LE LINEE GUIDE SUI DATA MONITORING COMMITTEE

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Definitions

EMA:

A DMC is a group of independent experts external to a study assessing the progress, safety data and, if needed critical efficacy endpoints of a clinical study.

In order to do so a DMC may review unblinded study information (on a patient level or treatment group level) during the conduct of the study. […] the DMC provides the sponsor with recommendations regarding study modification, continuation or termination.

FDA:

A clinical trial DMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from one or more ongoing clinical trials.

The DMC advises the sponsor regarding the continuing safety of trial subjects, as well as the continuing validity and scientific merit of the trial.

When a single DMC is responsible for monitoring multiple trials […], logistics may be more complex, multiple conflict of interest determinations may be needed for each DMC member.

Notation on terms

DMCs also go under different names like Data and Safety Monitoring Boards (DSMBs) or Data and Safety Monitoring Committees (DSMCs).

Assessing the need for a DMC - FDA

All clinical trials require safety monitoring, but non all trials require monitoring by a formal committee.

Three general guiding rules:

- What is the Risk of Trial Participants?
- Is DMC Review Practical?
- Will a DMC Help Assure the Scientific Validity of the Trial? (the sponsor who knows interim data may well find itself in a position where a protocol change that appears to be in the interest of the trial or even essential for continuing the trial, cannot be made without potentially introducing biases that can be neither quantified nor corrected)

Assessing the need for a DMC - EMA

- Indication
- Study Endpoint(s)
  - Life-threatening diseases, DMC is needed for ethical reasons
- Study Duration
  - Large study, long duration and multi-center
  - DMC may not be practical for trials of short duration as it does not allow for appropriate preparation of information.
    - Exceptions may be trials with important safety concerns

Assessing the need for a DMC - EMA

- Study population
  - There is a need to set up a DMC in potentially fragile population (e.g. pregnant women, the very elderly), or other vulnerable population such as paediatric population even in a non-critical indication
    - The same applies to terminally ill or mentally disable patients
  - Population at elevated risk of death, or other serious outcome
- Study drug
  - DMC is indicated in case of prior knowledge or strong suspicion that a treatment under consideration has the potential to harm the patients
- A particular safety concern (e.g. invasive treatment)
- Possibility of serious toxicity with the study treatment

Assessing the need for a DMC

Trial type	Safety concern	Integrity concern	Recommendation
Long-term, multi-center, large patient exposure trials	Yes	Yes	External DMC
Trials involving mortality or serious morbidity	Yes	Likely	External DMC
Trials with safety issues requiring monitoring (a priori reasons for a particular safety concern (e.g., administrations particularly invasive)	Yes	Possibly	External DMC
Trials with IA to allow for early stopping for efficacy/futility	Possibly	Likely	External DMC
Trials with adaptive designs	Possibly	Possibly	External DMC
The study is being performed in a potentially fragile population or other vulnerable populations	Yes	Possibly	External DMC
Early phase trials	Possibly	Unlikely	Internal DMC
Short-term trials	Possibly	Unlikely	Unlikely to be required

DMC Responsibilities

The sponsor and the investigators participating in a clinical trial bear the final responsibility for the conduct of the trial.

This responsibility cannot be transferred to a DMC

DMC Responsibilities

Specifically, the sponsor:

- Manages the study by a close contact with investigators
- Assures a careful data collection
- Submit to the DMC, SAEs and other safety related problems
- Prepares safety reports

DMC Responsibilities

- SAFETY:
  To regularly review safety data gathered from an ongoing clinical trial
  - Risk/benefit assessment to weigh possible safety disadvantages against a possible gain in efficacy
- EFFICACY:
  To evaluate efficacy of the interventions being studied, where required

DMC Responsibilities

- STUDY QUALITY:

  To monitor the study conduct and its integrity.

  (e.g. Evaluation of protocol adherence and patient withdrawals as numerous protocol deviations and/or high dropout rate could be a signal of possible problems with respect to safety, efficacy, or feasibility of study procedures

DMC Responsibilities

- Recommendation on further study conduct
  - To continue as planned without changes
  - To modify some aspects of the trial (e.g. I/E criteria, addition of some lab tests, exclusion of a particular subgoup)
  - To temporarily suspend or definitely enrollment and/or trial intervention until some uncertainty is solved
  - To terminate the study earlier than planned

Establishing a DMC

Three major aspects with respect to membership should be considered when establishing a DMC

Composition:

- As DMC work is a multidisciplinary task, a DMC needs expertise from different scientific areas.
- Qualified clinicians
- At least one expert in biostatistics
- A member with expertise in ethical questions (e.g. for trials with unusually high risks or with broad public health implications)
- Patients' representative

Establishing a DMC

Three major aspects with respect to membership should be considered when establishing a DMC

Qualification:

- Scientific expertise relevant to the indication being studied
- Practical experience with conducting clinical trial
- Good understanding of problems and limitations of clinical trials
- Prior experience in DMC for some of the members (more important for the chair than for other DMC members)

Establishing a DMC

Three major aspects with respect to membership should be considered when establishing a DMC

Independence:

- Complete independence not possible because:
  - DMC is appointed by the sponsor
  - The sponsor pays expenses and honorarium
- Financial conflict of interest
  - DMC members should not have financial interest in the outcome of the study
  - DMC members should not be involved simultaneously in an other study in the same indication, but with a different sponsor

Establishing a DMC

Three major aspects with respect to membership should be considered when establishing a DMC

Independence:

- Non-financial / intellectual conflict of interest
  - To avoid the planned autorship of DMC members in publications on study results
  - Those who may have previously formed a deep-rooted opinion on the characteristics of the treatments under investigation
  - Study investigator directly involved in the trial (active site recruiting subjects/patients)

References

- EMA:

Guideline on Data Monitoring Committees (EMEA/CHMP/EWP/5872/03)

- FDA:

Guidance for Clinical Trial Sponsors. Establishment and Operation of Clinical Trial Data Monitoring Committees (OMB control no. 0910-0581)

- ICH:

Note for Guidance E3 (Structure and Content of Clinical Study Reports)

Note for Guidance E6 (Good Clinical Practice)

ICH Note for Guidance E9 (Statistical Principles for Clinical Trials)

- European Commission:

Directive 2001/20/EC relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

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