

Data Monitoring in Clinical Trials: Considerations in a Seamless Drug Development Paradigm



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Independent Data Monitoring Committees (IDMCS) or Data Safety Monitoring Boards (DSMB's)

- Equipoise
- Needs of trial patients vs science and public health
- When does one need one?
- When is it set up?
- Who is on an IDMC?
- What do they do?
- Whom do they communicate with?
- Considerations for pragmatic trials
- Considerations for seamless (Phase II/III) designs

Equipoise

- The DMC integrates the interim data and asks is the “benefit/risk” to continuing the trial positive? Is there still Clinical Equipoise:
 - *A state of genuine uncertainty as to the advantages or disadvantages of each therapeutic arm in a clinical trial (thefreedictionary.com)*
- Clinical Equipoise is usually limited to the outcomes under study. Does not address larger questions about balancing the interests of research subjects with those of society and science, such as economic considerations, protection of vulnerable populations, and access to treatment.
- Ethical imperative included in the original Declaration of Helsinki
 - *‘Measures to minimise the risks must be implemented. The risks must be continuously **monitored**, assessed and documented by the researcher.’*
 - *‘When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study’*



DMC's and Safety*

- “Predefined statistical stopping boundaries for benefit provide a useful objective guideline, but the reality of making wise judgements on when to stop involves an evaluation of the totality of evidence available and a full assessment of the implications of early stopping both for patients in the current trial and for future clinical practice at large”.
- “The functioning of a DMC is rather different when considering whether a new treatment is unsafe or inferior to the control treatment. First, it is common practice to look more frequently at interim data from a safety perspective”
- “Second, it is generally difficult to define formal statistical guidelines when it comes to the plethora of potential safety problems that a new treatment might give rise to”

*Pocock, S. J. (2006). Current controversies in data monitoring for clinical trials. *Clinical Trials*, 3(6), 513-521



DMC's and “Benefit to Risk”

- Ethical imperative to include B-R included in original DoH in 1964 and all subsequent versions: *Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.*
- Interim quantitative assessments of primary efficacy or key safety outcomes has been well-studied; numerous methods to control type I and II errors from early looks
- **HOWEVER**, integration of risk of harm and potential benefit has been done mainly through clinical judgment of experts on the DMC, without consistent structure
- Recent advances in quantification of B-R have been made through creation of models incorporating weights of predictable harms and benefits *
- Further quantification of B-R for use in interim trial decisions has two distinct advantages
 - Reproducibility of IDMC decisions and clear view of impact of preferences or weights of evidence
 - Impact of medical advances, such as a new method to prevent or treat a key harm or to identify patients not at risk, can be assessed through updated preferences (weights) and used as a basis for further study.

*Phillips LD. Benefit-Risk Modeling of Medicinal Products: Methods and Applications in Sashegyi A, et al. Benefit-Risk Assessment in Pharmaceutical Research and Development, CRC Press, 2013)



Process: When do you have an IDMC?

- When clinical studies utilize irreversible endpoints (e.g., mortality)
- When studies involve unusual or possible risks related to the pharmacological action or toxicity of the compound or procedure under study or due to the underlying disease or population
- When it is necessary to assess the continuing validity (e.g. futility), safety (related to unblinded review of data) and/or scientific merit of a clinical study and/or clinical programme
- When clinical studies are conducted among many investigator sites over a long period of time
- When there is a regulatory requirement for an IDMC (e.g., study conducted in the United States in an emergency setting) or because an IRB requires one.
- When clinical studies are conducted in vulnerable populations (e.g., pediatric, pregnant women, immune-compromised)



Other questions to help determine the need for and value of an IDMC for a given study:

- Would the scientific validity of the study be compromised by people with financial or intellectual connections (e.g. sponsor or PI) review of interim unblinded data?
- Is the study evaluating mortality or another major endpoint, such that inferiority of one treatment arm has safety as well as effectiveness implications for current patients?
- Would it be ethically important for the study to stop early if the primary question addressed has been definitively answered, even if secondary questions are not yet fully addressed?
- Is the study to have a major public health impact, even if no major safety issues are anticipated?
- Will there be multiple trials in a program that meet any of these criteria and require a program IDMC?
- If the trial is not blinded would any of the above still necessitate the need for an IDMC?
- **In a seamless design the need for an independent perspective may always dictate the need**



Avoid significant conflicts of interest in IDMC membership

- Any perceived or actual conflict of interest between the study sponsor, PI, and the IDMC, and between IDMC members and their responsibility for independent monitoring of the study should be avoided.
- Sponsor institution and PI representatives should not be on IDMC's. (**This is essential for a seamless phase II/III design.**)
- IDMC members should be queried about disclosure of activities and these responses should be filed, including negative statements.
- Participation as investigators in the study is considered inappropriate for IDMC members.
- Independence vs Ignorance vs Informed



Analysis

- Design and analysis plan are the responsibility of the study sponsor and PI.
- This includes primary endpoint and stopping guidelines for treatments, subgroups etc.
- Stopping “rules” vs “guidelines” - essential to discuss ahead of time
 - Efficacy
 - Safety
 - Type I error control vs patient welfare
 - Current vs future patients
- IDMC reviews study design, analysis plan, protocol, and stopping rules
- Data may not be all adjudicated or incomplete or lag behind (especially in a pragmatic design)
- Normally their role is **advisory** but does a lot of carry weight



Data for IDMC review

- IDMCs will operate most effectively when they have free access to data relevant to their remit.
 - Data types to be reviewed by the IDMC will be described in the charter. Summary outputs may be revised as required upon request of the IDMC to the SDAC.
 - IDMC members may want the minimum data required to make their assessment; teams should consider the balance between providing sufficient data for the IDMC to perform a meaningful review and resource implications for both the project team staff and the IDMC/SDAC.
 - **In the seamless design, given the need to establish a clear benefit risk picture to move into the next phase the IDMC may be asked to review more data in this scenario.**
 - Data may not not be completely adjudicated (“clean”)
 - ***In pragmatic (EHR based data) trials data may be less complete or lag behind***
 - Biostatistics/safety/clinical functions can advise on the amount/type of data to be reviewed as part of the charter development process.



Study Structure and Communications

The following principles for IDMCs apply and should be reflected in the charter, as appropriate:

- IDMCs are advisory to the sponsoring institution and the authority to terminate studies or programs rests with the sponsor. Stakeholders usually take the DMC's advice
- ***In fact in seamless design the recommendations make decisions and maintain the blind.***
- The specification for information flow in the charter includes the route of feedback between the IDMC, Steering Committee (if one exists), sponsor, PI, and with the Regulatory Authorities, if appropriate. Could be especially important in the “seamless setting”, and essential if trial is blinded
- Potential for bias to arise is typically minimized by:
 - Provisions to avoid contact between the IDMC and investigators. Where IDMCs oversee studies of long duration or entire programs, contact between the IDMC and investigators may be unavoidable, it is strongly recommended that such contact be kept to a minimum.
 - Restricting the review of unblinded interim data or interim data analyses to IDMC members (or supporting staff e.g. unblinded statistician or SDAC) only.



Contact with the IDMC

- Aim for clear points of contact within the sponsoring organization whose accountability for interacting with the IDMC are clear. The number of trial staff interacting directly with the IDMC should be minimized.
 - A designated scientist and/or statistician is usually identified who will facilitate sponsor interactions with the IDMC and trial team.
 - That point of contact is designated as the recipient of IDMC recommendations once the study has started, provided these do not compromise the study blind
 - Once the study has started the the team statistician may interact with the independent statistician/SDAC or IDMC members directly for clarification of statistical issues or queries, provided these do not compromise the study blind.
- Most issues impacting successful functioning of an IDMC/DSMB are caused by issues in this area.



Steering Committees

- Many (most industry for instance) studies do not have a steering committee. They may exist for trials that are extremely large, have massive public health or policy implications. If they do exist:
 - The IDMC is sub-committee of the Steering (Executive) Committee but it is also an independent advisory board to the study sponsors and PI.
 - Timely communication of recommendations is expected, in parallel to both the representative for the sponsor clinical study team and the Steering Committee (if a Steering Committee exists).
 - The IDMC is made aware if any of the Steering Committee members are investigators, so the potential for bias is minimized in their communications with the Steering Committee.
 - While sponsor or PI representatives should not be on IDMC's they are likely on the SC so care should be taken in by the IDMC when communicating with the SC to minimize bias.



FDA Perspectives on Data Monitoring in Seamless Designs*

“The use of an independent data and safety monitoring committee whose role is to review clinical trial data and make recommendations regarding changes to the trial’s conduct may also provide important quality control.

That a trial being conducted to support potential regulatory approval warrants independent oversight is not a new concept, nor is it intended to be burdensome.

In a multiple-expansion-cohort trial, such a committee would take scheduled pauses to review safety and efficacy data from existing cohorts, advise investigators about the addition or closure of cohorts, provide external transparency, and ensure the trial’s statistical integrity.”

*Prowell, T. M., Theoret, M. R., & Pazdur, R. (2016). Seamless Oncology-Drug Development. *New England Journal of Medicine*, 374(21), 2001-2003.



Seamless Design Methodology*

“Clear definitions in the protocol and DMC charters are necessary to ensure that hypothesis selection at interim is totally independent of the second stage data.the second stage data can be defined as all data obtained after the implementation of the adaptation.”

Schmidli, H., Bretz, F., Racine, A., & Maurer, W. (2006). Confirmatory seamless phase II/III clinical trials with hypotheses selection at interim: applications and practical considerations. *Biom J*, 48.



Additional IDMC Considerations for Seamless designs

- IDMC knowledge of treatments based on phase II
- People will know arms that keep going are at least not harmful so some bias could creep in
- Stopping trial vs stopping arms
- Might need more data to review since IDMC is making multiple assessment not just a recommendation
- Phase II data may not be “final” due to lag
- Possible more of a formal decision role than strictly “advisory”
- Communication issues heightened.



Discussion