Statistics in Trials Interest Group

The processes involved in a Data and Safety Monitoring Board/Committee with special reference to the role of the various statisticians

Revision History

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Abbreviations

Abbreviation	Definition
ACTA	Australian Clinical Trials Alliance
DSMB	Data and Safety Monitoring Board
DSMC	Data and Safety Monitoring Committee
STInG	Statistics in Trials Interest Group

Definitions

Term	Definition
Data and Safety Monitoring Board/Committee (DSMB/DSMC or DSMB/C)	An independent and multidisciplinary group established by the trial sponsor to provide high level oversight for a clinical trial entailing review, at intervals, of accumulating trial data, to monitor the progress of a trial and to make recommendations on whether to continue, modify or stop the trial early for safety, efficacy or futility reasons [1, 2]. The role of the DSMB/C for each trial may be different, and are specified in charter. The two terms will be used as synonyms in this document. Several other terms are also used such as Independent Data and Safety Monitoring Board (iDSMB), Safety Monitoring Committee (SMC), Data Monitoring Committee (DMC)
DSMB/C Charter	A document that generally provide details of the DSMB/C's operational procedures. These include membership, the roles and remit of the DSMB/C, what recommendations are permissible, the minimum number of attendees to constitute a quorum, how often the DSMB meets, to whom they report and how decisions are made.
Open report	Report providing study data in an aggregate fashion (i.e. with the treatment groups combined, thus not revealing the treatment allocation). This report is provided to the trial team and DSMB/C.
Closed report	Report providing study data presented by treatment group (revealing treatment allocation by original names) or semi-unblinded fashion (using pseudo-names). This report is not provided to the trial team, only to the DSMB/C.
Open session	Meeting to discuss the open report, generally attended by the DSMB/C members, trial team/sponsor, and the reporting statistician (for some DSMB/Cs).
Closed session	Meeting to discuss the closed report, attended by the DSMB/C members and the reporting statistician (for some DSMB/Cs).
DSMB/C statistician	Statistician who is a member of the DSMB/C and independent from the trial.
Trial statistician	Statistician who is part of the study team and involved in the statistical decisions, which could include the day-to-day statistical activities of the trial, blinded to the treatment allocation.
Reporting statistician (Also sometimes referred to as independent statistician)	Statistician who prepares the DSMB/C reports, including the closed report which involves unblinded information. They may attend the closed session meeting to answer queries. This statistician may be a member of the trial team or be completely independent of the trial team.

Introduction

Data and Safety Monitoring Boards/Committees (DSMB/Cs) are increasingly used to provide high level oversight for clinical trials, in particular with regards to safety issues. Statisticians are essential members of DSMB/Cs. As a consequence, statisticians working in clinical trials are often approached to serve on a DSMB/C. In addition to familiarity with clinical trial design and analysis, training and/or previous experience serving as the statistician on a DSMB/C are critical in effectively navigating the statistical issues and challenges arising during the review of accumulating trial data by a DSMB/C. The number of statisticians able to fulfill these requirements does not meet the growing demand.

The role of the DSMB/C is to review all aspects of study progress, including patient enrolment, protocol compliance, data quality and completeness, reported adverse events, and other safety data. In studies with futility or efficacy analyses the DSMB/C also reviews the interim efficacy data. A DSMB/C would typically recommend that the study continue as is, be modified in some way or is stopped. The specific role of any DSMB/C would be specified in the DSMB/C charter.

Objectives

The aim of this document is to summarise the processes and role of statisticians in conducting a DSMB/C meeting.

Planning a DSMB/C meeting and timelines

There is often a long delay between collection of the last data point to be included in the DSMB/C report and the DSMB/C meeting. The timelines vary for different studies, but the following is an illustration:

Event	Day	Time to next event
Notify sites that a DSMB/C meeting is planned and that key data for visits up to a specific date (cut-off date) should be clean and complete in the database on a specific date (database lock date)	1	30 days
Close data collection – data collected after this time will not be included in the DSMB/C report	31	7 days
Complete data cleaning on data entered before the close of data collection up to the cut-off date. Database lock occurs.	38	3 days
Clean data provided to statistician(s)	41	7 days*
Statistician(s) provides the report(s) to the DSMB/C members	48	7 days#
DSMB/C meeting	55	

* This time should be negotiated with the statistician based on workload and complexity of report. If the programming to produce the report is developed prior to receiving the clean

data it should be possible to provide the report more quickly. We have put 7 days in the table, but in many instances this might be too short. Between 7-21 days might be reasonable.

Reach agreement with the DSMB/C how long in advance of a meeting they want to receive the report(s). 7 days seem to be standard, but up to 2 weeks is not unusual.

This timeline means that the trial team should generally start to plan a DSMB/C meeting 2 months in advance. It is often hard to find a time when all of the DSMB/C members are able to meet, so setting the meeting well in advance is a good idea. It is recommended that the trial statistician work closely with the principal investigator, trial manager, and data manager to plan a DSMB/C meeting.

It is the responsibility of the Principal Investigator to arrange and plan the DSMB/C meeting, in consultation with the DSMB/C.

Composition of a DSMB/C

DSMB/Cs generally consist of a minimum of three members, one of whom is a statistician and other members are medical/clinical content experts, ideally with trials experience. The chair of the DSMB/C is generally a content expert who has previous experience as a member of a DSMB/C. At a minimum this person should have experience chairing meetings. Recommendations provided by the DSMB/C would ideally be reached by consensus but can be decided using voting, in which case it is helpful to have an uneven number of DSMB/C members. The DSMB/C charter would specify what constitute a quorum for the DSMB/C meeting to go ahead.

The various roles of statisticians in a DSMB/C

There are often 3, and sometimes more, statisticians involved in a DSMB/C meeting. Each statistician has a different role. These include:

1. **The DSMB/C statistician**. This statistician should be independent of the clinical trial team and is a member of the DSMB/C. The role of the statistician on the DSMB/C is to provide independent statistical expertise to the DSMB/C and to help guide interpretation of the DSMB/C reports. They attend both the open and closed sessions of DSMB/C meetings and have voting rights within the DSMB/C. This statistician usually does not have access to the raw data from the trial, but receives tables, figures and listings of data via the open and closed report submitted to the DSMB/C. The role of this statistician does not involve conducting any analyses or preparing any reports for the DSMB/C. The DSMB/C statistician should ideally not work in the same research institute or department as the trial investigators (including the trial statistician).
2. **The trial statistician.** The trial statistician is intimately involved with the management and oversight of the trial and is responsible for the statistical aspects of the trial, including contributing to protocol development, writing the statistical analysis plan, reviewing database structure and content, assessment of ongoing data quality, and conducting or overseeing the statistical analysis and the presentation of the final study results. The trial statistician is often involved in drafting the charter for the DSMB. They may be involved in putting together open reports for the DSMB/C and a template for the closed report. They may also prepare the blinded coding/programming for closed reports, but they should not

prepare or have access to the contents of the closed report. They would normally attend the open but not closed sessions of DSMB/C meetings. The trial statistician is not a member of the DSMB/C and does not have voting rights within the DSMB/C. For blinded trials, the trial statistician should remain blinded to treatment allocation and any interim results until the final analysis of the trial data.

3. **Reporting/Unblinded/(Sometimes called independent) Statistician (Confusingly, no term is consistently used for this statistician).** This statistician is not part of the trial team and is not involved in the day-to-day running of the trial, or with the final analysis of the trial data. The reporting statistician is often employed within the same team as the trial statistician or within the research team of the coordinating trial investigator. Their role is to prepare closed reports, and sometimes the open reports. The reporting statistician has access to the unblinded treatment group information for the trial, if needed for the closed report. They attend the open session of the DSMB/C meeting, taking care to minimise their contributions due to unconscious bias from any knowledge of the results in the closed report. They often attend the first part of the closed session where they may present the unblinded results in the closed report to members of the DSMB/C, but then may leave the meeting while the DSMB/C discussion takes place. They are not a member of the DSMB/C and do not have voting rights within the DSMB/C.

   As the reporting statistician is independent from the trial, they may not be familiar with trial specific details of the database and statistical analysis to prepare the report. Therefore, the trial statistician could write the analysis code to prepare both open and closed reports for the DSMB/C meeting. Since the trial statistician does not have access to the unblinded treatment assignment, the trial statistician would write the code using a dummy treatment indicator, but cannot compile the closed report. The trial statistician would give the analysis code to the reporting statistician, who would add the unblinded treatment assignment data to it and prepare the closed report.

   As the reporting statistician is independent from the trial, this is often not the best person to answer specific analysis or data related questions that the DSMB/C may have.

Sessions of the DSMB/C meeting

A DSMB/C meeting generally consist of various open and closed sessions. These are (generally in this order):

1. **An open session**
   During this session members of the DSMB/C, trial team/sponsor including the trial statistician, the reporting statistician and sometimes a delegate who takes the minutes are present. During this session the trial progress is discussed, usually lead by the Principal Investigator using the open report. The investigators can use this session to raise any issues they want the DSMB/C to consider. This session is generally chaired by a member of the trial team but can be chaired by the DSMB/C chair.
2. **A closed session**
   During the closed session the trial team leaves and only the DSMB/C members and the reporting statistician remain in the meeting. During this session of the meeting the closed report is used to lead the discussion.

3. **Closed deliberations of the DSMB/C**
   After discussion of the closed report, the reporting statistician typically leaves the meeting or remains at the meeting at the discretion of the DSMB/C. The DSMB/C members deliberate and reach a consensus about the recommendation to be given to the trial team. The reporting statistician should not provide any input into the recommendations, even when asked.
4. **An open session (optional)**
   There could be an additional open session following the closed session where the same team members who were present in the first open session return to the meeting. During this session additional clarifying questions may be asked or the team updated about the decision the DSMB/C have reached.

Content of DSMB/C open and closed reports

The content of the open and closed reports will be determined by the study protocol, DSMB/C charter and the roles and responsibilities of the DSMB/C. The following is commonly included in the reports:

Open report:
These summaries will be provided across the whole study sample, not stratified by treatment arm.

- Summary of any protocol modifications that have been or are planned to be made by investigators (e.g., to inclusion criteria, trial endpoints, or sample size)
- Assessment of data quality, including completeness
- Summary of screening and recruitment and whether timelines are likely to be met, often by recruiting centre/site
- Summary of loss to follow-up and adherence to study intervention
- Summary of demographics and baseline characteristics (if applicable)
- Summary of compliance with the protocol by investigators and clinical team
- Summary of relevant safety data – this could include incidences of serious adverse events, with supporting clinical information, summaries or listing of all adverse events, laboratory data, vital signs, etc.
- Assessment of the impact and relevance of any new external evidence on continuing recruitment to the trial, or content of the trial documents (e.g., protocol, patient information and consent forms)

Closed report:
Mostly, the same information will be provided in the closed report but be presented by treatment arm. Sometimes the treatment groups are displayed in a semi-blinded fashion in the closed report (by calling them Group A and Group B, for example). The reporting statistician could have a key to unblind the groups if the DSMB/C felt it is necessary.

Some information, for example screening and recruitment information need not be reported again. Baseline information describing the study arms would also be provided, showing any stratification factors by treatment arm.

Lastly, only if specified in the protocol or charter:

- Any interim efficacy analyses. Interim analyses of efficacy data need to be pre-planned during the design of the trial, justified and the statistical implications of doing interim analyses should be considered. This is usually described in the study protocol and DSMB/C charter and include specifying stopping rules, methods for alpha spending, details of efficacy boundaries to be used.
- Futility analyses (i.e., inability for the trial to meet its primary objective) including conditional power (i.e., the probability to observe a statistically significant final study result given the pattern in the data seen up to the interim analysis and [generally] assuming the same pattern for the remainder of the data that is still to be collected).

It goes beyond the scope of this document to elaborate on the statistical details of interim analysis for the purpose of early stopping for efficacy or futility. An introduction to these topics can be found in Ellenberg, Fleming and DeMets (2002).

In general, the same processes should be followed for open label and blinded trials, where both open and closed reports are prepared. Even in open label trials, the trial team should not have access to comparisons between the treatment arms. There could be exceptions to this, for example, if a DSMB/C review for an open label trial consisted only of a review of safety data, the safety data could be listed by treatment arm in one report, making it unnecessary to have both an open and closed report.

Number and timing of DSMB/C meetings

The number and timing of DSMB/C meetings are prescribed by the study protocol or DSMB/C charter. The timing of meetings can be determined by calendar time e.g. yearly or according to number or proportion of participants recruited. It is common to have at least a yearly meeting. Generally, there would be one additional DSMB/C meeting prior to the start of the study. This initial meeting might not have any trial data that is presented to the DSMB/C, rather this meeting is used as an introductory meeting for the trial team to:

- Introduce themselves (the study team) and the members of the DSMB/C to each other
- Familiarise the DSMB/C with the study and its protocol
- Review the DSMB/C charter
- Reach agreement with the DSMB/C on their role, responsibilities and sign off on the DSMB/C charter
- Discuss with the DSMB/C the format of the open and closed reports

Minutes and recommendations

The study team should provide someone to take minutes during the open session. During the closed session, the chair of the DSMB/C may minute the discussions or there may be a designated minute taker organised by the study team. Closed session minutes are normally held by the DSMB/C secretariat or chair until the study is closed. It is expected that the minutes for the open session, including the recommendation by the DSMB/C should be available within 14 days of a DSMB/C meeting.

The DSMB/C should communicate their recommendations, without divulging any details of the blinded results, to the trial management committee, usually via the DSMB/C chair. This

official letter with recommendations should be kept in the trial management file and shared with the ethics committee.

References

Data Monitoring Committees in Clinical Trials: A Practical Perspective. S Ellenberg, Thomas R Fleming, David L DeMets (2002)

Establishment and Operation of Clinical Trial Data Monitoring Committees. FDA Guidance (2006)

Data Safety Monitoring Boards (DSMBs). NHMRC (2018) (https://www.australianclinicaltrials.gov.au/sites/default/files/content/For%20researchers/Data%20Safety%20Monitoring%20Boards_1.pdf)