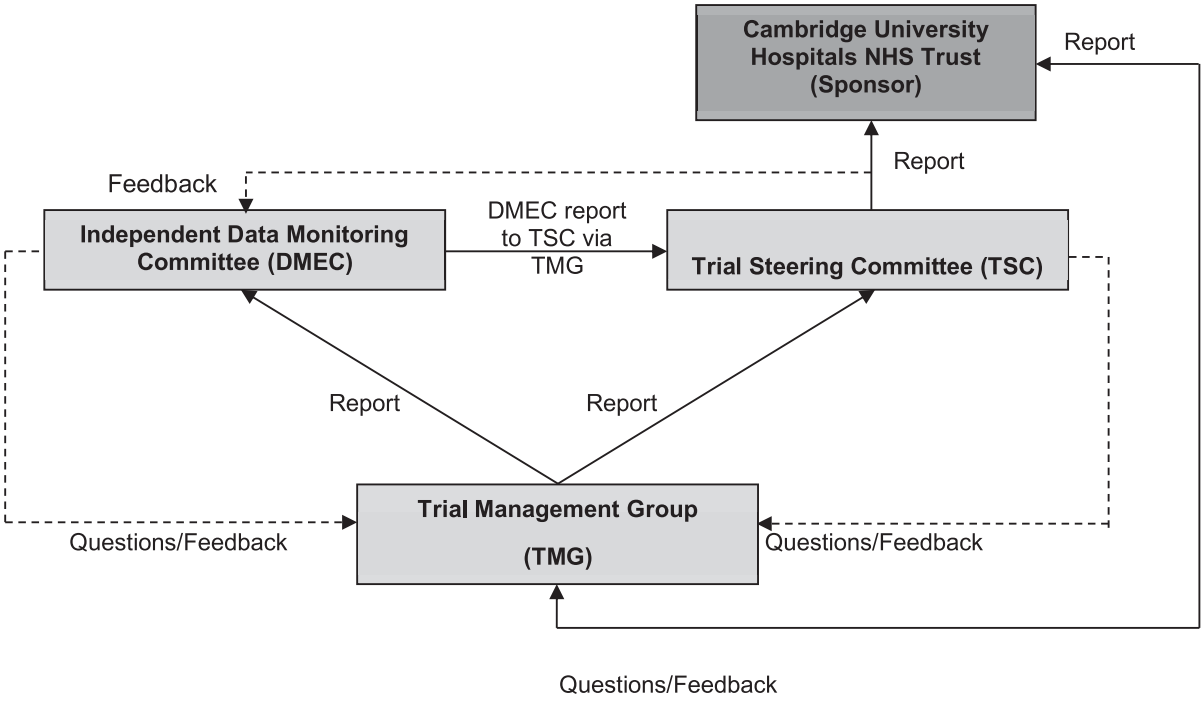
What will happen to the confidential papers after the meeting	The DMEC members should store the papers safely after each meeting so they may check the next report against them. After the trial is reported, the DMEC members should destroy all interim reports. A copy of all the reports will be held at the Cambridge Clinical Trials Unit.
8. DECISION MAKING	
What decisions/recommendations will be open to the DMEC	Possible recommendations could include: • No action needed, trial continues as planned • Early stopping for clear evidence of harm due to a treatment in terms of its safety profile, strong evidence in favour of either treatment in terms of the primary endpoint, or external evidence. • Extending recruitment or extending follow-up • Sanctioning and/or proposing protocol changes
The role of formal statistical methods	There is no planned interim analysis but DMEC will meet following recruitment of 50 participants. Formal statistical methods will be used as guidelines rather than absolute rules. This is because they generally only consider one dimension of the trial. Reasons should be recorded for disregarding a stopping guideline.
How decisions or recommendations will be reached within the DMEC	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. Every effort should be made for the DMEC to reach a unanimous decision. If the DMEC 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.
Members who cannot attend	If the report is circulated before the meeting, DMEC members who will not be able to attend the meeting may pass comments to the DMEC Chair for consideration during the discussions.
What happens to members who do not attend meetings	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 DMEC.
Whether different weight will be given to different endpoints (eg safety/efficacy)	The role of the DMEC will be to review safety.

CONTENT	CHARTER DETAILS
9. REPORTING	
To whom will the DMEC report their recommendations/ decisions, and in what form	The DMEC will write to the TSC and trial coordinator within 3 weeks. A copy of the DMEC recommendation will be stored in the trial master file.
The Chair will be responsible for organizing minutes to be taken and stored.	Minutes will be taken for open and closed sessions. The DMEC Chair should sign off any minutes or notes. Minutes from open sessions to be circulated to TMG.
What will be done if there is disagreement between the DMEC and the body to which it reports	If the DMEC has serious problems or concerns with the TSC decision a joint meeting of these groups should be held. The information to be shown would depend upon the action proposed and the DMEC's concerns. Depending on the reason for the disagreement confidential data will often have to be revealed to all those attending such a meeting. The meeting should be chaired in the first instance by the TSC Chair. If there remains a disagreement the sponsor will nominate an independent expert to chair the meeting.
10. AFTER THE TRIAL	
Publication of results	At the end of the trial there may be a meeting to allow the DMEC to discuss the final data with the key members of TMG and give advice about data interpretation
The information about the DMEC that will be included in published trial reports	DMEC members should be named and their affiliations listed in the main report, unless they explicitly request otherwise. A brief summary of the timings and conclusions of DMEC meetings should be included in the body of this paper.
Whether the DMEC will have the opportunity to approve publications, especially with respect to reporting of any DMEC recommendation regarding termination of a trial	The DMEC will be given the opportunity to read and comment on publications before submission. This will usually be concurrent with the trial investigators and independent members of the TSC reading and commenting. The commenting period will usually be 2 to 3 weeks.
Any constraints on DMEC members divulging information about their deliberations after the trial has been published	The DMEC may discuss issues from their involvement in the trial when permission is agreed with the overseeing TSC.

Figures

Relationship between TMG, DMEC and TSC



Annexe 1: Agreement and potential competing interests form

Real Time Continuous Glucose Monitoring in the Neonatal Intensive Care

Please complete the following document and return to the REACT RCT Co-ordinator.

(Please initial box to agree)

	I have read and understood the DMEC Charter version 1.0, dated 10 March 2015
	I agree to join the DMEC for this trial
	I agree to treat all sensitive trial data and discussions confidentially

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

Possible competing interest should be disclosed via the Cambridge Clinical Trials Unit – Paediatric Theme (CCTU-PT). In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) DMEC member should remove the conflict or stop participating in the DMEC. Table 1 lists potential competing interests.

	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: _____

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 (including Chief Investigator for other Cambridge Clinical Trials Unit – Cancer Theme trials)
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) or career tied up in competing products
Involvement in the publication in the form of authorship

Annexe 2: Agreement and confidentiality agreement for observers

Real Time Continuous Glucose Monitoring in Neonatal Intensive Care

Please complete the following document and return to the Trial Co-ordinator.

(Please initial box to agree)

	I have received a copy of the DMEC Charter version 1.0, dated 10 March 2015
	I agree to attend the DMEC meeting on ___/____/_____
	I agree to treat as confidential any sensitive trial information gained during this meeting unless explicitly permitted

Name: _____

Signed: _____ Date: _____

Annexe 3: Suggested report from DMEC to TSC where no recommendations are being made

[Insert date]

To: Professor Kate Costeloe

Via: Trial statistician

Dear Professor Costeloe

The Data Monitoring Ethics Committee (DMEC) for the REACT (RCT) met on *[meeting date]* to review its progress and interim accumulating data. *[List members] attended* the meeting and reviewed the report.

The DMEC should like to congratulate the investigators and trial team on the running of the trial and its recruitment, data quality and follow-up. 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,

Professor David Field

On behalf of the DMEC

DMEC members:

Professor David Field

Professor Diana Elbourne

Dr Jane Hawdon

Annexe 4: REACT RCT Contacts

REACT (RCT) TMG contacts

Chief Investigator:

Dr Kathryn Beardsall

[redacted]

Trial Co-ordinator:

Catherine Guy

[redacted]

Trial Statistician

Dr Simon Bond

[redacted]

REACT (RCT) TSC Independent Chair Contacts

Professor Kate Costeloe