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OFFICE OF THE DEAN (RESEARCH), JIPMER

CIRCULAR

Sub: Data and Safety Monitoring Board guidelines-reg

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The Division of Research, JIPMER has compiled Data & Safety Monitoring Board guidelines with the approval of competent authorities and same is being circulated for compliance and necessary action.

This is issued with the approval of the Director, JIPMER

19/9/2024

Dean (Research)

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Copy to:

- The Director/ MS/Dean (Academic) for information
- HOD to circulate to all faculty.
- The chairman/Member secretary, UGRMC/PGRMC/JSAC/IEC for information.

2024

DIVISION OF RESEARCH, JIPMER
Data and Safety Monitoring Board (DSMB)

Guidance on setting up of Data and Safety Monitoring Boards for research studies and clinical trials at JIPMER, Puducherry.

What is a DSMB (Data and Safety Monitoring Board)?

Data Safety Monitoring Board or DSMB is a committee of experts that monitors the data emerging from a clinical trial on a periodic basis and a**dvises** the sponsor, researcher, and Ethics committee regarding the continuing safety of the trial participants, and the continuing validity and scientific merit of the trial.

Indian guidelines on DSMB

Item 4.8.12 of the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants (2017) from ICMR contains a table (Table 4.3) that states that "*Adequate provisions must be made for monitoring and the conduct of the research, including the constitution of a DSMB, if applicable (for example in clinical trials).*" Further, item 4.11.7 of the document in the section on the Ethics committee continuing review of studies states, "*Reports of monitoring done by the sponsor and DSMB reports may also be sought".* The Chapter on 'Clinical Trials of Drugs and Other Intervention', in the section on 'Investigator-initiated clinical trials' (7.16.3) states that: "*The institution must have or introduce policies that establish mechanisms to ensure quality of the data generated and safety of the intervention, such as monitoring, auditing, DSMB, etc.*"

However, the document does not provide specific guidelines to either institutions or investigators on how to constitute DSMBs or how they should function. DSMBs are also not specifically referred to in the New Drugs and Clinical Trial Rules, 2019, though these do refer to monitoring of drug trials.

Purpose and Scope of this document

This guidance is meant to help setting up of DSMBs for studies conducted at JIPMER. It applies to:

- Investigator-initiated studies done at JIPMER
- Investigator-initiated multi-institutional studies where JIPMER is the lead center, and/or
- Studies where the IEC/ JSAC has directed the constitution of a DSMB.

Some of the material of this document has been derived from guidelines available from agencies in the USA and Europe.

- US FDA: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/establishment-and-operation-clinical-trial-data-monitoring-committees
- Europe (EUPATI): https://toolbox.eupati.eu/resources/clinical-trial-data-safety-monitoring-board-dsmb/

What does a DSMB do that is not done by the Ethics Committee?

A clinical trial and its data are monitored by both the institutional ethics committee (IEC; also referred to as Institutional Review Board or IRB) and DSMB, with the following differences:

- DSMB has access to a greater depth of data and hence is in a better position to make study-specific decisions. It can look at interim data not only on safety but also on efficacy.
- DSMB often has a statistician who may access blinded and unblinded data, allowing them to analyse data while the study team remains blinded.
- In multicenter trials, individual centres have separate IEC but usually only one DSMB monitoring the entire data (except if an IEC mandates a DSMB to monitor safety data from its own centre).
- DSMB reports to IRB but not vice versa

Which studies need DSMBs, and which studies do not?

- All trials need a data safety monitoring plan (DSMP), but a formal DSMB is not always required. When there is no DSMB, it is assumed that the Principal Investigator (+/- co-investigators) will implement the DSMP (i.e. perform the work done by the DSMB).
- One DSMB can monitor multiple studies if needed. This is particularly done when the studies are related, e.g. several trials in the same population or with the same intervention.
- DSMB adds to the administrative complexity of a trial, and additional resources are required, so DSMBs should be added only when needed.

Studies that may need a DSMB?	**Studies where a DSMB may not be required?**
1. Particularly invasive or toxic intervention with a potential for harm. 2. Novel interventions with limited prior human data. 3. Vulnerable or fragile populations being recruited 4. The study endpoint is such that a highly favorable or unfavorable result may impact patient outcomes. Even interim futility may be important to judge and stop a highly toxic drug trial. Alternatively, if the interim results show an intervention to be highly effective, equipoise may no longer exist, and it may not be ethical to continue to allocate subjects to the other treatment arm(s). 5. Long duration, multiple centers, large sample size (where resources and money being spent are more), to avoid unnecessary expenditure when the study results are unlikely to prove conclusive.	1. Studies focused only on symptom relief. 2. A study that is likely to be completed quickly, e.g. small phase I and pilot studies where recruitment and intervention are completed by the time DSMB analyses the outcomes. 3. A study where most of the enrolment and administration of interventions are likely to happen quickly, but outcome data are expected to come in much later. 4. Interventions that are known to be safe based on adequate prior data.

DSMB recommendations and their implications:

A DSMB may recommend stopping a trial at any time point for any of the following reasons:

- Too much toxicity and harm in any one or both trial arms **(safety).**
- The test arm is clearly superior, and it would be unethical to continue and deny the benefits of the intervention to the participants **(loss of equipoise)** (*based either on analysis of interim data from the study or on conclusive data emerging from other studies).*
- The test arm is clearly not beneficial, and further recruitment is unlikely change the conclusion **(futility).**
- Improper study conduct/ data maintenance by the study team or violations of GCP detected by the DSMB.
- Change in situation rendering the conduct of the trial difficult (e.g. covid-19 intervention trials which had recruitment issues due to abatement of the pandemic), or the result of the trial irrelevant (e.g. emerging newer and better interventions changing the standard of care).

However, early stoppage of a trial may have its own problems. For example:

- Early stoppage for perceived efficacy: Estimates of treatment effects may be unstable at early time points. Thus, nominally statistically significant benefit may be observed at an interim point, which may not persist if the trial is continued and completed as planned. Thus, early

stoppage may lead to false positive conclusions. An important consideration is the "multiple hypothesis testing" as repeated evaluation of the same data set increases the risk of alpha error. Ideally, the DSMB should have accounted for this at the beginning of the trial, by building appropriate safeguards into the statistical plan (e.g. by defining the number and timings of interim analysis and the alpha error allowed at each of these, such that overall alpha error is within acceptable limits).

- Early stop for perceived safety issues: When recommending termination for reasons of safety, the DSMB must consider potential benefits that may still be accruing and may not be apparent.

How to establish a DSMB?

- DSMB is established by the study sponsor and consists of members independent of the study investigators.
- For investigator-initiated studies within JIPMER or multi-centre studies with JIPMER as the lead centre, JIPMER/ PI would be considered as the sponsor. In either case, the DSMB will be constituted by the Dean (Research).

Selection of members

A DSMB usually has at least 3 members (usually 3-5, preferably an odd number) encompassing a variety of expertise.

- Mostly clinicians with at least one biostatistician, with or without ethicists, pharmacologists, epidemiologists.
- Domain expertise about the disease condition and interventions is important; expertise in clinical trials is desirable.
- Previous DSMB experience is important for the Chairperson, and desirable for at least some members. Other members who lack DSMB experience are useful so that they gain experience and can join future DSMBs

For example, a DSMB for a trial involving a new drug for ovarian cancer may consist of:

  - Clinician with expertise in conduct of clinical trials, preferably with previous DSMB experience: Chairperson
  - Biostatistician (preferably with DSMB experience)
  - Gyne-oncologist (preferably with DSMB experience)
  - Medical oncologist (with or without DSMB experience)
  - Pharmacologist (with or without DSMB experience)

The members of the DSMB may be from within the Institute or from outside, depending on the domain expertise required and the study complexity. For studies with high risk, it may be preferable to have either the Chairperson or some members from outside the Institute

The senior-most member may be designated as the Chairperson. One of the members (can be the Chairperson) would serve as the member-secretary of the DSMB to help initiate and coordinate the meetings, prepare and circulate the minutes and serve as the contact point between the PI, the members, and the relevant IEC.

The members must be able to devote sufficient time for the DSMB processes (meetings, approval of minutes, and even analysis of the data in case of the statistician), should not have any serious conflicts of interest, and must agree to maintain confidentiality of the data that is shared with them.

What are the documents, data and items that the DSMB will review?

- Research protocol and any amendments.
- Data on enrollment, details of the processes for randomization, allocation concealment, blinding, etc.
- Interim data for adverse events (this can be done at any time; additional analyses beyond those originally planned are acceptable since increasing alpha error due to multiple hypothesis testing is not a consideration for safety endpoints)
- Interim analyses for efficacy (as per the statistical analysis plan; any additional analyses are generally not advisable because of the risk of excessive alpha error)
- Data quality, completeness
- Compliance and adherence to planned interventions
- Any other information that may impact the conduct of the trial, e.g. other studies published in the subject area, etc.

DSMB Charter

This document details the procedures to be followed by the DSMB. It is created at the beginning of the study. It can be a part of the protocol or separately submitted to the IEC.

Who should draft the DSMB charter?

This is the responsibility of the sponsor/PI. However, members of the DSMB are expected to review the draft document along with the trial protocol and approve it before use. The IEC will also be notified of this whenever it is finalised.

Information in the DSMB charter

- Details of the trial protocol, protocol version number, and funding details
- Approval page with signatures of the DSMB members, including the confidentiality clause
- Purpose and study overview
- Roles and responsibilities of the members
    - Specifications as to who will have access to interim data
    - Who will attend the DSMB meetings
- Monitoring plan (timing, frequency)
    - Analysis plan for efficacy and safety outcomes
    - Methods and timing of providing interim reports to DSMB
    - Protocol on how to do the interim data assessment
- Schedule and format of meetings and communications
    - Format for presentation of data
    - Meeting frequency (determined by study-specific considerations; at least once a year, but more frequently in rapidly enrolling trials and trials with interventions that are novel or likely to be associated with safety concerns)
    - When and how extra meetings can be called (e.g. whenever specific issues come up)
    - Whether meetings will be in person or online

Conduct of DSMB meetings

First meeting

The initial meeting of the DSMB should happen before patient enrolment. Here the members will review and approve the DSMB charter and overall plan.

- Typically, BEFORE the start of the study
- Establish the procedures of the DSMB, schedule of meetings, etc.
- Suggest modifications in the DSMB Charter if needed
- Confirm the format for reports and meeting minutes, define quorum, etc.

Subsequent meetings

DSMB meeting typically have separate open and closed sessions. In the initial open session, the DSMB reviews the data provided by the study team, and the PI (+/- others in the PI's team) are present to clarify any issues which arise or need to be discussed. Thereafter, the PI (and others in the team) are asked to leave.

The 'closed session' that follows is meant for deliberations by the DMSB members. The DSMB biostatistician in the DSMB presents any analysis of the study data that he may have done (after breaking the blind, if needed). The DSMB, then, arrives at recommendations regarding the trial conduct.

Interim results need not be informed by the DSMB unless there is a specific need (like recommendations to stop the trial).

Open data (which are not coded, and which is already known)

- May be discussed with the PI. This type of data is not likely to influence trial conduct but may be important for trial management.
    - Data in aggregate, like pooled toxicity and efficacy data
    - Data concerning the conduct of the trial
        - Accrual
        - Dropout rates
        - Timeliness of data entry
        - Eligibility rates and reasons for ineligibility
- The DSMB report of open data can be shared, and the study team may attend during the discussion.

Closed data

Refers to DSMB report not to be shared as such with the study team and is confidential (especially in the context of randomized trials). These include interim data comparing the 2 groups like outcome data and safety data

Reports of the DSMB?

- Reports to the Sponsor: This may indicate whether the DSMB recommends that the study should continue or be discontinued. The DSMB may not choose to divulge details of the analysis that may have been done as part of the study to the PI if the study is being continued.

- Reports to the Ethics Committee: The DSMB conveys its recommendation on study continuation and safety aspects to the EC with clear recommendations regarding study continuation or stoppage, or suggest modifications, such as in inclusion criteria (e.g. when recruitment rate is too low), dose modification or change in the intervention.
- The IEC may choose whether to act on the recommendations of the DSMB.

Confidentiality

- The report of the DSMB should avoid biasing the sponsor and investigators (e.g. by revealing results of the interim analysis), especially when the study is being continued. Hence, DSMB should ensure that the confidential information made available to it continues to remain confidential, and that only the information considered "open" is included in the report to be shared with the PI and/or sponsors.
- Even in open-label trials, interim results should be available only to the DSMB members.
- To ensure the above, confidentiality procedures must be established a priori and must be part of the DSMB charter.

The DSMB report

It may consist of the following elements, as relevant, while paying attention that it does not contain any information that is expected to bias the study team or include information:

- Summary of protocol
- Recruitment and follow up information
- Baseline data
- Check regarding the randomization processes
- Assessment of safety
- Assessment of outcomes (where it is part of the DSMB charter)
- Recommendations about study continuation and/or modifications, if any

However, it must not include information (e.g. blinded study data, interim analysis results, etc.) that may bias the study team.

Report is to be shared with the sponsor, steering committee and IEC.