Associated Document 1: Further guidance for Trial Committees

Contents

Independent:

The Chair should not be an employee of Barts Health or Queen Mary. They should not be named on any funding application associated with the study and should not have been involved in the study design or study planning stages. They should not be colleagues or close research collaborators of the trial team. See guidance for more

Independent (in relation to the statistician for TSC and DMC):

For selected studies, it may be considered acceptable for the independent statistician to be an employee of Queen Mary or Barts Health, but they should not be directly related or involved with the study design or funding application, the day to day running of the study, or its final analysis, and so cannot be the named study statistician. It is acceptable to contract a suitably qualified statistician to perform this role.

Charter:

A document which describes the role and function of the committee. The charter (also referred to as the "Terms of Reference") should also cover the committee's membership and quorum, how often it meets, how decisions are reached and whether they are "advisory" (which is the norm) or "executive". The charter will make clear the need for confidentiality, the liability of the committee members, and the obligation to declare any conflicts of interests. The members of the committee will formally register their assent by confirming that they agree to be on the committee, and that they agree with the contents of the charter.

Trial Steering Committees (TSC)

The role of the TSC is to provide overall supervision of the study on behalf of the study Sponsor and study funder and to ensure that the study is conducted in accordance with the principles of GCP and relevant regulations. The CI is responsible for convening an appropriate TSC. The CI is also responsible for liaising with the funding body to ascertain whether they require a TSC or have committee guidance as a funding condition.

Composition:

The TSC will normally be limited to:

- An independent chair (mandatory).
- At least two other independent members, usually representing clinical areas under study.
- One or two Principal or Co-investigators.
- Two service / patient representatives (where possible).
- Independent statistician (where possible and deemed necessary).
- A sponsor representative
- Where required, a funder's representative

Study Statisticians, Data Manager, Study Manager etc. should attend TSC meetings as appropriate.

Document the TSC membership in the protocol

Prior to commencement of study

- Meet and agree roles and responsibilities. This meeting may be held jointly with the DMC.
- Review and agree the final study protocol before regulatory submission.
- Agree an appropriate timescale for meetings, at least annually.
- Agree the minimum quoracy for meeting to conduct business (See the *Damocles Charter* for more details).
- Agree data that should be presented at each meeting.
- Create and agree a committee charter.

During the study

The TSC will meet according to its charter (at least annually) in order to:

- Monitor the progress of the study.
- Monitor adherence to protocol.
- Review available information relating to patient safety.

- Consider new information of relevance from other sources.
- Make executive decisions about the study as suggested by the TMG (e.g. protocol amendments where practical).
- Consider and act on the recommendations of the DMC, Research Ethics Committee and competent authority (Medicines and Healthcare Regulatory Agency (MHRA)) as appropriate, including the termination the study.

If the TSC charter identifies a need for statistical reports to be prepared in order to advise the committee, it is the CI's responsibility to ensure the TSC receives this information. It is the responsibility of the statistician named on the protocol to advise the CI on data to be presented at the TSC meetings and appropriate timescales, so that there is sufficient time to check the data and carry out the analysis before circulation to the committee.

Data Monitoring Committee:

An Independent Data Monitoring Committee (DMC) -group also referred to as Data Monitoring and Ethics Committee (DMEC), Data Safety and Monitoring Committee (DSMC), or Data Safety and Monitoring Board (DSMB) - is a group of experts independent of the study team who review accumulating data from an on-going clinical trial. Definitions of what constitutes independence vary, but members should not be hold a position where they could be seen to be exposed to undue influence of the trial team. The broad remit of a DMC is to safeguard the interests of the study participants, as well as future patients whose care may be influenced by the trial findings. The DMC will monitor the safety and the treatment efficacy of the interventions during the study. The DMC is not necessary for all studies, it is the TSC decision. may also assess other aspects of a clinical trial such as efficacy, study integrity, design aspects, recruitment and some ethical considerations (such as early analysis and publication). In general a DMC is required when a trial is randomised, and the trial team should not access data which gives any insight into the potential findings until the trial is complete. In addition to providing independent advice on safety and efficacy, the DMC ensures the blinding of the research team to the interim trial findings. Rather than making decisions, the DMC makes recommendations to the Trial Steering Committee, which may include recommending the termination of a study for safety reasons, due to evidence of the studies futility, or the studies overwhelming statically proven benefit. The DMC usually includes at least one clinician with relevant expertise and at least one statistician.

The role of the DMC is to review unblinded accruing study data, and is the only body that has access to unblinded data. The DMC may also be asked by the TSC, Study Sponsor or Study Funder to consider data emerging from other studies. The DMC should advise the TSC. The DMC should be independent of the investigators and the funder / sponsor.

The CI is responsible for liaising with the funding body to establish if they require a DMC as a condition of funding (or have guidance on such committees), and where appropriate liaising with the study statistician and / or sponsor to determine the need for a DMC. Where it is necessary or appropriate for the study to have a DMC, the CI is responsible for identifying appropriate members. The membership of a DMC, or a justification of why a DMC has not been formed, should be documented in the protocol.

Composition

- Small, usually 3-4 members, all independent.
- At least one clinician experienced in the clinical area.
- At least one expert study statistician.
- A chair with previous experience of serving on DMCs.
- All members should be independent of the investigators, funder / sponsor, the host institution and the TSC.

Prior to commencement of the study

- Meet and agree a DMC charter. This meeting may be held jointly with the TSC.
- Review study protocol.
- Determine a schedule of meetings at least annually and timed so that reports can feed into TSC meetings.
- Agree the minimum quoracy for meetings to conduct business (see the *DAMOCLES Charter* for more details).

- Agree a DMC charter specific to the study (see *Associated Document 2: Sample DMC Charter Template*).
- Provide the study team with details of any potential conflicts of interest for each committee member (or confirmation that no such conflicts exist) and a copy of their CV and evidence of GCP training.

During the study

The DMC will meet regularly in accordance with the agreed protocol and charter. It is the responsibility of the CI / delegated study staff to provide DMC with a comprehensive report for each meeting as agreed in the DMC charter. It is the responsibility of the statistician named on the protocol to advise the CI on data to be presented at the DMC meetings and appropriate timescales, so that there is sufficient time to check the data and carry out the analysis before circulation to the committee. The DMC will review the studies progress which may be through the following information:

- Review whether there are any safety concerns on one or more treatment arms (by considering e.g. toxicity data, Serious Adverse Event (SAE)/ Suspected Unexpected Serious Adverse Reaction (SUSAR), deaths), or any ethical reasons why the study should not continue.
- View whether the data shows significant benefit on one or more treatment arms.
- Whether there is evidence that, should the study continue, it would fail to show clear benefit on any treatment arm.
- Suggest any additional data analyses (using unblinded data where necessary) where it is relevant to advising whether the study should continue or be terminated early.
- Monitor the sample size (including recruitment targets and losses to follow-up) and make recommendations.
- Advise on substantial protocol amendments that may impact upon data or safety, such as changing the primary end points.
- Consider any new information relevant to the study, including reports from TSC and any related external research.
- Make recommendations to the TSC and / or TMG whether to continue, modify or stop the study.

Additional considerations

- In conjunction with the Study Manager / Coordinator, the DMC chair may prepare reports for the TSC and open reports for the DMC, in accordance with the agreed charter or terms of reference.
- The DMC may arrange for any interim statistical analysis to be carried out by a statistician independent of the study and assist as appropriate.
- If an unblinded interim statistical analysis is required by the DMC this should be undertaken by a qualified statistician independent of the study. There are various ways that this can be arranged; it is acceptable for this person to be an independent statistician within the sponsor's organisation.
- It is the responsibility of the CI to arrange regular meetings of the DMC and it is the Chair's responsibility to retain copies of the minutes for future reference.
- Copies of open DMC minutes should be filed in the TMF and the Statistical Master File along with a note of who holds the closed report and minutes.

- It is the responsibility of the CI to circulate copies of the minutes to the sponsor (JRMO) and to the funder if required.

Format of the DMC meeting

The format of the DMC meeting may have two parts:

1. **Open DMC session** which all TMG members (blinded and unblinded) may attend to review general study progress and pooled data.
2. **Closed DMC sessions** to review unblinded results (see *Associated Document 1: Sample DMC Charter Template*). During the closed session, blinded members (e.g. investigators) cannot be present.

Attendance of the CI or co-investigators at the open session of the DMC meetings should only be at the invitation of the DMC Chair.

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Trial Management Group (TMG)

The role of the TMG is to deliver the study and monitor all aspects of the conduct and progress of the study, and to ensure that the protocol is adhered to and that appropriate action is taken to safeguard participants and the quality of the study itself. The TMG should meet as frequently as is required by the progress of the study, and as determined by the members of the group.

The TMG should:

- Ensure the protocol is adhered to and take action as necessary to remedy any difficulties.
- Consider and act on the recommendations of the TSC and DMC, Health Research Authority (HRA), Research Ethics Committee (REC) and competent authority (MHRA) as appropriate.
- Consult co-investigators prior to protocol amendments in a timely and efficient manner.
- Refer any possible protocol amendments to the TSC.

It is the CI and TMG groups' responsibility to inform the sponsor (and where applicable the funder) of decisions made by the TSC or DMC. See *SOP 47 Template 1: Trial Management Group Remit* for further guidance.

References, Related External SOPs, Web links

With thanks and acknowledgements to:

- Pragmatic Clinical Trials Unit SOP on trial committees
- Barts Clinical Trials Unit SOP on trial committees
- Centre for Experimental Cancer Medicine SOP on trial committees
- Committee for medicinal products for human use (CHMP), Guideline on data monitoring committees, July 2005
- ICH Topic E6 (R2) Guideline for Good Clinical Practice, 14 June 2017. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002874.pdf
- ISO 14155:2020 Clinical investigation of medical devices for human subjects — Good clinical practice
- DAMOCLES study group. A proposed charter for clinical trial data monitoring committees: helping them to do their job well. Lancet, 2005. 365: 711-22.
- Clinical Trials Toolkit: http://www.ct-toolkit.ac.uk/glossary

Medical Research Council. MRC Guidelines for Good Clinical Practice in Clinical Trials 1998. Available from: http://www.mrc.ac.uk/documents/pdf/good-clinical-practice-in-clinical-trials/