Clinical Directorate Clinical Research Governance Team

Standard Operating Procedure

Oversight Committees for University sponsored CTIMPs

SOP023

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1. Introduction

It is important to ensure that a Clinical Trial of an Investigational Medicinal Product (CTIMP) is conducted to the highest ethical and scientific standards. This means periodically reviewing the conduct and output of the trial from the perspective of patient safety, in order to ensure that patients participating in the trial are not exposed to any increased risk of harm, which could have been prevented and that, where necessary, the trial protocol be amended or the trial ended early.

This oversight can be achieved via a Trial Management Group (TMG), a Trial Steering Committee (TSC) and an Independent Data and Safety Monitoring Committee (IDSMC). The key remits of these bodies are firstly to ensure that patients are not exposed to any increased risk of harm which is avoidable; and secondly to ensure the scientific integrity of data collection and analysis. The final responsibility for the conduct of the clinical trial rests with the Sponsor.

The University, as Sponsor, expects that a TMG, TSC and IDSMC is set up for all multi-centre, blinded CTIMPs, however each this requirement will be assessed on a case by case basis.

Smaller CTIMPs may combine the roles of the TSC and IDSMC, but this should be agreed with the Sponsor.

2. Scope of Procedure

This SOP defines the roles of the TMG, TSC and IDSMC and the factors that need to be considered when assessing the need for oversight committees for University Sponsored CTIMPs.

3. Who

This SOP applies to all members of University staff involved in the set-up, management and conduct of University Sponsored CTIMPs.

4. When

This SOP should be referred to at the initial stages of setting up a CTIMP to assess the need for a TMG, TSC and IDSMC and during the study conduct for the role of the TMG, TSC and IDSMC.

5. Role of the TMG

It is expected that all University Sponsored CTIMPs will convene a TMG to take responsibility for the day-to-day management of the trial, such as the. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. This includes;

- Progress of study and site opening
- Recruitment rate (actual versus predicted)
- Site issues
- Data quality and return rate
- Protocol amendments

- General research study issues

6. Membership of the TMG

The TMG is generally made up of the direct trial team, and other key stakeholders This includes, but is not limited to;

- Chief Investigator
- Trial Manager
- Sponsor representative
- Lead statistician
- Research nurse
- Data manager
- Public and Patient Involvement representative

7. TMG meeting frequency

It is expected the TMG meets frequently, generally on a monthly basis.

Minutes of meetings should be sent to all members and be retained in the Trial Master File.

8. Role of the TSC

It is expected that all University Sponsored CTIMPs will convene a TSC to take responsibility for the scientific integrity of the trial and focus on trial progress including protocol adherence and subject safety.

The main roles of the TSC are:

- To provide advice, through its Chair, to the project's funder, sponsor, Chief Investigator, host institution, and contractor
- To concentrate on the project's progress, adherence to the protocol, and patient safety (where appropriate), and to consider new information of relevance to the research question
- The rights, safety and well-being of the participants are the most important considerations and should prevail over the interests of science and society
- 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
- To provide advice to the investigators on all aspects of the project

Where it is decided that a TSC is not required this should be fully documented and reported to the Sponsor.

The composition of the TSC and the frequency of meetings should be specified in advance in the TSC Charter. Recommendations are made in the sections below.

9. Membership of the TSC

Independent members must make up a minimum of 75% of the Committee membership and it is recommended the below representatives sit on the TSC;

- An Independent Chair (UK based and/or holding a substantive UK based appointment)
- An Independent statistician (where relevant)
- At least one Public member, preferably independent
- Others with clinical or other expertise relevant to the project, such as health economics, social care, public health etc.
- Chief Investigator
- Trial Manager
- Sponsor representative

10. TSC meeting frequency

Although there may be periods when more frequent meetings are necessary, the TSC should meet at least annually.

Where a IDSMC is also convened TSC meetings should be scheduled to follow shortly after their meetings so that reports from that group can be considered if appropriate.

Minutes of meetings should be sent to all members and be retained in the Trial Master File.

The responsibility for calling and organising Steering Committee meetings lies with the Chief Investigator, in association with the Chair.

11. Establishing the need for IDSMC

The European Medicines Agency (EMA) guideline on Data Monitoring Committees 2005 states that an Independent Data Monitoring Committee (IDSMC) assesses trial progress, unblinded safety data and if required, critical efficacy endpoints. The IDSMC will then report to the Sponsor or other trial oversight committees with recommendations on study modification, continuation or termination.

IDSMCs are not required for all Clinical Trials of Investigational Medicinal Products (CTIMPs), but the below areas should be assessed by the Chief Investigator (CI) and Clinical Trials Unit (CTU) managing the trial, or the team managing the CTIMP to determine the need for IDSMC;

- The safety profile of the IMP (any significant risk of harm, any unknown or uncertain risks)
- The size of the trial (for multi centred trials consideration should be given for the need to review data from all sites)
- End points and other data requiring regular review that may mean the trial completes before recruitment is completed
- The potential for high morbidity or mortality during the trial

- Recruitment from vulnerable populations
- If the CTIMP is blinded or open labelled

If the CTIMP is found to have higher levels of risk in the above categories, or is a blinded trial the University, as Sponsor, recommends that a IDSMC is established to enable unblinded review of data and to make independent recommendations to the Sponsor regarding the CTIMP.

Where it is decided that a IDSMC is not required this should be fully documented and reported to the Sponsor.

12. Role of the IDSMC

The main roles of the IDSMC are;

- It is the only body involved in a trial that has access to the unblinded comparative data
- The role of its members is to monitor these data and make recommendations to the Steering Committee on whether there are any ethical or safety reasons why the trial should not continue
- The safety, rights and well-being of the trial participants are paramount
- The DMEC considers the need for any interim analysis advising the Steering Committee regarding the release of data and/or information
- Criteria should be agreed at which continuation of the trial is considered futile and the DMEC would only indicate if these had been passed or not as this would limit the potential for un-blinding.

13. Composition of IDSMC

Where a IDSMC is required the CI will identify the independent members to sit on the committee. All IDSMC members must be independent of the trial and the trial team. Membership of the DMEC should be small (3- 4 members) and comprise experts in the field, e.g. a clinician with experience in the relevant area and expert trial statistician.

14. IDSMC meeting frequency

The IDSMC should meet at least annually, or more often as appropriate, and meetings should be timed so that reports can be fed into the Steering Committee

Minutes of meetings should be sent to all members, the sponsor, the funder, and the TSC, and a copy should be placed in the Trial Master File. It should be noted that the minutes may have confidential or unblinded items redacted from some copies.

15. Committee Charters

The CI or Trial Coordinator must ensure there are formal Charters in place for the TMG, TSC and IDSMC that all members sign up to. This should include details of methods of communication between the oversight committees and the Sponsor, frequency of meetings, how decisions will be made, how reports will be produced and distributed to protect the blind, how recommendations

are implemented and overseen and how the committee documentation is maintained in the Trial Master File.

The TMG, TSC and IDSMC must be formed, and all members must sign the DMC charter, before the trial opens to recruitment. All members should also complete a Conflict of Interest form which is filed in the Trial Master File. This will be confirmed as part of the Sponsor Permission to Proceed Process (see SOP004). It is recommended that the TMG, TSC and IDSMC meets before the opening of the trial to get to know each other, to discuss the protocol in detail (although it is expected that the DMC members accept the protocol before agreeing to become a member) and to discuss potential responses to hypothetical situations. Further meetings should be between 6 monthly and annually, although more frequent meetings can be called at regular recruitment milestones, or in the event of greater than expected SAE/SUSAR reporting.

Where the CTIMP is being managed by a Clinical Trials Unit (CTU) it expected their template Charters are used. In cases where this is not possible please use Sponsor templates TEM035[1], TEM036[2], TEM037[3].

16. Roles and Responsibilities

The CI is responsible for ensuring appropriate oversight committees are set up for CTIMPs

The CI is responsible for ensuring TSC and IDSMC meetings are properly minuted and these minutes and reports are provided the Sponsor.

The Sponsor is responsible for oversight of the TSC and IDSMC.

17. Abbreviations

CI Chief Investigator

CTIMP Clinical Trial of investigational Medicinal Product

IDSMC Independent Data and Safety Monitoring Committee

IMP Investigational Medicinal Product

SAE Serious Adverse Event

SOP Standard operating procedure

SUSAR Suspected, Unexpected Serious Adverse Event

TMG Trial Manager

TSC Trial Steering Committee

[1] Template Trial Management Group Terms of Reference
[2] Template Trial Steering Committee Terms of Reference
[3] Template Independent Data and Safety Monitoring Committee Charter

18. Associated Documents and References

EMEA guidelines on Data Monitoring committees July 2005

Damocles Study Group (2005) A proposed charter for clinical trial data monitoring committees: helping them to do their job well. Lancet 365: 711-722

SOP004 – Sponsor Application and Approval Process

TEM035 - Template Trial Management Group Terms of Reference

TEM036 - Template Trial Steering Committee Terms of Reference

TEM037 - Template Independent Data and Safety Monitoring Committee Charter

19. Training and Resources

CIs, students, trial coordinators and other members of University Staff involved in the set-up, management and conduct of CTIMPs should be aware of and familiar with this SOP. Training can be provided by the Clinical Research Governance Team upon request.

20. Monitoring and Audit

An internal audit of Clinical Directorate SOPs will be conducted at a minimum of every two years.