ROTTAPHARM
BIOTECH

Il DMC charter e l'impatto sul protocollo

Beatrice Barbetta
Rottapharm Biotech

VIII Congresso nazionale BIAS
Verona, 30 giugno 2016

D(ata)M(onitoring)C(ommittee)

A DMC is a group of **independent experts,** external to a study, that **reviews on a regular basis accumulating data** from a clinical trial.

DMCs are considered to have '**stewardship**' of a trial. DMC has responsibilities to both participants (in term of safety) and the Sponsor (in terms of trial credibility).

Three steps to set up a DMC

1. Decide if you need a DMC

All clinical trials require safety monitoring, but not all trials require monitoring by a formal committee external to the trial.

Factors to consider:

- Risk of the trial participant
- Duration of the trial
- Scientific validity of the trial

Three steps to set up a DMC

2. Choose DMC members

The Sponsor generally appoints members of a DMC.

Factors to consider:

- Relevant expertise
- Experience in CT and DMC
- Absence of serious conflicts of interest

Three steps to set up a DMC

3. Write a DMC charter

The purpose of this document is to describe the roles and responsibilities of the DMC, including the timing of meetings, methods of providing information to and from the DMC, frequency and format of meetings, statistical issues and relationships with other Committees.

Charter should be agreed and signed by both DMC members and the Sponsor.

The charter

- Introduction
- Roles and responsibilities
- Composition of the DMC
- Organization of DMC meetings
- Procedures to ensure confidentiality
- Statistical monitoring guidelines
- Content of the DMC’s report

The charter: Introduction

This Charter is for the Data Monitoring Committee for the Study Protocol XXX whose title is 'YYY'.

The Charter defines the primary responsibilities of the DMC: its relation with other trial components, its membership, and the purpose and timing of its meetings. The Charter also provides the procedures for ensuring confidentiality and proper communication and the statistical monitoring guidelines to be implemented by the DMC.

This Charter is designed to comply with guidelines regarding data and safety monitoring from the Food and Drug Administration and the European Medicine Agency.

The charter: Roles and responsibilities

DMCs have the followings responsibilities:

- Performing the planned interim data analysis;
- Reviewing data for the ongoing safety evaluation;
- Preparing minutes of the meetings;
- Recommending appropriate actions to the Sponsor:
  - No changes to the trial/re-estimation of the SS
  - Early termination of the trial/treatment arm
  - Request for additional analyses
  - Modification of the selection/recruitment/retention of patients
- Evaluating validity and scientific merit of the trial.

The charter: Roles and responsibilities

The DMC is in charge to protect the scientific validity of the study. The DMC has the responsibility to provide recommendations related to the protection of the participants' safety (also considering factors external to the study) and to provide recommendations about the study completion according to the study protocol or re-estimation of the number of subjects to be enrolled. The DMC may also formulate recommendations relating to the study procedures for data management and quality control.

The DMC acts as advisor to the Sponsor, who is in charge of and responsible for the final decision.

In details the DMC has the following responsibilities:

The charter: Composition of the DMC

There is no ‘one size fits all’ for DMCs: different models may be needed for different situation.

A DMC consists of at least three members: a Chairman, a Clinician and a Biostatistician.

All members have no financial, scientific, or other conflict of interest with the study.

DMC members can be removed.

The charter: Organization of DMC meeting

Initial DMC meeting

- Attended by DMC members and the Sponsor;
- Takes place prior to the finalization of the study protocol.

Formal Interim Analysis meeting

- Attended by DMC members only;
- Review interim analysis results.

The charter: Organization of DMC meeting

Ongoing Safety/Trial Integrity Review

- Attended by DMC members only;
- Review safety data that may have occurred since the previous meeting.

Final Study meeting

- Attended by DMC members only;
- Review efficacy and/or safety data and provide recommendations to the Sponsor for future trials.

The charter: Procedures to ensure confidentiality

To enhance the integrity and credibility of the trial, procedures are implemented to ensure the DMC has the sole access to evolving information regarding comparative results of efficacy and safety data, aggregated by treatment arm.

At the same time, procedures are implemented to ensure that a proper communication is achieved between DMC members and both Investigator and Sponsor.

The charter: Procedures to ensure confidentiality

Closed sessions

- Attended by DMC members only;
- Review the **efficacy and safety data in unblinded format**, in relation to the conduct and progress of the study.

Open sessions

- Attended by DMC members and the Sponsor/study team/Steering Committee/Investigators;
- Provide specific clarification or respond to any issue arisen;
- Discussion **focus on** the **conduct** and **progress** of the study, and pay special attention to the **pooled safety and efficacy data**.

The charter: Statistical monitoring guideline

Statistical monitoring procedures used by DMCs to guide their recommendations regarding termination or continuing the trial should be defined.

Procedures describe:

- interim data analysis;
- ongoing safety review.

The charter: Statistical monitoring guideline

Interim Analysis

Interim analysis is conducted with the aim to decide **whether** to **complete** the study according to the study protocol or to **re-estimate** the sample size. Interim analysis can be conducted also to decide whether to recommend **early termination** on the ground that the trial in unlikely to meet its objectives and therefore there is no basis for continuing enrolment and/or follow-up or for safety.

The charter:
Statistical monitoring guidelines

Ongoing safety review

The DMC is responsible for monitoring patient safety and study progress, providing the Sponsor with recommendations related to the protection of the patient's safety.

The charter: Statistical monitoring guideline

Details to be specified:

- Objectives (early efficacy/re-estimation of the sample size/futility interim analysis);
- Timelines;
- Primary efficacy variables;
- Other variables collected;
- Planned descriptive analyses;
- Planned efficacy analyses;
- **Blinded/unblinded** data;
- How and from who DMC receives data;
- Additional data.

The charter:
Content of the DMC's report

Open minutes

- Describe the proceedings in the Open Session meeting
- **Summarize**, in a **blinded and non-confidential manner**, all recommendations by the DMC.

Closed minutes

- Describe the proceedings from the Closed meeting;
- **Contain unblinded information,** it is important that they are not made available to anyone outside the DMC.

The charter: Content of the DMC's report

On June 29, 2016, the DMC met/ performed the TC for the purpose of conducting the monthly review of blinded data collected in the above titled study.

The Committee was provided with enrolment data, patient profiles, primary, secondary endpoints data, and adverse event data on the subjects enrolled up to June 16.

After reviewing the materials and data provided, the Committee requests/doesn't have any request:

1) xxxxx

2) xxxxx

3) xxxxx

The Committee recommended that the protocol continue as approved.

OR

The Committee recommended that the protocol should be amended for the continuation of the trial as follows:……..

OR

The Committee recommended to STOP the recruitment because……..

The next review a conference call/meeting will be take in July 2016 and will consist of an partially unblinded review.

The charter:
Content of the DMC's report

After each meeting the **DMC makes a recommendation to the Sponsor** to continue, modify or terminate the trial.

- Based primarily on safety and efficacy considerations;
- **Take into consideration statistical monitoring guidelines** defined in the charter;
- Take into consideration all available data from the study or relevant information external to the study may be necessary to arrive to a more complete judgement.

The charter:
Content of the DMC's report

The recommendation should be communicated in writing to the Sponsor and should include:

- **Exact title of the study reviewed**,
- Date and version of the study,
- Date and place when/where the recommendation was made,
- **Clear statement of the recommendation**,
- Clearly stated reason for this recommendation,
- **Signature (dated) of the chairman**.

The charter:
Content of the DMC's report

In this document **DMC has to refrain from revealing** to the Sponsor **information that would lead to compromising the integrity of the trial**, unless such release is required to protect participants' safety.

Sponsor should define in advance procedures for implementing the recommendation of the DMC.

DMC: Impact on the Study Protocol

- Description of the DMC tasks;
- Description of the Statistical Methods and their impact on type I and type II error;
- Impact on Sample Size estimation or on other changes to the study design;
- Impact on Stopping rules;
- Interaction with other Groups (Steering Committee, Executive Committee).

Thanks for your attention!