UNIVERSITY OF LEEDS / NHS The Leeds Teaching Hospitals NHS Trust Standard Operating Procedure	Title	**Researchers Guide to Trial Steering Committees and Data Monitoring Committees**				
	Scope	Describes the requirements, set up, structure and duties of a Trial Steering Committee and a Data Monitoring Committees				
	Version	**2.0**	Date	**03/06/2020**	SOP ID	**QCRES_10**

Details:

Original author:	Clare Skinner - Head of Research Integrity and Governance
Last reviewed by:	Elizabeth Taylor - QA Clinical Trial Monitor
Version no. of replaced SOP:	1.0
Effective date of replaced SOP:	18/04/2018

Approval:

Version no. of SOP	Name of person approving this SOP	Date	Signature of the person approving this SOP
2.0	Stephanie Britt *QA Manager (Clinical Trials)* UoL / LTHT Joint Sponsor QA Office (CTIMPS) University of Leeds / Leeds Teaching Hospitals NHS Trust	12/06/2020	
	Clare Skinner, *Head of Research Integrity and Governance* Secretariat University of Leeds	19/06/2020	

Distribution & Storage:

Distribution to:

Investigators and all members of research teams conducting or assisting with a CTIMP trial sponsored by the University of Leeds or Leeds Teaching Hospital NHS Trust.

Location of document:

Paper: QA Department, Room 5, Research and Innovation Centre, St James' University Hospital

Electronic: http://www.leedsth.nhs.uk/research/information-for-researchers/key-documents
http://lthweb.leedsth.nhs.uk/sites/research-and-development/resources/Sponsored%20CTIMPs%20%28Quality%20Assurance%29

Contents

Please note: *This SOP should be used and followed in conjunction with other UoL / LTHT SOPs developed for researchers to support study set up and management. These can be found on the LTHT website or by contacting R&I / QA directly. For clinical trials where Leeds is not the trial Sponsor, please refer to any Sponsor SOPs for further information.*

Section A: Introduction

1.1 This Standard Operating Procedure (SOP) defines the requirements for Trial Steering Committees (TSC) and Data Monitoring and Ethics Committees (DMEC) for Leeds Teaching Hospitals NHS Trust (LTHT) / University of Leeds (UoL) sponsored Clinical Trial of an Investigational Medicinal Product (CTIMPs).

1.2 Arrangements for the management of trials will vary according to the nature of the trial, but all should include an element of expert advice that is entirely independent of the Chief Investigator (CI) / Principal Investigators (PI) and the host institution involved.

1.3 This will often take the form of a TSC and an Independent Data Monitoring and Ethics Committee (DMEC or DMC, DMC to be used hereafter).

1.4 A TSC and a DMC may not always be appropriate, but the arrangements for independent expert advice and the inclusion or exclusion of the use of a TSC/DMC must be detailed and justified in the trial risk assessment and protocol.

Section B: Applicability

1.1 This SOP is applicable to all members of staff working on CTIMPs sponsored by the UoL or LTHT (with the exception of those managed by a Clinical Trials Research Unit (CTRU or a Clinical Research Organisation (CRO)).

Section C: Researchers Guide to Trial Steering Committees and Data Monitoring and Ethics Committee.

1. What is a Trial Steering Committee?

1.1 The role of the TSC is to provide **overall supervision of the trial** to ensure the trial is conducted to rigorous standards (MHRA GCP Grey Guide, 7.2.1.2).

1.2 The TSC will concentrate on the progress of the trial, including adherence to the protocol, subject safety and considerations of new information. This can include a review of recommendations made by the DMC, if applicable.

1.3 The TSC will consider and act, as appropriate, on the recommendations of the DMC or equivalent, and ultimately carry the responsibility for deciding whether a trial needs to be stopped on grounds of safety or efficacy. For example, having reviewed the trial data, the DMC may recommend halting trials based on changes to the risk-benefit ratio. These circumstances may include unexpected rises in mortality and/or significant increases in the number of adverse events.

1.4 The role and function of a TSC are as follows:

- To provide advice, through its Chair, to the CI, Sponsor, Funder, Host Institution and any Contractors on all appropriate aspects of the trial.
- To monitor progress of the trial, adherence to the protocol, patient safety (where appropriate) and the consideration of new information of relevance to the research question.
- To protect the rights, safety and well-being of the participants.
- To ensure appropriate ethical and other approvals are obtained in line with the project plan.
- To agree proposals for substantial protocol amendments and provide advice to the sponsor and funder regarding approvals of such amendments.

2. When is a TSC required?

2.1 The need for a TSC will depend on the complexity of the trial and should be considered as part of the pre-trial risk assessment. For example, a risk assessment would be likely to identify that a TSC is not necessary for a very small, investigator initiated pilot trial of a topical product (MHRA GCP Guide, 7.1.1.2).

2.2 If a research team decide **not** to use a TSC, this decision **must be discussed with the sponsor and fully justified in the risk assessment and trial protocol** (please see '*CTT04A / CTT04B: Clinical Trial Risk Assessment (CTRA)'* forms for further information).

2.3 When assessing the need for a TSC consideration should be given to the following points:

- **Investigational Medicinal Product (IMP)**
  - The level of risk associated with the IMP
  - Is it a well-known authorised drug, commonly used and easily administered?
  - Consider the IMP licensing, dosing, availability and distribution.
- **Safety**
  - Consideration should be given to safety implications or unusual trial specific assessments being conducted that require additional review and may inform subsequent key decisions.

- **Size of Trial**
  - Single site or trials with a small number of sites are less likely to require a TSC, whereas multi-centre or multi-national trials are more likely to require a TSC to provide a greater level of oversight.
- **Complexity of Trial Protocol**
  - Where procedural aspects potentially add a level of risk or complexity that requires close monitoring, a TSC will always be needed.

3. Formation of a TSC

3.1 Where it has been decided that a TSC is required, formal procedures for its formation, remit and membership must be in place.

3.2 The arrangements must be described in a formal trial document such as the trial protocol or a TSC Terms of Reference (ToR).

3.3 The ToR document must clearly identify:

- The members of the TSC.
- The responsibilities of the TSC, including the key decisions it is responsible for.
- How meetings and decisions will be documented and to whom these outputs will be circulated.
- Who is responsible for maintaining the TSC documentation during the course of the trial and the requirement for it to be maintained as part of the Trial Master File (TMF).

3.4 The TSC should be made up of a small number of personnel directly involved in the trial and individuals who are independent of the trial (MHRA GCP Guide, 7.2.1.2).

3.5 The committee should have **an independent chair** (not involved directly in the trial other than as a member of the TSC), as well as representations from independent member(s), PI(s), the Trial's Co-Ordinator, Statisticians, and lay members.

3.6 It is appropriate and may be encouraged to invite the Sponsor Representative to the TSC meetings

3.7 Independent members may also be members of the public.

3.8 Members included as lay members (i.e. non-professional members of the TSC), can in a collaborative capacity be involved in the trial and unlike trial participants, do not require specific ethics approval (see www.invo.org.uk/resource-centre/publications-by-involve).

4. TSC meetings

4.1 The first meeting should be organised by the CI/ P I and take place **during trial set-up** to approve the final protocol. Subsequent meetings may be called by the CI/PI, or the Chair.

4.2 The trial protocol should be presented as an agenda item at the meeting and the TSC should review and approve any material changes to the protocol during the course of the trial.

4.3 If applicable, during or prior to the first meeting, the TSC members should review and agree the trial monitoring plan and based on this, agree the frequency of future meetings and content of future reports.

4.4 In addition, the TSC ratifies any existing decisions to have or not have a DMC and/or reviews the composition of the DMC.

4.5 If a DMC has not been setup, then the TSC should meet at least annually, however more frequent meetings can be called if necessary.

4.6 Ad-hoc meetings or consultation via phone / email can be used where specific issues arise and a face to face meeting cannot be convened within a reasonable timescale, however all discussion must be documented within the TMF.

4.7 Frequency of meetings must be specified in the trial protocol.

4.8 Meeting agendas and reports must be sent to Sponsor Quality Assurance (QA) for their information, with an accompanying email highlighting any particular issues requiring the Sponsor's attention.

5. What is a Data Monitoring Committee (DMC)?

5.1 A DMC is formed of a group of experts who review accumulating data from on-going trials (particularly in relation to safety and efficacy end points of the trial), advising the TSC or trial team of any important information. Examples could include highlighting potential safety issues that should be brought to the subject's attention or identifying reasons why the trial may not continue (MHRA GCP guide, 7.2.11).

5.2 The DMC reviews safety and efficacy data but may also see quality and compliance data.

5.3 The DMC is **completely independent** of the sponsor and typically consists of 3-5 members, one of which must be a statistician.

5.4 If a TSC has been setup, the DMC would normally report to them. If not, the DMC would directly report to the sponsor.

5.5 The role and function of a DMC is as follows:

- To monitor the unblinded data and make recommendations to the TSC or Sponsor QA on trial conduct.
- To advise, based on their monitoring of the data, if there is a need for a protocol amendment, or if safety concerns have been raised prompting a recommendation for early termination of the trial.
- The DMC may be asked by the TSC (if reporting to the TSC), to consider data from other related trials.

6. When is a DMC required? (See Appendix A)

6.1 A DMC is not required for all clinical trials. The need for a DMC depends on the complexity and end points of the trial, and therefore should be considered as part of the risk assessment during study set up (please see '*CTT04A / CTT04B: Clinical Trial Risk Assessment (CTRA)'*).

6.2 When deciding if a DMC is necessary, it is recommended that consideration be given to:

- **Safety Profile of the IMP**
  - Is there any significant potential risk of harm, or unknown or uncertain risks?
- **Size of the trial**
  - Multi-centre trials are more likely to need a DMC (overview of data from ALL sites should be given further consideration), compared to smaller, single-site studies.
- **Data requiring regular review and monitoring of trial end points**
  - It may be that the end point has been reached before the end of recruitment, thereby allowing for the trial to finish earlier than anticipated.
- **If the trial is a high risk**
  - For example, a potential for high morbidity or mortality, patients with life threatening illnesses or vulnerable populations.

7. Forming a DMC

7.1 Where it has been decided that a DMC is required, formalised procedures for its formation, remit and membership must be in place (MHRA GCP guide, 5.9).

7.2 Once agreed the arrangements must be described in a formal trial document such as the trial protocol or a DMC ToR. The document must clearly identify:

- The core members of the DMC.
- The responsibilities of the DMC, including the key decisions it has to make.
- How meetings and decisions will be documented and to whom these outputs will be circulated.

- How the communication between the DMC, Sponsor and the investigator teams and transfer of data to the committee (where applicable) is to be managed.
- The frequency of planned meetings (should be at least on an annual basis), and how the committee will meet for triggered meetings.
- How key decisions will be made. Are there to be any closed sessions and how will they be managed? What will the voting process be?
- How reports / meeting minutes are to be documented to ensure the safeguarding of blinded data. Will closed minutes be produced for the sponsor but open minutes for the DMC?
- How will decisions and recommendations made by the DMC be expedited and addressed in an appropriate manner?
- Who is responsible for maintaining the DMC documentation during the course of the trial and how it is maintained as part of the Trial Master File (in order to comply with Regulation 31A (4) of SI 2004/1031)?

8. DMC meetings:

8.1 Ideally, DMC meetings should be timed to ensure that all relevant information can be fed to the TSC for discussion.

8.2 In order to verify compliance, DMC meeting outputs and procedures followed must be clearly documented.

8.3 A clear audit trail and documentation must verify that the data used to make decisions are robust.

8.4 The documentation must also verify who prepared and checked any reports and listings for the DMC and when this was done. This is particularly important for unblinded reviews by the DMC during the course of the trial, ensuring trial team and investigator sites remain blinded.

9. Research Ethics Committee (REC) oversight of a DMC

9.1 The Research Ethics Committee (REC) receives only some interim data and is not responsible for assessing this data. The DMC therefore provides assurances to the REC because of its inclusion of expert members capable of in-depth monitoring of the data.

9.2 Via the REC application and trial protocol, the REC should be assured of the following:

- Whether a formal DMC is to be convened
- If a formal DMC **is not** to be convened, whether this is justified given the nature of the trial and the interim monitoring plans in place
- If a DMC **is** to be convened, whether it will be independent and what its role and function will be.

Section D: References

MHRA Good Clinical Practice Guide 2012

National Centre for Biotechnology Information Charters for Trial Steering and Data Monitoring Committees, 2014 (http://www.ncbi.nlm.nih.gov/books/NBK262226/**).**

CT Toolkit Glossary (NETSCC 2017) (http://www.ct-toolkit.ac.uk/glossary/?letter=T&postcategory=-1)

NIHR, 'Trial Steering Committees and Study Steering Committees' (2019). Available from: https://www.nihr.ac.uk/documents/research-governance-guidelines/12154

Section E: Acronyms

CI	Chief Investigator
CRO	Contract Research Organisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTRU	Clinical Trial Research Unit
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
IMP	Investigational Medicinal Product
LTHT	Leeds Teaching Hospitals NHS Trust
MHRA	Medicines and Healthcare products Regulatory Agency
PI	Principal Investigator
QA	Quality Assurance
REC	Research Ethics Committee
SOP	Standard Operation Procedure
TSC	Trial Steering Committee
TMF	Trial Master File
ToR	Terms of Reference
UoL	University of Leeds

Section F: Previous versions of Document

Version no.	Valid from	Approved by	Date approved
1.0	18/04/2018	Louise Brook David Wardle	19/03/2018

Appendix A: Examples of trials requiring DMC

Example 1: A randomised controlled trial to assess whether patients with lung cancer live longer if they take a new chemotherapy agent.

A trial is planned to assess whether a new biological therapy, R1, should be given in addition to standard treatment with chemotherapy, C, for patients with small cell lung cancer. The current standard treatment is associated with a number of toxicities. Data from Phase I and II studies of R1 in patients with lung cancer and early phase III data from colorectal cancer suggest that R1 may cause some of the same unwanted side-effects as C. The investigators have named overall survival as their primary outcome measure as they hope that the combination of C+R1 will help patients to live longer. However, they are concerned that the side-effects may be additive or multiplicative. The trial plans to recruit 1200 consenting patients over 4 years and allocated half to each trial arm. Patients will be followed up for survival. The main analyses are expected 6 years after the start of recruitment. An Independent Data Monitoring Committee (IDMC) will meet 6-monthly for the first 2 years to review unblinded safety and efficacy data; the IDMC will determine the frequency of future meetings.

Example 2: A randomised controlled trial to assess the role of surgery in patients with leg ulcers

A trial planned to assess both the benefits and the costs of surgery for patients with venous leg ulcers. Leg ulcers, which have a major effect on quality of life, often causing pain and depression, may affect 1% of the UK population at some time and cost the NHS £400 million in 1991. The trial planned to recruit around 1000 consenting patients across the UK over a period of 3 years. All patients would receive standard long-term 4-layer compression bandaging. Many ulcers, but not all, will heal with bandaging alone. Patients would be randomised to receive surgery in addition or not. The trial would assess whether leg ulcers heal quicker and, if they heal, whether they recur less often with surgery. Blinding is not possible but the primary outcome measures are objective and verifiable. It is suspected that many patients will not comply with bandaging and this might differ according to the treatment arm. An Independent Data Monitoring Committee (IDMC) will meet throughout the treatment and follow-up period to review the accumulating data by allocated treatment and to comment on the continued value of the trial.

Reference: Health Research Authority. Available from: http://hra.nhs.uk