Understanding Oversight of Clinical Trials by Independent Data Monitoring Committees

If an Independent Data Monitoring Committee (IDMC) or Data Safety Monitoring Board (DSMB) is necessary for your study, understanding the process and getting the right support is crucial to ensure smooth implementation. Here we answer 4 key questions on IDMCs that help to clarify the complex process of independent clinical trial oversight.

What does an IDMC do?

The primary purpose of an IDMC is to evaluate the safety of participants in the clinical trial and so avoid unnecessary risk to them. The IDMC committee do this by regularly reviewing and analysing interim study data to monitor for:

- Findings of harm/adverse events
- Futility in obtaining a meaningful outcome
- Changes in care during the trial that negates the trial question
- Early establishment of efficacy

For double blind studies, the trial sponsor, participants and clinicians involved are unaware of who is receiving the treatment under investigation or control (placebo or active control). However, the IDMC is not involved in the everyday running of the trial and therefore can independently review interim data in an unblinded fashion without impacting the integrity of the trial. This forms the basis for recommendations to continue, amend or stop the trial based on:

- The benefit/risk assessment
- The quality of trial conduct
- The evolving context of the disease
- The treatment regime under evaluation
- Therapeutic alternatives
- Relevant information external to the trial

What does IDMC oversight involve?

The IDMC oversight process for a large clinical trial involves a network of interactions between different clinical trial stakeholders as outlined in Figure 1.

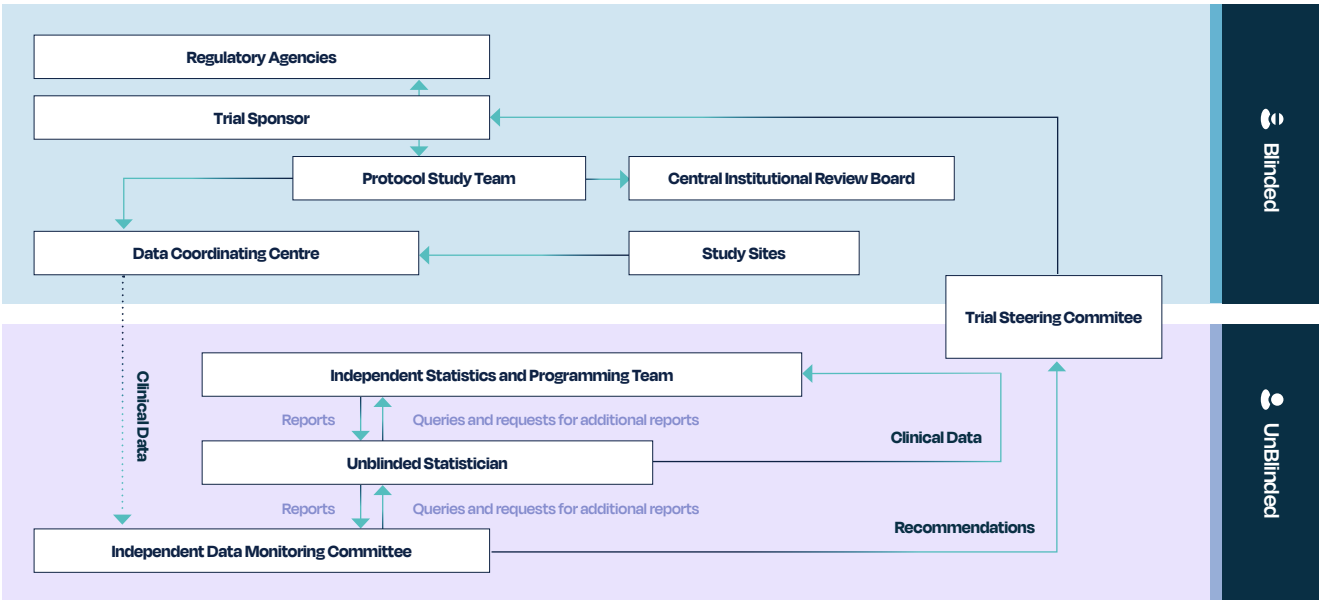

Figure 1. An overview of the flow of data and reporting during IDMC oversight.

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Optimal IDMC oversight requires several steps by these different stakeholders.

1. With **IDMC** input, the **Protocol Study Team** produces a charter outlining IDMC objectives, operations (including decision criteria and data to be reviewed) and its meeting schedule.
2. The **IDMC** reviews an analysis plan for the **IDMC** report to ensure it contains the required data summaries for effective trial monitoring. Additional data summaries are added at **IDMC** discretion if issues arise.
3. During the trial, the **Data Coordinating Centre** (DCC) for the clinical trial receives blinded data from study sites. It provides trial data to an **Independent Statistics and Programming Team** (ISPT) which has access to treatment codes for unblinded data analysis.
4. The **ISPT** prepares a report for the **IDMC** for each of its data review meetings. This summarises key safety and efficacy data by treatment group according to the analysis plan. It is often supplemented with summaries addressing issues that arise from the data.
5. The **IDMC** meet in closed session to review and discuss data and the report findings in an unblinded fashion fully independent of the **Protocol Study Team.**
6. **IDMC** recommendations are delivered without divulging unblinded information to a **Trial Steering Committee** selected by the **Trial Sponsor**. These indicate whether to continue, to stop, or to modify the trial.
7. The **Trial Steering Committee** can then choose whether to accept or reject the recommendations and delivers their judgement to the **Protocol Study Team** for implementation.
8. The **Trial Sponsor** provides the required reports to the **Regulatory Agencies** (e.g., the FDA and EMA).
9. The **Protocol Study Team** provides the reports required by the **Central Institutional Review Board** (CIRB), a single IRB that reviews research protocols. The CIRB monitor the research carried out at all the sites involved in a clinical trial. This leads to fewer regulatory submissions and a more efficient review process.

Who is on an IDMC?

The IDMC usually consists of 3-5 members. They are selected by the Trial Sponsor to have extensive clinical experience in the trial disease area and in the management of large complex clinical trials. Two key positions within the committee are the **Chair** and the **IDMC Statistician**:

The **Chair** should have in-depth IDMC and relevant clinical experience in the disease area of interest. They are responsible for leading deliberations, signing the agreed minutes and communicating with the **Trial Sponsor**.

The **IDMC Statistician** should have statistical and IDMC expertise. Ideally, they should also have experience in the relevant therapeutic area.

All IDMC members should have some prior IDMC experience due to the complex decision-making that is involved in interim data analysis.

How do statisticians support ISPTs and IDMCs?

Statisticians are essential in both ISPTs and IDMCs, carrying out several important functions.

An ISPT Statistician will be involved in:

Data Review and Monitoring

They assist with programming and reviewing the safety and efficacy outputs produced by the ISPT programming team.

Interim Analysis

They perform interim data analyses at pre-specified time points during the trial. These analyses help assess whether there are any safety concerns or if the trial should be terminated early for efficacy or futility reasons.

Safety Evaluation

They are often the first to review safety outputs, and so need some understanding of the therapeutic area to identify safety concerns that should be discussed with the IDMC or Medical Monitor.

Efficacy Assessment

Following relevant study document specifications, they may implement statistical methods to produce outputs for the assessment of evidence of a treatment effect, such as a reduction in disease symptoms or an improvement in health outcomes.

Sample Size Reassessment

If pre-specified in the trial protocol, they may implement methods to reassess the sample size of the trial based on the accumulating data to ensure the study is adequately powered to detect meaningful treatment effects. They prepare this information and present it to the IDMC so it can make recommendations on whether the sample size should be changed, and by how much.

Advisory Role

They attend the IDMC meeting and provide statistical guidance and expertise as impartially as possible, helping its members interpret the data and make informed decisions about the continuation, modification, or termination of the trial.

Report Preparation

They prepare and review the statistical outputs provided to the IDMC in a way that complies with the study documentation and is easily understood.

Confidentiality

They maintain a high level of confidentiality to ensure that interim results do not inadvertently influence the conduct of the trial or become public prematurely.

Communication

They play an important role in communicating study results to the IDMC members to ensure a well-rounded assessment of the trial's progress and safety.

An IDMC statistician will be involved in:

Data Review and Monitoring

They review and monitor outputs produced from the accumulating data from the clinical trial by the independent programming team. They assess the quality, completeness, and integrity of the data to ensure it meets the study's objectives, and that the protocol for the study, including statistical methods, can be fully executed.

Interim Analysis

They assess the outputs produced for the interim analysis and advise, in discussion with other IDMC members, if the trial should be terminated early for efficacy or futility reasons.

Safety Evaluation

They play a vital role in assessing the occurrence and frequency of adverse events and determining whether there are emerging safety concerns related to the investigational treatment. This sometimes involves summarizing available information in a bespoke way if safety signals emerge or requesting additional outputs from the ISPT.

Efficacy Assessment

An IDMC may need to assess both benefit and safety as part of their role. The IDMC Statistician may assess the efficacy of the treatment being studied using pre-specified outputs of efficacy endpoints produced by the ISPT to determine if there is evidence of a treatment effect, such as a reduction in disease symptoms or an improvement in health outcomes.

Sample Size Reassessment

If sample size reassessment is prespecified, they assess the outputs for this decision, reviewing that the methods have been implemented correctly, and assisting the other IDMC members in understanding these outputs to decide whether the sample size should be increased or not.

Advisory Role

They provide statistical guidance and expertise to the IDMC, who are usually eminent clinicians or professors, helping them interpret the data and make informed decisions about the continuation, modification, or termination of the trial.

Confidentiality

They must also maintain a high level of confidentiality to ensure that interim results do not inadvertently influence the conduct of the trial or become public prematurely.

Communication

They collaborate and communicate closely with other IDMC members to ensure a well-rounded assessment of the trial's progress and safety.

Statistical expertise for IDMCs

IDMCs are recommended for all randomised clinical trials, particularly those with key clinical endpoints such as survival or cancer progression. With so much at stake, it pays to find the right biostatistics partner for an IDMC. Exploristics has extensive statistical IDMC and ISPT experience and can provide the infrastructure for confidential data, clarity of communication and flexibility you need to support oversight of your clinical study.

Further reading:

FDA guidance "Establishment and Operation of Clinical Trial Data Monitoring Committees"

EMEA "Guideline on Data Monitoring Committees"

WHO guidance "Operational Guidelines for the Establishment and Functioning of Data Safety Monitoring Boards"

Let's talk!

If you'd like to discuss the IDMC support we offer, please **book a call** for a consultation with our Biostatistics Services team.

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