CLINICAL GOVERNANCE - STANDARD OPERATING PROCEDURE
TRIAL STEERING COMMITTEE
CG-QMS SOP CGXX

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Version History	**Reason for change**

NOTE: All SOPs are subject to regular review.

Please ensure that the version of this SOP is the most up-to-date.

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1. PURPOSE

The purpose of this SOP is to set out the terms of reference for a Trial Steering Committee (TSC).

2. SCOPE

This SOP is applicable to the following groups of people involved in a trial/study (see flowchart at end of document):

- Trial Management Team/Group (they need to be aware of the expectations and role of the TSC so that they can provide relevant information to the TSC).
- TSC members and TSC Chair
- Data Monitoring Committee/Data Monitoring and Ethics Committee (DMC/DMEC)

3. BACKGROUND

3.1 All clinical trials and clinical studies where this is a requirement of the funder, should have an executive Trial Steering Committee (TSC) who provide oversight to the Trial Management Group (TMG). However, the TSC and TMG may be the same in some clinical studies, particularly those involving a single site or where funders do not stipulate this requirement .

3.2 The SOP will define the general roles and responsibilities of members of the TSC and make recommendations for membership selection and decision-making processes.

3.3 The overall responsibility of a TSC is to have oversight of all the processes involved in running a clinical trial or similar study. TSC members should be involved in designing and monitoring the trial/study and be prepared to give appropriate advice, support, endorsement and guidance to the trial management team/group in order to ensure the safe and effective conduct of the trial/study. The TSC members should be happy to give constructive review of any publications or reports arising from the results of the study. In addition, the TSC can also make recommendations to the sponsor or funder if any changes are required in the trial/study processes.

3.4 The TSC should approve the protocol and any amendments, monitor the recruitment, review progress/completion of key milestones of the trial, review relevant information from external sources, consider the recommendations of the Data Monitoring Committee/Data Monitoring and Ethics Committee (DMC/DMEC) and funder, and resolve problems brought by the trial co-ordinating team.

3.5 The TSC also has a role in flagging up early issues that might indicate ethical dilemmas, such as deviation from the trial protocol, events that impact on patient safety, rights or wellbeing, and the potential effects of new external information. When such issues are identified, they should be fed back to the trial co-ordinating team and a course of action agreed on in a case-by-case basis. If considered necessary by the TSC or the trial Sponsor, then issues may also be discussed further with the Ethics Committee

4. CROSS REFERENCES

4.1 CG-QMS Data Monitoring Committee

4.2 CG-QMS Trial Management Group

5. PROCEDURE

ROLE OF THE TSC

The general roles of the TSC are as follows:

5.1 To approve the protocol and associated trial documentation so that the trial/study can commence and continue in accordance with the pre-planned time schedule.

5.2 To monitor progress of the trial in terms of patient/participant recruitment, adherence to the protocol, completion of milestones (as expected by the funder or defined in the study Gantt Chart and/or funding application) and patient safety.

5.3 To consider any new information that is published in relation to the trial/study research question and evaluate the impact of that on the continuation of the trial/study and related procedures. This important particularly if the new information highlights any safety issues is or gives compelling evidence that the treatment/intervention under investigation is unsafe or ineffective. Under such circumstances, it would be wise to discuss this and if needed, review the protocol and new information with advice from the ethics committee and sponsor. Such action could help ascertain whether the study/trial protocol should/could be amended or (in extreme circumstances), whether the study should be suspended or even stopped.

5.4 To have oversight of the safety and well-being of the trial participants.

5.5 To consider the advice of the DMC/DMEC, ethics committee and Sponsor in relation to any review they conduct of any complaints by participants or any adverse events and deaths as defined by the protocol.

5.6 To provide advice (via the TSC Chair) to the Chief Investigator (CI), the trial Sponsor and the trial funder on all aspects of the trial.

TASKS TO BE UNDERTAKEN BY THE TSC

The specific <u>protocol, documentation and publication-related tasks</u> to be undertaken by the TSC include but are not limited to the following:

5.7 To provide minutes of all TSC meetings to the Chief Investigator and the trial sponsor (and the funder if required).

5.8 To approve amendments to the protocol.

5.9 To approve any proposals by the TMG concerning any change to the design of the trial, including additional sub-studies.

5.10 To have oversight of the timely reporting of trial results in accordance with the study Gantt chart/ milestones as described in the protocol or funding application.

5.11 To help to develop, comment upon and ultimately approve, the statistical analysis plan.

5.12 To help to develop, comment upon and ultimately approve, any publication and dissemination plans for the study/trial.

5.13 To help to develop, comment upon and ultimately approve, the final reports for the funder, ethics committee and any arising publications.

5.14 To approve external or early internal requests for release of data or subsets of data or samples including clinical data and stored biological samples.

The specific <u>progress monitoring tasks</u> to be undertaken by the TSC are as follows:

5.15 To review recruitment figures provided by the trial management group (TMG) and work with the TMG to develop strategies to deal with any recruitment problems.

5.16 To monitor the completeness of data and work with the TMG to develop strategies for improving satisfactory data collection for the trial.

5.17 To monitor follow-up and withdrawal rates at all study sites and advise the TMG if improvements or protocol changes are needed.

The specific TSC tasks relating to the <u>safety and well-being of trial participants</u> are as follows:

5.18 To review and approve TMG strategies to deal with problems including sites that deviate from the protocol.

5.19 To regularly review summary data on the number of adverse events, deaths and withdrawals of trial participants.

5.20 To agree a pre-defined format for DMC/DMEC reports in collaboration with the DMC/DMEC.

5.21 To receive feedback from the DMC/DMEC and support the TMG to make any necessary changes to the protocol or study processes which improve participant safety or enhance safety reporting.

5.22 The TSC chair should be aware of the dates of the DMC/DMEC meetings and be happy to take part in ad-hoc discussions of any urgent issues arising with the CI and DMC/DMEC chair. If needed, a short notice TSC meeting may be required.

5.23 To make decisions if needed as to the future continuation (or otherwise) of the trial.

TSC MEMBERSHIP

5.24 The TSC should include a mixture of independent and non-independent members however on balance, there should be more independent members. This is to ensure that when consensus cannot be reached, and voting is required, that decisions are not disproportionately influenced by trial team members who have a more personal investment in the trial.

5.25 Rules about what constitutes as independence may be set by the funder (e.g. MRC and HTA have clear expectations about this) however if this is not the case, then the following guidelines should be applied:

5.26 The TSC independent members should ideally not be from the same institution as the Sponsor, co-Sponsor, co-applicant, or the Clinical Trials Unit involved in the management of the trial. Where this is not completely possible, there should be confirmation that there is no direct working relationship between the TMG members and the proposed TSC member and this should be backed up by approval by all stakeholders involved in the trial (i.e. Sponsor, funder, CI, other TSC members as a minimum).

5.27 All the independent members (with exception of PPI representatives) should have previous non-independent experience of working on clinical trials and/or studies as CIs, co-applicants, site investigators, researchers/collaborators or members of a TMG.

5.28 The membership composition of the TSC should take into account any rules that are set by the funder or sponsor but if these are not pre-specified then it should include the following people:

- An independent chair*
- At least two other independent members**
- Two independent collaborators***
- Two members of the public (PPI representatives who are independent of the TMG).
- The investigators and the trial project staff are ex officio. The chief investigator would normally attend TSC meetings along with admin staff to take minutes and relevant trial support staff such as a trial or data manager (to help to provide up to date trial progress information).
- Representatives of the trial Sponsor and the funder should be invited to all TSC meetings and copied into the minutes arising.

NOTE: *The TSC chair does not necessarily need to be a clinician (unless specified by the funder or Sponsor) however they should have previous experience with being a TSC member, have previously attended TSC meetings and have knowledge/experience relevant to the clinical condition(s) and/or intervention(s) that are being investigated during the course of the trial/study.

**The independent members should bring relevant experience and they should for example, include a statistician, epidemiologist, trial methodologist or a diagnostician.

*** An independent collaborator could be an investigator/expert from a participating study site providing that they were not from the same institution as the Sponsor, co-Sponsor, co-applicant, or the Clinical Trials Unit involved in the management of the trial.

There should always be an option to co-opt in additional independent experts should unexpected problems arise which require further areas of expertise.

TSC MEETINGS

TSC meetings should be organised as follows:

5.29 The Chief Investigator is responsible for calling and organising the TSC meetings.

5.30 The TSC should meet at least annually and/or in accordance with the project Gantt chart, although there may be periods when more frequent meetings are necessary. Ideally TSC meetings should follow shortly after DMC meetings.

5.31 There may be occasions when the trial Sponsor or the funder will wish to organise and administer TSC meetings in exceptional circumstances.

5.32 At the meetings, the TMG and TSC members will provide evidence to support any requests for extensions, including that all practicable steps have been taken to achieve targets.

5.33 The TSC will maintain confidentiality of all trial information that is not already in the public domain.

5.34 A TSC report should be prepared in advance of each TSC meeting by the trial team. This can be accompanied by a presentation by the CI and any trial team members at the TSC meeting if needed.

5.35 The trial/study protocol and the statistical analysis plan should have been received, reviewed and approved by all TSC members in advance of the first TSC meeting.

5.36 At the first TSC meeting any risk assessments and the patient information sheets, patient consent forms and CRFs/questionnaires/data collection tools should be reviewed and approved.

5.37 At the first TSC meeting a format for TSC reports should be proposed by the TMG and agreed.

5.38 Helpful additional guidance of any supporting documents that may require review/approval by the TSC is given in the following publication but this will be very dependent on the nature of the trial/study in question (see *Exploring the role and function of trial steering committees: results of an expert panel meeting. Harman et al. Trials (2015) 16: 597).*

TSC REPORT CONTENTS AND MEETING AGENDAS

5.39 The TSC reports should be written in such a way that the TSC should not view post-baseline data split by treatment group (any blinding must be maintained). However, an exception could be made for baseline data, provided that the justification was clear and that this was agreed on in advance by both the DMC and the TSC.

5.40 The Agenda of TSC meetings and content of the TSC report should allow for discussion/review of but not be limited to, the following items:

- **Protocol changes**: Any protocol amendments and sub-studies
- **Recruitment progress**: Actual recruitment versus final target
- **Acceptance rate:** as a proportion of those invited to participate, and (if known), all eligible participants
- **Follow-up and loss to follow up**: Percentage of participants proceeding through each trial stage to allow monitoring of the recruitment and retention, including missing outcome data. This information does not necessarily need to be split by treatment/intervention arm, but CONSORT style diagrams may be helpful to present this information.
- **Overall withdrawal rate and level of withdrawal**: summarising those patients who have withdrawn from treatment but are still in follow-up and those who withdraw with no future contact.
- **Data management metrics (if needed)**: e.g. rate of returns of questionnaires, forms or scans, volume of queries, time to return, enhanced metrics via electronic data capture
- **Completeness of data collected**
- **Summary of adherence to treatment/intervention.** Not split by treatment/intervention arms (to avoid unblinding and bias while study in progress).
- **Summary of adverse events** (including any deaths, adverse events, serious adverse events and suspected unexpected serious adverse reactions). This can be split by treatment arm as long as the actual treatment allocation is kept blinded (for example, the arms could be called “A” and “B”).
- **Review of existing publication plans and progress**

- **Review of existing statistical analysis plans and progress**
- **Updates on any planned publications and presentations**
- **Review of any protocol deviations overall and by site**
- **Summary of any data monitoring and ethics committee (DMC/DMEC) recommendations**
- **Any organisational problems or other trial issues**

The above list is not exhaustive but is largely based on the list provided in the following publication: *Exploring the role and function of trial steering committees: results of an expert panel meeting. Harman et al. Trials (2015) 16: 597.*

TSC DECISION MAKING PROCESSES

5.41 The TSC membership should only be considered as quorate for decision making when the number of voting independent members is larger than the number of non-independent voting members.

5.42 Decisions should ideally be reached by consensus following consultation with all members (non-independent and independent) on the preferred plan of action for addressing an issue. Voting may be necessary when consensus cannot be reached, but the voting rights of members should be made clear.

Recommended voting rights:

5.43 The following members should be allowed to vote:

- Independent chair
- Other independent members
- Independent collaborators
- Members of the public (the PPI representatives)
- The Chief Investigator, and any key trial team members of the TSC e.g. trial manager, data manager, statistician or health economist)

NOTE: Representatives of the trial sponsor and the funder should be invited to all TSC meetings and copied into the minutes arising but will not vote.

GUIDANCE FOR MANAGING DIFFICULT SITUATIONS

The following difficult situations could arise and may require some actions/considerations by the TSC:

5.44 Should the DMC recommend stopping the trial in extreme circumstances, the TSC should request formal clarification about whether that decision was unanimous and can if needed, request to be unblinded. A record should be formally made in TSC minutes of any TSC members who become unblinded and these members should not be removed from the committee.

5.45 Should the funder withdraw funding, a decision about whether the trial will stop will ultimately lie with the Sponsor. However, the TSC should consider and feed back to Sponsor whether they agree with trial closure, and if not, may offer advice and guidance to the trial team on continuation and alternative sources of funding.

5.46 In either of the above scenarios, the TSC and Sponsor should consider whether the trial should close to new recruits but continue to allow the planned follow-up of patients/participants who have already enrolled and/or received interventions. Such a plan is likely to be needed in order to continue to monitor and support existing patients/participants and report study/trial outcome data.

5.47 In scenarios where either funding is withdrawn or the DMC recommends stopping, the TSC should formulate and approve a plan for the trial close-down in collaboration with TMG and Sponsor.

6. FLOWCHART

Oversight and Management Structure Diagram:

This oversight and management structure should be followed unless otherwise agreed with the Sponsor, funder and Trial Management Group: