

Austria-Japan Joint Statistics Workshop
Data monitoring committees in clinical trials

Guidance on Data Monitoring Committee: Regulatory Perspective in Japan

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Guideline on Data Monitoring Committee

- Started guidance development from 2011
- “Guideline on Data Monitoring Committee” (PFSB/ELD notification No.0404-1) was issued in April 4, 2013.

Background of guidance development

- Rapid accumulation of clinical study data allowed by advance of information technology
 - Use of electronic Data Capture (EDC)
- Active use of interim analysis
 - Efficiency of clinical development
 - Use of adaptive design
- Globalization of drug development
 - Participation in large-scale MRCTs
 - (implementation of Asian clinical trials)

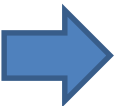
Background of development of DMC guidance

- Accumulated experiences in clinical trial consultation meetings and new drug review
 - Use of adaptive design
 - Necessity of appropriate safety data monitoring
 - Necessity of establishment of DMC
 - Appropriateness of management of DMC
 - Relationship of DMC and trial sponsor
 - Independency of statisticians
- ➡ Necessity of guidance document on basic principle of establishment and management of DMC

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1. Introduction and background

- Purposes of the guidance
 - To provide general guidance, at the current moment, related to the necessity, role, establishment, and management of a DMC in a clinical study (trial) of a drug or medical device by a sponsor (including those who conduct clinical trials by themselves).
 - Background
 - Discussion on earlier decision-making and interim change of the design
 - Globalization of drug development and participation in global clinical trials
-  Necessity of guidance for DMC, which plays important roles in interim decision making in Japan

1. Introduction and background

- Why the guidance on “~~Independent~~ Data Monitoring Committee”?
 - DMC: Data Monitoring Committee
 - IDMC: Independent Data Monitoring Committee
 - DSMB: Data and Safety Monitoring Board
- DMC was proposed as an organization for evaluating the data of an ongoing clinical study from a standpoint different from that of whom actually conduct the clinical study.
- DMC does not necessarily have to be independent from the sponsor .
- The guidance was developed for “DMC” to cover DMCs of broad kinds of studies including early phase clinical study which need safety evaluation.

1. Introduction and background

- “Data monitoring”
 - Two types of monitoring
 - Investigation of the implementation status of the entire clinical study
 - the evaluation of efficacy and safety data accumulated while the study is being conduct
 - In this guidance, “data monitoring” is used for later meaning.
- “Interim analysis”
 - In this guidance, the analysis that is conducted under unblinded conditions during the course of the study in association with data monitoring in a between-group comparative study, with the purpose of between-group comparison of efficacy or safety.

2.1 Judgment of necessity for establishing DMC

- Data monitoring by DMC is not required for all clinical studies.
- A thorough consideration should be given to the necessity of DMC.
 - Establishing a DMC requires a certain amount of resources and results in more complicated study management.
 - Objective of the clinical study, study design, endpoints, study duration, and patient population should be considered.
- For example, a DMC is established by the sponsor for
 - controlled studies using death or other serious outcome as the endpoint
 - large-scale and long-term clinical studies
 - early phase clinical studies conducted with relatively little safety information available in advance
 - studies with a high expected risk as judged from the characteristics of the drug or subjects,when independent monitoring of efficacy and safety data is necessary during the course of the study period.

2.2 Roles and responsibilities of DMC

- The DMC evaluates the data of an ongoing clinical study and provides appropriate advice and recommendations to the sponsor, in order to
 - ensure the safety for subjects
 - assure the integrity of the clinical study as much as possible
- Termination of a clinical study and a change in the study plan may be subject to
 - social effects such as expectations from society for new drugs
 - organizational influence by those involved in the development with different roles
 - intellectual curiosity of persons concerned
 - market pressure
- Although the criteria for study termination/continuation in the study protocol is important, the DMC should thoroughly consider and discuss the issue from other various viewpoints as well.

2.3 Roles and responsibilities of DMC members

- The DMC members
 - should be knowledgeable about the methodologies of clinical studies and about the roles of the DMC
 - should be fully competent to bear the responsibilities
 - must be qualified to express unbiased opinions required for the DMC; they should not have any serious conflict of interest with the sponsor
- Each of the DMC members must fully recognize the roles and responsibilities of the DMC, and also should be fully aware of being in a position to have access to the results of the interim analysis and strictly avoid leaking available information or exploiting the information for private interest.
- A DMC consists of multiple members with different specialties, so they should express evidence-based opinions, respect the specialty and opinion of other members

2.4 DMC activities

- Safety monitoring
 - Recommendation of premature study termination for safety reasons
 - Comparison of the incidence of adverse events between the test treatment and the control
 - Detailed investigation of clinically significant adverse events
 - Recommendation of study continuation with protocol revisions such as change in enrollment criteria in order to minimize the risk of adverse events
- Evaluation based on pre-defined interim analysis
 - premature study termination because of the efficacy or futility

2.4 DMC activities

- Monitoring of study conduct status
 - Such as subject enrollment, eligibility of study subjects, incidence of drop-outs, and protocol compliance
- Use of external information
 - The DMC may be required to evaluate the effect of external data such as results of related studies on the ongoing clinical study, from a neutral position.
 - There is a possibility of information exchange between DMCs in ongoing related studies is useful
 - It should be considered that there may be inflation of type I error rate and the credibility of the study results may be damaged due to insecure independence of the other study.

2.5 Relationship with other clinical study-related organizations

- Sponsor
- Institutional Review Board (IRB)
- Event/endpoint assessment/adjudication committee

3.1 Structure of DMC

- DMC members are appointed by the sponsor.
 - In most cases, the DMC consists of at least 3 members including clinicians at least 1 statistician familiar with clinical study design, data, and statistical analysis
 - Considering experience and conflict of interest
- Conflict of interest
 - The most important point is to ensure that the DMC rightfully expresses its opinion from a neutral standpoint and, for this purpose, to appropriately control the conflict of interest.
 - Disclosure of conflict of interest
 - Process of the DMC reaching a conclusion should be available for post-hoc check by a third party

3.1 Structure of DMC

- Points to be considered in global clinical trials
 - Ideally members should be selected from each of the participating regions or at least from a subset of regions.
- DMC management
 - Establishment of secretariat to support the management
 - Appointment of statisticians (including programmers) in charge of interim analysis
 - Use of CRO : Contract Research Organization
 - Sponsor should be responsible for selecting appropriate CROs

3.2 Handling of interim data

- There is a possibility that the sponsor or investigator happen to know unblinded data, which may affect study conduct and/or analysis of data
- Unblinded data and results of comparison based on the interim analysis should be accessible only to the DMC and to the statistician who prepares the report of the interim analysis to be submitted to the DMC.
- The sponsor should take appropriate measures to prevent the leakage of the interim data and the results.

3.3 Procedures for monitoring and recommendations, and points to be considered

- 3.3.1 Preparation of DMC charter
 - DMC works according to the procedure (DMC charter) agreed upon by the sponsor and the DMC.
 - Objectives of the DMC
 - Members of DMC
 - Control of conflict of interest
 - Relationship between DMC and other study-related individuals
 - Schedule and form of planned meetings
 - Attendees of DMC meetings
 - Data to be discussed at DMC
 - Procedure for interim data analysis, data unblinding
 - Persons qualified to have access to the unblinded interim data
 - Procedure for making recommendations to the sponsor and for the action to be taken by the sponsor

3.3 Procedures for monitoring and recommendations, and points to be considered

- 3.3.2 Holding of DMC meeting
 - Open session
 - DMC members, representatives of the sponsor, the steering committee members, and other study-related persons
 - Information mainly related to the study implementation status is provided to the DMC for discussion.
 - Closed session
 - Only DMC members, the statistician in charge of the interim analysis, and the DMC secretariat
 - Non-disclosed efficacy and safety-related monitoring data submitted by the statistician in charge of the interim analysis
 - What recommendations should be made to the sponsor.

3.3 Procedures for monitoring and recommendations, and points to be considered

- 3.3.3 Recommendations
 - DMC's recommendations to the sponsor should be made in writing while maintaining the blindness of the study.
 - Study continuation (no change in the study protocol, change in the study protocol)
 - Study continuation with modification of study plan
 - Temporary suspension of the study
 - Study termination
 - Generally details of the study results are not conveyed.
 - The sponsor is responsible for the decision of study termination, change in the study plan, in response to the DMC's recommendations.
 - It is possible to consult the regulatory agency in advance regarding the possible effect of such a decision.

3.3 Procedures for monitoring and recommendations, and points to be considered

- 3.3.4 Necessary records
 - The DMC must prepare and store the minutes of all meetings related to the DMC.
 - The meeting minutes of open sessions
 - The meeting minutes of closed sessions
 - Should be prepared in such a way that the process leading to the conclusion can be confirmed a posteriori by the third party.
 - DMC in the clinical study related documents
 - Clinical study protocol
 - Clinical study report

4.1 Independence of DMC

- DMC as an organization independent from the sponsor
 - Highly objective data monitoring
 - Prevents study results being affected by biases
 - Expected to lead to improved credibility of the study and to adequate assurance of safety for subjects
- The security of the independence of the DMC
 - Not participate in the study as other roles
 - Not to have any financial or other important conflicts of interest
- Consideration should given so that necessary information can be exchanged between the DMC and the sponsor, under a certain restriction.

4.2 Relationship with the sponsor

- Sponsor's responsibility
 - Selecting and appointing DMC members
 - Creating an environment that allows smooth management of DMC
 - Ensuring the independence of the DMC in decision making
 - Decision making in response to the recommendations by the DMC

4.3 Independence of statistician in charge of interim analysis

- Statistician in charge of interim analysis
 - Can access to unblinded data
 - The unblinded data should be appropriately controlled so that the data are not accessible to anyone except the statistician in charge of the analysis
- Independency of statistician in charge of interim analysis
 - It is appropriate that the statistician be not involved in decision making in designing of the study and its changes or in the management of the study
 - Basically, the statistician in charge of the interim analysis should not serve as the statistician of the DMC.

5. Statistical considerations associated with the interim analysis

- The DMC statistician should,
 - recognize statistical problems particular for the interim analysis, such as inflation of the type I error rate due to multiple statistical analyses
 - examine the validity of the statistical analysis plan at the planning of the clinical study
 - make necessary recommendations to the sponsor
- DMC members other than the statistician should understand the statistical problems in the interim analysis

Summary

- Only basic principles are described in the guidance document.
- There are possibility of variations for trial designs and implementation system.
- In order to ensure the safety for subjects and the integrity of the clinical trials, it is important to have discussion continuously, with the issuance of guidance
 - Optimal implementation system for each trial design
 - Implementation of clinical trials with interim changes of the design