UTS IMPACCT Trials Coordination Centre

Standard Operating Procedure

5.17.2 Data and Safety Monitoring Committees (DSMC)

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Introduction/background

Each Phase III or high-risk trial should consider the establishment of a Data Safety Monitoring Committee (DSMC), initiated by the Sponsor, to assess the progress of a trial. This includes safety and critical efficacy endpoints, and to recommend the continuation, modification or suspension of a trial.

Trials such as Phase II, feasibility and/or pilots should engage a medical monitor (*refer* SOP 5.17.1 Medical Monitor).

All DSMC's should have written operating procedures and written records of all meetings as part of the Trial Master File (TMF).

Objective

The purpose of this document is to describe the roles and responsibilities of the Data and Safety Monitoring Committee (DSMC) for all IMPACCT Trials Coordination Centre (ITCC) Phase III or high-risk trials including:

- the timing of meetings,
- methods of providing information to and from the DSMC,
- frequency and format of meetings,
- adverse event reporting procedures and monitoring,
- statistical issues and
- relationships with other committees.

Scope

This SOP provides a template SOP for adaptation and use by individual, study specific DSMCs established for ITCC trials. Details and specific processes should be changed on a needs basis.

Ownership and Responsibility

The study specific DSMC

The project team members of the ITCC

The Coordinating Principal Investigator of the specific trial

Procedure

Data and Safety Monitoring Committee (DSMC) Standard Operating Procedures for the study: *Full study title*

Short Title: Short title

Introduction

Name of Committee:
Data and Safety Monitoring Committee (DSMC) for the trial: *Study Title.*

Trial Type:
Phase XX study.

Principal Investigator: Name of CPI

Objectives of Trial:

Primary objective

The primary objective is to [insert primary study objective]

Secondary objectives are to [insert secondary objectives]

1. Secondary objective 1
2. Secondary objective 2
3. Secondary objective 3
4. Secondary objective 4

Roles and Responsibilities

Aims of the Committee:
To safeguard the interests of trial participants, potential participants, investigators and the sponsor; to assess the safety and efficacy of the trial's interventions, to monitor the trial's overall conduct, and protect its validity and credibility within an acceptable ethical framework.

Terms of Reference:
The DSMC should receive and review the progress and accruing data of this trial, review any adverse events and determine if they are linked to the study drug, and provide advice on the conduct of the trial to the Trial Investigators Meetings through the supply of minutes of the Open meeting and/or presentation by the Chair if requested by the CPI/Trial Investigators Meeting members/ITCC.

Specific Roles:
To undertake interim review of the trial's progress by:

- assessing data quality, including completeness of the data received from the ITCC (thereby encouraging collection of high quality data);
- monitoring recruitment figures and losses to follow-up from the data received from the ITCC;
- monitoring compliance with the protocol by participants and investigators;

- monitoring evidence for treatment differences in the main efficacy and safety outcome measures – and thus recommending action when/whether the main trial question has been answered;
- monitoring evidence for treatment harm e.g. toxicity, SAE's, deaths;
- recommending whether the trial should continue to recruit or follow-up [see section on decision making];
- advising on any major protocol modifications suggested by investigators (e.g. changes to the inclusion criteria, endpoints, data collection, etc);
- assessing the impact and relevance of any external evidence provided; and
- monitoring compliance with previous DSMC recommendations.

Before the Trial

Trial Protocol:
All potential DSMC members will have sight of the protocol/outline before agreeing to join the committee (ITCC to email protocol and draft SOP).

Before recruitment begins the trial will have undergone peer review by the internal Scientific Advisory Committee and a Human Research Ethics Committee [Provide details of protocol review committee and date, and details of HREC approval.]

Therefore, if a potential DSMC member has major reservations about the trial they should report these to the DSMC chair and may decide not to accept the invitation to join. DSMC members should be independent and constructively critical of the ongoing trial, but also supportive of aims and methods of the trial.

Trial Sites listing:

Site number	Site Name

DSMC Set-Up Meeting:
The DSMC will meet early into the trial. The first meeting will be after the completion of the first four (4) participants and is then estimated to then be every four to six months thereafter until the trial is closed.

The aims of the first meeting are to discuss the workings of the DSMC, specifically:

- Schedule of meetings;
- Format for the reports to the DSMC;
- Timing of the delivery of the collated SAEs by ITCC to the DSMC prior to the DSMC meetings;
- Definition of a quorum;
- Handling of meeting minutes;
- Other relevant aspects of the process; and
- Develop recommendation guidelines for stopping rules.

Consideration should be given to shell (empty) tables for the data not yet available. One aim of this meeting is to familiarise the DSMC members with the format that will be used in the reports and to give them the opportunity to suggest changes and additions.

DSMC Members Agreement:
DSMC members will agree to this document to register their assent. This can be in the form of a letter or email and should confirm:
(1) that they agree to be on the DSMC and
(2) that they agree with the contents of this SOP and
(3) that they complete the standard Confidentiality Agreement.
There will be no other formal contracts.

Composition
Membership:
The membership will consist of three (3) voting individuals including a clinician, clinical pharmacologist, and a statistician. Members have been chosen because they are experienced in trials and/or the disease area. The clinical advisors have been recommended by ITCC and the investigator and approved by the investigator team who has oversight of this trial.

The members should be independent of the trial (e.g. should not be involved with the trial in any other way or have some involvement that could impact on the trial). Members considering or currently serving on DSMCs of similar, concurrently active trials must inform the DSMC chair and the Trial Investigator Meeting to determine if membership is appropriate as this could compromise the independence of the trial and possibly the confidentiality of the results of the individual trials. Any competing interests, both real and potential, should be declared. A short competing interest form should be completed and returned by the DSMC members (Appendix 1).

The members of the DSMC for this study are:
1. Chair:
2. Vice-Chair/Statistician:
3. Clinical Advisor:
4. Secretariat: ITCC

Responsibilities of the Chair:
- Facilitate and coordinate the DSMC
- Chair DSMC meetings
- Provide deciding vote as per ordinary committee rules
- Provide a report to the lead investigator by two (2) weeks post meeting
- Sign off the minutes as a true and accurate record

Responsibilities of the Statistician/Vice Chair:
- Provide DSMC members with a report two (2) weeks prior to the DSMC meeting
- Provide statistical analysis on AEs and SAEs
- Present an oral report at the DSMC meeting in relation to analysis
- Guide the DSMC if statistical issues arise during the discussion of the accumulating data
- Perform the blinded interim analysis (if required).

Responsibilities of the Clinical Advisor/s:
- Provide advice on serious and other adverse events and make recommendations to the DSMC
- Review all SAEs and provide clinical outcome decisions on causality
- Review a random sample of deaths deemed not related to the study and confirm absence of causality link.

Responsibilities of Secretariat/ITCC:
- Organise meetings as required
- Send out an agenda at least one (1) week prior to a scheduled meeting
- Notify the ITCC National Project Officer at least three (3) weeks prior to the DSMC meeting date of the requirement for a CONSORT statement and the need to provide the DSMC statistician with all relevant study data (blinded)
- Take formal minutes of the DSMC meetings, provide the DSMC members with a draft of the minutes within two (2) weeks of the meeting
- Store in a password protected folder within the ITCC files all written documentation of the DSMC
- Report all adverse events other than serious adverse events to the DSMC at each meeting
- Provide the DSMC with a consort statement flow chart of recruitment three (3) weeks prior to a DSMC meeting (if requested)
- Provide the DSMC with all the relevant study data (blinded) three (3) weeks prior to a DSMC meeting (if requested)
- Perform a literature search looking for new evidence which has emerged since the commencement of the study or since the last DSMC meeting and present the findings to the DSMC

Responsibilities of the Participating Recruiting Sites:
- Report all serious adverse events to the DSMC within one (1) working day of occurrence or notification to the ITCC
- Reporting will be undertaken by the ITCC National Project Officer or nominee in the following manner:
  1. Via email, to prompt an email discussion between the members for those events as per the criteria below under *Reporting of SAEs.*
  2. Via the DSMC meeting schedule with provision of:
     a. Summary report of all SAEs to date
     b. Full data of the SAEs since the last meeting of the DSMC.

Relationships
The DSMC are advisory to the investigator team and will report and make necessary recommendations through the DSMC Chair to the CPI as per the funding agreement between the University of Technology Sydney (UTS). The full investigator team will receive the reports from the DSMC if requested to do so.

Competing interests should be disclosed by all members of the DSMC. These are not restricted to financial matters – involvement in other trials or intellectual investment could be relevant. Although members may well be able to act objectively despite such connections, complete disclosure enhances credibility. Most competing interests are acceptable if disclosed (Appendix 1).

Meetings
Frequency:
It is recommended that the DSMC meet at least six monthly and will otherwise depend on the wishes of the DSMC of the CPI. Any member of the DSMC can call a meeting if they deem one is necessary.

At least one meeting per annum will be face-to-face. Where possible all subsequent meetings should be face-to-face however teleconference facilities may be utilised. The CPI Investigator should attend in person rather than be represented by a proxy.

Documentation:
A formal agenda will be distributed to the DSMC members at least one (1) week prior to the meeting by the DSMC secretariat.

Definitions:
Closed session: Only DSMC members and, sometimes, other invited guests of the DSMC where the need arises to clarify clinical details or assist with deliberations, should be present in closed sessions.

Open session: Attended by those at the closed session, plus the CPI, PaCCSC/CST National Manager, and any other relevant staff. Those attending only the open session may attend in person or, if appropriate, by phone.

The format will be:
1. *Closed session*: All parts of the report are discussed, and DSMC discussion.
2. *Open session*: Discussion with other attendees on any matters arising from the closed session (this assumes that others will have read the “open” report in advance).
3. *Closed session:* extra closed session if necessary.

Trial Documentation and Procedures:
The following material will be made available at DSMC meetings:

Open sessions:

Accumulating information relating to recruitment:
- No of pre-screens entered and reasons for not proceeding
- No of randomisations
- Study recruitment tracking graph

- No of completions (primary endpoint)
- Consort Diagram (as per above)
- Other data issues.

Accumulating information relating to data quality and safety:
- SAE's reported (excel spreadsheet (from the database)) of the SAEs reported since the last meeting
- Summary of SAE's reported to date
- Do they also need protocol violations?

Any external evidence relating to the study identified by the CPI and the trial team (this might include new evidence in the literature).

Closed sessions: In addition to all the material available in the open session, the closed session material may at the request of the committee include efficacy and safety data summary by blinded treatment group. Closed sessions may also occur ad hoc should the DSMC call a meeting to discuss an SAE or group of SAEs.

Blinding:
DSMC members will initially be blinded to treatment allocation; however, at any point in the progress of the trial, the DSMC may choose, after careful consideration, to unblind itself if separation of the groups is sufficient to contemplate a recommendation or special analysis, change or cessation of the trial.

Interim Data Analysis:
If an interim data analysis is conducted, it will be available only to those present in the closed sessions. DSMC members must **not** share confidential information with people outside the DSMC, including the CPI.

External Evidence:
Identification and circulation of external evidence (e.g. from other trials/systematic reviews) is not the responsibility of the DSMC members. The CPI and the ITCC National Office will collate any such information.

Reporting Recommendations:
The DSMC will report its recommendations in writing to the CPI and Trial Investigator Meeting members. If the trial is to continue largely unchanged then the DSMC will include a summary paragraph suitable for trial promotion purposes (see Appendix 2).

Storage:
The DSMC members should store the papers safely after each meeting so they may check against the next report. After the trial is reported, the DSMC members should destroy all interim reports. All electronic documentation will be password protected with the password known only to the members of the DSMC. The DSMC statistician will retain all copies of documentation including all data, tables, figures and analyses used in the reporting of adverse events.

Adverse Events
Adverse Event Reporting:
All adverse events will be reported via an online reporting system to ITCC; the DSMC is not responsible for identifying adverse events. ITCC has an SOP for AE reporting which will be made available to DSMC members.

Definition of an Adverse Event:
Adverse events are defined as any untoward or unexpected occurrence in a patient or clinical investigation participant where the occurrence does not necessarily have a causal relationship with the study intervention. Only events of a grade 3 or higher will be routinely reported. The events for reporting are listed below, however this list is not exhaustive and the DSMC will be provided with reports on ALL events that occur of a grade 3 or higher.

Symptoms of Interest for AE Reporting (where the events have developed since baseline. i.e., worsening to grade 3 or higher). Specifically, for this study, the symptoms of interest will be:

-
-
-

Grading:
A grade of 3 or 4 in severity will activate an adverse event report.
A grade of $\geq$ 4 in severity will activate a serious adverse event report.

The following conditions are recognised as being excluded from AE reporting:
- An expected effect from a study intervention, such as constipation in opioid use unless the side effect required additional treatment or assessment
- Signs or symptoms associated with the disease or disorder under study unless they are more severe than expected.
- Admission to hospital solely because of caregiver factors

Definition of a Serious Adverse Event
Serious adverse events are any untoward medical occurrence that;
- results in death;
- is life-threatening;

(These events will be reported to all sites immediately)
- results in attempted suicide;
- requires inpatient hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability/incapacity;
- requires ongoing medical or professional attention; or
- are judged to represent significant hazard.

Reporting of Serious Adverse Events
The expected study population have an underlying disease that is expected to significantly shorten life expectancy; and some participants are expected to die or deteriorate within a relatively short period of time. If the site investigator and consultant in charge are confident that there was no possibility of an event being related to the trial participation, the conditions recognised as being excluded from 24 hour reporting to HREC as an SAE are as follows:

- Where participants are admitted as a planned admission due to respite, family or social issues, or for pre-planned treatment.
- Where participants are admitted (or admission is prolonged) due to a documented expected deterioration or exacerbation in their condition due to the underlying disease process, or where the admission is prolonged for this reason.
- Where participants die due to a well-documented decline in their condition due to the

underlying disease process.

Criteria for Assessing Causality
Grading the degree of certainty about such a relationship will be based on the guide: www.niaid.nih.gov/ncn/sop/adverseevents.htm.
Grading will be:

- **Unrelated:** Where the adverse event is clearly not related
- **Unlikely:** Where the adverse event does not have a clear relationship to the intervention
- **Possible:** Where the adverse event follows a known pattern of response
- **Probable:** Where the adverse event reduces or ceases with withdrawal of the intervention
- **Definite:** Where the adverse event ceased with withdrawal of the intervention and recurs with re-exposure.

Decision Making
Possible decisions:
The possible recommendations are numerous and could include:

- No action needed, trial continues as planned;
- Early stopping due to, amongst other things, clear benefit or harm of a treatment, safety concerns on secondary outcome, futility, slow recruitment, or external evidence;
- Stopping recruitment within a subgroup;
- Extension of recruitment or follow-up; or
- Advising on or proposing protocol changes;

Statistical Stopping Rules:
A recommendation to discontinue recruitment, in all patients or in selected subgroups, will be made only if the result is likely to convince a broad range of clinicians, including those supporting the trial and the general clinical community. The statistical stopping boundaries will be regarded as guidelines to aid the DSMC decisions as opposed to absolute rules. In making a decision regarding stopping a trial the DSMC will take into account other factors such as:

- whether the trial is likely to ever be repeated;
- the number of patients and events observed (data maturity);
- safety;
- feasibility;
- information from other trials; and
- resources in terms of patients and finances.

Interim Analysis:
ITCC can provide blind tables and listings to the DSMC at intervals requested by the DSMC (if at all). Full data cleaning process is not required for this analysis.

A blind review of the retention rate and standard deviation of the primary endpoint will be performed by the trial statistician at one third and two thirds the way through recruitment. Full data cleaning process is not required for this analysis.

Committee Decisions:
The role of the chair should be to summarise discussions and encourage consensus. In each area of discussion, the chair should give their own opinion last. Every effort should be made for the DSMC to reach a consensus. If the DSMC cannot achieve consensus, a vote should be taken, although details of the vote should not be routinely included in the report to the investigator team, as it may inappropriately convey information about the state of the trial

data. In the event that the decision to stop the trial is conceivable, the DSMC is free to invite external experts to aid in the decision-making process.

Quorate for Decision Making:
Effort should be made for all members to attend. The DSMC secretariat will try to ensure that a date is chosen to enable this. Members who cannot attend in person should be encouraged to attend by teleconference. If, at short notice, any DSMC members cannot attend at all then the DSMC may still meet if at least one statistician and one clinician, including the Chair (unless otherwise agreed), will be present. If the DSMC is considering recommending major action after such a meeting the DSMC Chair should talk with the absent members as soon after the meeting as possible to check, they agree. If they do not, a further teleconference should be arranged with the full DSMC.

Reporting
Structure:
The DSMC should report in writing to the CPI, usually within three (3) weeks after the meeting. Unless the DSMC is recommending that the trial protocol be changed in some way, the report should not usually reveal any confidential information. An example of a report from a DSMC to the CPI, recommending no action is presented in Appendix 2.

Minutes:
All meetings will have formally taken minutes, and separate minutes of open and closed sessions will be made. The minutes for each session will be prepared by the DSMC secretariat. All members of the DSMC should see and comment on the minutes and the DSMC chair will be responsible for signing off all minutes. The minutes of the open session will be circulated to the DSMC, the CPI, and the Trial Investigator Meeting members. The minutes of the closed session will be circulated to the members of DSMC only.

Recommendations and conflicts:
The Trial Investigator Meeting (TIM) members have ultimate responsibility for the trial and assumes primacy. However, the TIM should report to the DSMC how they have acted upon the DSMC's recommendations. If the DSMC has serious problems or concerns with the TIM decision, a meeting of these groups should be held. The information to be shown would depend upon the action proposed and the DSMCs concerns. The meeting should be chaired by an external expert who is not directly involved with the trial. Depending on the reason for the disagreement confidential data will often have to be revealed to all those attending such a meeting.

After the Trial
Publication of Results:
The CPI has responsibility that trial results will be published in a correct and timely manner in line with the ITCC SOP 6.15 Authorship. This is not overseen by the DSMC.

DSMC members may be named (unless they specifically ask not to be) in the primary published report. A brief summary of the timings and conclusions of DSMC meetings should be included in the body of this paper.

DSMC members should be given at least two (2) weeks, and if possible, a month, to read and comment on any draft publications that report outcome measures and/or details of the DSMC. This may be done simultaneously to other groups reviewing the draft manuscript (e.g. Trial Investigator Meeting members, trial investigators).

The DSMC should not discuss confidential issues from their involvement in the trial until 12 months after the primary trial results have been published unless permission is agreed with the Trial Investigator Meeting. They should not trade in stock of companies affected by the trial until the results are public knowledge.

Figure 1: Trial design flow chart

Appendix 1: Conflicts of interest forms

Potential competing interests of Data and Safety Monitoring Committee (DSMC) members for this trial.

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

Possible competing interest should be disclosed via the ITCC. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) DSMC member should remove the conflict or stop participating in the DSMC. Table 1 lists potential competing interests.

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
- 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) in competing products
- Involvement in the publication

Please complete the following section and return to the DSMC secretariat.

☐ **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: _____

Appendix 2: Suggested report from DSMC to the CPI where no recommendations are being made

[Insert date]

To: CPI name
CPI
Name of Study
UTS

Dear CPI name,

The Data and Safety Monitoring Committee (DSMC) for *Study title* met on *[meeting date]* to review its progress and interim accumulating data. *[List members] attended* the meeting and reviewed the report.

We congratulate the trial organisers and collaborators on the progress and conduct of the trial and the presentation of the data. 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,

Chair name

Chair, Data and Safety Monitoring Committee

On behalf of the DSMC
DSMC members:
(1) Statistician
(2) Clinical Advisor

Related SOPs

6.15 Authorship

Related documents

Individual clinical trial protocols.

References

Acknowledgements

History			
Version	Date	Author	Reason
1.0	29/11/2021	[name of author]	New procedure

Approval		
Version	Approval Name	Approval Signature
1.0	[name of approver]	