**Appendix 1 - Data Safety Monitoring Committee Charter for University of Leicester Sponsored Research**

# DSMC CHARTER – WORKING INSTRUCTIONS:

* Use the following template to create a study/trial specific data safety monitoring committee charter
* Please ensure that this page of this document is deleted from the final version of this charter.
* Update the footer to include trial identifiers (i.e., trial name, version number and the date)
* Within the template guidance notes are given in *red italic text*, and examples are provided in *green italic text*. Please ensure these are deleted from the final version of this charter.
* Once the document is updated, ensure the contents table is also updated so that any deleted or additional sections are included.

*<Insert Trial Title and Logo>*

**CHARTER OF THE DATA SAFETY MONITORING COMMITTEE (DSMC)**

*Version <number>, <date>*

|  |
| --- |
| **Document Name:** <Trial name> Data Monitoring Committee (DSMC) Charter**Author:** <name>**Reviewer(s):** <name(s)> |

|  |  |
| --- | --- |
| **Sponsor** | University of Leicester |
| **Sponsor Reference** |  |
| **IRAS ID** |  |
| **REC Reference** |  |
| **Funder** |  |
| **Funder Reference** |  |
| **Trial Registration Reference** |  |

*<Insert Funder logo if relevant>*

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# ACRONYMS/REFERENCES:

**CI:**  Chief Investigator

**DSMC:** Data Safety Monitoring Committee

**ID:** Identification

**IRAS:** Integrated Research Application System

**PIC:** Patient/Participant Identification Centres

**REC:** Research Ethics Committee

**ST:**  Statistics

**SAE:** Serious Adverse Event

**SAP:** Statistical Analysis Plan

**TSC:** Trial Steering Committee

**TMF:** Trial Master File

**TMG:** Trial Management Group

# DSMC CONTACTS

The table below can be amended to suit the members of the relevant trials DSMC

|  |  |  |
| --- | --- | --- |
| **Role** | **Name** | **Email** |
| **Chief Investigator:** |  |  |
| **Trial Manager/Administrator:** |  |  |
| **Trial Statistician:** |  |  |
| **Unblinded Statistician:** | *(Remove if not applicable)* |  |
| **TSC Chair:** |  |  |
| **Independent DSMC Members:** |  |  |
| **DSMC Chair** |  |  |
| **DSMC member** |  |  |
| **DSMC statistician** | *(Add more lines if needed)* |  |

# REVIEW HISTORY

|  |  |  |
| --- | --- | --- |
| **Version Number** | **Effective Date** | **Details of Changes to Plan** |
| *<insert first approved version>* | *<insert first effective date>* |  |
|  |  |  |
|  |  |  |

# TRIAL SUMMARY

|  |  |
| --- | --- |
| **Trial Title** |  |
| **Trial Acronym** | *If applicable or delete row* |
| **Trial Design** |  |
| **Trial Participants** |  |
| **Eligibility Criteria** | Inclusion Criteria:Exclusion Criteria: |
| **Randomisation** | Intervention:Control:Ratio: |
| **Sample Size** |  |
| **Trial Period** | Start Date:End Date: |
| **Follow up duration** |  |
|  | **Objectives** | **Outcome Measures** |
| **Primary**  |  |  |
| **Secondary**  |  |  |

# INTRODUCTION

*The purpose of this document is to describe the* *roles and responsibilities of the Data Safety Monitoring Committee (DSMC) throughout the life cycle of the trial. It outlines how the committee will perform these responsibilities, including the making and communicating of decisions and how this may impact and interact with other committees within the trial.*

# PRIMARY ROLES AND RESPONSIBILITIES OF THE DSMC

## Broad statement of aims of the DSMC

*The DSMC will be responsible for safeguarding the interests of trial participants, assessing the safety and effectiveness of the intervention during the trial, and for monitoring the overall conduct of the trial to the highest research governance. It should be noted that the day-to-day management of the trial is the responsibility of the Chief Investigator (CI), and as such the CI has set up a separate Trial Management Group (TMG) to assist with this function.*

## Terms of reference

*The DSMC should receive and review the progress and accruing data of this trial and provide appropriate supervision in relation to trial conduct, protocol adherence and patient safety during the trial. The DSMC will report subsequent recommendations to the Trial Steering Committee.*

## Specific roles of the DSMC

*To uptake interim review of the trial’s progress by:*

* *Assessing data quality (including completeness) and encouraging collection of high-quality data*
* *Monitoring recruitment figures and losses to follow-up*
* *Monitoring compliance with the protocol by participants and investigators*
* *Monitoring trial conduct – organisation and implementation of the protocol*
* *Monitoring evidence for treatment harm (e.g., SAEs, deaths)*
* *Deciding whether to recommend that the trial continues to recruit participants or whether recruitment should be terminated either for everyone or for some treatment groups and/or some participant subgroups*
* *Suggesting any appropriate additional data analyses*
* *Advising on protocol modifications suggested by investigators or Sponsor (e.g. to inclusion criteria, trial endpoints, or sample size)*
* *Reviewing the statistical analysis plan (SAP) prior to database lock. The SAP will be prepared by the Trial Statistician and will contain full details of all statistical analyses*
* *Monitoring compliance with previous DSMC recommendations*
* *Considering the ethical implications of any recommendations made by the DSMC*
* *Assessing the impact and relevance of external evidence*
* *Considering the need/any requests for release of interim trial data and advising the TSC regarding the release of data and/or information*
* *Should further funding be required, providing to the TSC appropriate information and advice on the data gathered to date without jeopardising the integrity of the trial.*

*There are also rare occasions when the DSMC Chair might be asked, through the Chair of the TSC, by the Funder to provide advice based on a confidential interim or futility analysis if serious concerns are raised about the viability of the trial or if the research team are requesting significant extensions.*

# MEMBERSHIP OF THE DSMC

*The members should be independent\* of the trial, with at least one member being UK based and/or holding a substantive UK based appointment. Members should not serve on DSMCs of similar, concurrently active trials 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. The brief ‘Conflicts of Interest’ form (Appendix 1) should be completed and returned by all DSMC members to the Lead site/Central Co-ordinating Centre.*

*\*Definition of independence as follows:*

*Not part of the same institution as any of the applicants or members of the project team.*

*Not part of the same institution that is acting as a recruitment or investigative centre, including Patient Identification Centres (PIC), identifying and referring patients to a recruitment or investigative centre.*

*(In both cases above ‘not part of the same institution’ means holding neither a substantive or honorary contract with said institution).*

*Not related to any of the applicants or project team members.*

*For the Chair only; not an applicant on a rival proposal.*

*It is recognised that independence status may change during the duration of the trial.*

*Any DSMC members who develop significant conflicts of interest during the course of the trial should resign from the DSMC. DSMC membership is for the duration of the clinical trial, however if members leave (e.g., due to arising conflict of interest) during the course of the trial, the TMG, in consultation with the Sponsor, will promptly appoint replacements.*

## Composition

*The DSMC will comprise at least 3 members: one Chair, and 2 independent members. The DSMC members will include physicians with relevant clinical experience, as well as a statistician with clinical trial and prior DSMC experience. They may also include members of the public.*

## The responsibilities of the Chair

*The Chair is expected to facilitate and summarise discussions and be responsible for ensuring trial contacts outside of the independent members are not inappropriately exposed to unblinded data. There is no vice-Chairman. The Chair is also responsible for writing/reviewing and signing off the DSMC recommendations letter to the TSC.*

## The responsibilities of the DSMC statistician

*The DSMC membership includes a statistician whose role it is to provide independent statistical expertise and to further guide the other DSMC members through the report. The DSMC statistician is not expected to prepare the DSMC report*

## The responsibilities of the trial statistician

*Section 4.4 and 4.5 to be amended/deleted depending on use of blinded/unblinded statistical support for the trial*

*The trial statistician, in collaboration with the trial manager, will produce the open and closed reports presented to the DSMC (as appropriate) and will participate in DSMC meetings, guiding the DSMC through the report and will take minutes.*

## The responsibilities of the unblinded statistician

*Remove if not using blinded/unblinded stats support*

*The unblinded statistician will produce the open and closed reports presented to the DSMC (as appropriate) and will participate in DSMC meetings, guiding the DSMC through the report and will take minutes.*

## The responsibilities of the trial manager (or equivalent)

*The Trial manager will input into the production of the open DSMC report and will likely participate in the open session of the meeting. Typically the trial manager is responsible for;*

* *preparing and circulating the agenda and accompanying meeting documents*
* *circulating the finalised minutes of the open session (e.g. to the committee and the Sponsor)*
* *ensuring the DSMC recommendations letter is completed and sent to the TSC*
* *ensuring all the meeting documents are filed in the TMF*

## The responsibilities of the Chief Investigator and other members of the Trial Management Group (TMG)

*The Chief Investigator (or delegate) should be available, to attend open sessions of the DSMC meeting. The other TMG members will not usually be expected to attend but can attend open sessions when necessary (See Organisation of DSMC Meetings below).*

## DSMC members

### Voting Members

|  |  |
| --- | --- |
| **Role** | **Name and Affiliation** *(Insert name, job title, institution)* |
| **Independent Chair** |  |
| **Independent Statistician** |  |
| **Independent Clinician** |  |
| **Independent lay member (if applicable)** |  |

### Non-voting observers

|  |  |
| --- | --- |
| **Role** | **Name and Affiliation** *(Insert name, job title, institution)* |
| **Chief Investigator** |  |
| **Trial Manager (or title of equivalent member)** |  |
| **Senior Statistician** |  |
| **Trial Statistician** |  |

# BEFORE OR EARLY IN THE TRIAL

*All potential DSMC members should have sight of the protocol/outline and where possible the project plan e.g. Gantt chart before agreeing to join the committee. Before recruitment begins the trial will have undergone review by the funder/sponsor (e.g., peer review for public sector trials), scrutiny by other trial committees and a research ethics committee. Therefore, if a potential DSMC member has major reservations about the trial (e.g., the protocol or the logistics) they should report these to the trial office 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.*

## Any issues specific to the disease under study

*Insert any trial specific issues or delete as appropriate*

## Any specific regulatory issues

 *Insert any trial specific issues or delete as appropriate*

## Any other issues specific to the treatment under study

*Insert any trial specific issues or delete as appropriate*

## DSMC contract

*There is no contract for DSMC members, however DSMC members should formally register their assent by confirming (1) that they agree to be on the DSMC; (2) that they agree with the contents of this Charter; (3) complete and return Conflict of Interest Form (see Appendix 1).*

# DSMC MEETINGS

## Expected frequency of DSMC meetings

*Meetings will occur at least annually. The DSMC members may choose to hold meetings more regularly if required or deemed necessary or convene an emergency meeting if the need arises out of concern for participant safety.*

## Whether meetings will be face-to-face or by teleconference

*It is expected that meetings will take place virtually. Face-to-face meetings may be organised on request for the convenience of the DSMC members.*

## How DSMC meetings will be organised

*The meeting will have up to 3 parts;*

***Open session****: Attended by the independent committee members, trial statistician/unblinded statistician* *(delete as appropriate), CI(s) and trial manager. Representatives of the sponsor, funder, or regulator, may be invited if relevant. Discussion with other attendees on the open DSMC report covering trial progress, conduct, adherence to the protocol and emerging external evidence.*

***Closed session****: Attended by the independent DSMC members and the trial statistician/unblinded statistician* *(delete as appropriate)*. *Discussion amongst independent members of the closed report, considering unblinded evidence of patient harm, accumulating outcome data, interim analyses and any stopping/progression rules, guided by trial statistician/unblinded statistician* *(delete as appropriate)*.

***Executive session****: Attended by the independent DSMC members. Where required the independent DSMC members will discuss and develop a consensus on their list of recommendations, including that relating to whether the trial should continue, having reviewed both the open and closed reports.*

***Further open session****: If deemed necessary, a further discussion amongst those in the open session might take place on any matters arising from the closed or executive sessions*

# DSMC DOCUMENTATION AND PROCEDURES TO ENSURE CONFIDENTIALITY AND PROPER COMMUNICATION

## Report contents

*The open and closed sessions ensure proper communication is achieved between the DSMC, the co-investigators and the Sponsor and provides a forum for exchange of information among various parties who share responsibility for the successful conduct of the trial. The intent of this format is to enable the DSMC to preserve confidentiality of the comparative efficacy results while at the same time providing opportunities for interaction between the DSMC and others who have valuable insights into trial-related issues.*

***Open Session Report:*** *will cover trial progress, conduct, adherence to the protocol and emerging external evidence. Information relating to recruitment and retention based on pooled data and data quality (e.g., non-randomisations, CRF compliance, protocol adherence, withdrawals, loss to follow-up) will be presented, during which problems affecting trial integrity can be identified and resolved. Outcome data or data split by randomised treatment will not be presented in the open session report.*

***Closed Session Report:*** *In addition to the material available in the open session, the closed session will involve presentation of data around effectiveness and safety, recruitment and retention, treatment compliance and outcome data (where appropriate) by randomised treatment group.*

## Will the DSMC remain blinded to treatment allocation

*In the closed report the DSMC will/will not* *(delete as appropriate)* *be blinded to the identity of the treatment arms in the closed report.* *(If to remain blind add the following)* *Data will be presented split by randomisation allocation, but labelled A and B to conceal the identity of the intervention and control arms. Particular care should be taken to ensure data that may lead to unblinding of the groups in the report is concealed to maintain the blind*

## Responsibility for identifying and circulating external evidence (e.g., from other trials/ systematic reviews)

*Identification and circulation of external evidence (e.g., from other trials/ systematic reviews) is not the responsibility of the DSMC members. The CI (maybe the TMG, as a whole) and the trial team will collate any such information.*

## Availability of reports

*Open and closed reports are ideally circulated to DSMC members between 1-2 weeks before the meeting is due to take place. The DSMC members should store the papers safely after each meeting so they may check the next report against them. After the trial is reported, the DSMC members should destroy all interim reports.*

##  DSMC communication of decisions and recommendations

*The role of the DSMC 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 TSC, as it may inappropriately convey information about the state of the trial data. It is important that the implications (e.g., ethical, statistical, practical, financial) for the trial be considered before any recommendation is made. Only appointed members will be entitled to vote and the Chair will have a casting vote.*

*Possible recommendations could include:*

* *No action needed; trial continues as planned*
* *Early stopping due, for example, to clear harm of a treatment, futility, or external evidence*
* *Stopping recruitment within a subgroup*
* *Extending recruitment or extending follow-up*
* *Sanctioning and/or proposing protocol changes*
* *Assessing the trial stop/go progression criteria*

*The DSMC will communicate its formal recommendations, in writing to the TSC within 3 weeks of the meeting. This should be copied to the Trial Statistician and Trial Manager and should be sent in time for consideration at a TSC meeting (approximately one month later). The TSC will be responsible for promptly reviewing the DSMC recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in trial conduct are required. The letter to the TSC should not usually reveal any information considered trial sensitive or confidential.*

*If the DSMC wishes to make specific comments about the trial data, these should be relayed in confidence to the Trial Statistician at the meeting and/or in separate communication with the Trial Statistician.*

*Should a situation arise where the DSMC has serious problems or concerns with the TSC decision, a joint meeting of the TSC and DSMC should be held. The information to be shown would depend upon the action proposed and each committee’s concerns. Depending on the reason for the disagreement confidential data and/or data by centre may have to be revealed to all or some of those attending such a meeting: this would be minimised where possible. The meeting would be chaired by a senior member of the trial’s office staff or an external expert who is not directly involved with the trial.*

*If the trial is to continue largely unchanged then it is often useful for the DSMC Response Report to include a summary paragraph suitable for circulation to third parties (e.g., funders, etc.)*

## When is the DSMC quorate for decision-making?

*Effort should be made for all members to attend. The trial manager will try to ensure that a date is chosen to enable this. 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 will be present, one of which to be delegated Chair’s responsibility. If the DSMC is considering recommending major action after such a meeting, the DSMC Chair (or delegate) 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.*

## Non-attendance at meetings

*Where the report is circulated before the meeting, DSMC members who will not be able to attend the meeting may pass comments to the DSMC Chair for consideration during the discussions. If a member does not attend a meeting, it should be ensured that the member is available for the next meeting. If a DSMC member repeatedly fails to make themselves available the DSMC should consider replacing that position.*

## Minutes of the DSMC Meetings

*It is recommended that separate minutes of open and closed session be made. The minutes for each session should be made only by someone who attends that session, and will usually be the Trial Manager in the open session and the Trial Statistician in the closed session. This should be agreed at the start of the meeting. All members of the DSMC should see and comment on the minutes. The DSMC chair will be responsible for signing off all minutes.*

*The open minutes should describe the proceedings of the open session and summarise the recommendations made by the DSMC. The closed minutes should describe the proceedings from the closed session including the list of recommendations. As they should not be made available to anyone outside of the DSMC, copies should be made and archived by the DSMC Chair and/or the Trial Statistician responsible for preparing the closed reports and should be made available for distribution to the Sponsor, Lead Investigators, Senior Trial Manager and regulatory authorities at the time of trial closure.*

*Open session minutes will be sent to all members, Sponsor, Funder, TSC and will be stored in the Trial Master File (TMF).*

*In the case of closed sessions, if recording the sessions on Teams then the trial statistician or member of the unblinded team should send the meeting invite so that there is no inadvertent access to the recording by blinded staff, e.g. trial manager.*

# STATISTICAL MONITORING GUIDELINES

*No formal interim statistical analyses of the primary outcome measure is planned. It is expected that the trial recruitment will stop when the intended sample size has been achieved* *(if internal pilot, add the following)*, *unless the internal pilot shows it is unfeasible to continue. It is expected the trial will terminate on collection of* *(insert timeframe for last participant follow-up assessment)* *outcome data from the last participant.*

*Where formal interim statistical analyses are planned include here the details of the timing, methods to be used and what decisions should be reached i.e., guidelines or rules to be followed.*

# AFTER THE TRIAL

*The CI has responsibility that trial results will be published in a correct and timely manner. The TSC is the committee that should oversee this process. DSMC members should be named and their affiliations listed in the main trial report, unless they explicitly request otherwise. A brief summary of the timings and conclusions of DSMC meetings may be included in the body of this paper as an appendix if requested by the journal editor. The DSMC members will have the opportunity to read and comment on the proposed main publications of trial data prior to submission. This may be done simultaneously to other groups reviewing the draft manuscript (e.g., TSC, co-investigators, co-applicants).*

*DSMC members may be named and their affiliations listed in the main report, unless they explicitly request otherwise.*

*The DSMC should not discuss confidential issues from their involvement in the trial until after the primary trial results have been published, unless permission is agreed with the TSC. Members of the TSC, their family, friends or acquaintances must not trade in stock of companies affected by the trial until the results are in the public domain.*