

# **Guideline on Clinical Trial Data Monitoring Committees**

**(Draft for Public Review)**



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# **Guideline on Clinical Trial Data Monitoring Committees**

## **1. Introduction**

In clinical trials, it should be ensured that the subjects in the trial do not bear unnecessary risks due to ethical reasons. On the other hand, it is also important to ensure that the trial is not terminated prematurely to answer the preset scientific questions. Therefore, clinical trials sometimes require the establishment of Data Monitoring Committees (DMCs) to undertake these tasks. A DMC is an independent expert group with relevant expertise and experience to regularly review accumulating data from one or multiple ongoing clinical trials in order to ensure the safety of subjects in clinical trials, as well as the validity and scientific merit to continue the trials. The DMC is also referred to as the Data Safety Monitoring Board (DSMB) or Independent Data Monitoring Committee (IDMC). For the sake of uniformity, such group of experts is referred to as the Data Monitoring Committee (DMC) in this guideline.

This guideline focuses on the responsibilities, tasks, and composition of DMCs in clinical trials, as well as practical and statistical considerations during the operation of DMCs. It also emphasizes the independence of a DMC and the principle to avoid conflicts of interest and aims to provide guidance for the establishment and operation of DMCs to ensure its proper functioning and smooth implementation.

A list of ICH guidelines relevant to the topic of DMC, including but are not limited to the following, are available for reference when reading this guideline.

- ICH E3 (Structure and Content of Clinical Study Reports)
- ICH E6 (Good Clinical Practice)
- ICH E8 (General Considerations for Clinical Trials)
- ICH E9 (Statistical Principles for Clinical Trials)
- ICH E17 (General Principles for Planning and Design of Multi-Regional Clinical Trials)

## **2. DMC Responsibilities and Tasks**

The DMC, together with the sponsor, the investigators, and all other committees that oversee clinical trials share the same responsibilities for conducting high-quality clinical trials. The key difference between a DMC and other oversight parties is that the DMC can use the efficacy and safety data collected during the course of the clinical trial in an unblinded manner to perform periodic or ad hoc risk-benefit assessment, in accordance with a predefined protocol to provide the sponsor with recommendations. Other roles of a DMC include a review of protocol and related data analysis plans, approval of the DMC charter, and completion of the DMC meeting minutes. During the course of the study, the DMC should implement the plan pre-specified in the protocol and should not be directly involved in protocol amendments, in particular, those related to efficacy evaluations. It should also be noted that the primary role of the DMC is to provide recommendations that are accepted or rejected at the sponsor's discretion.

The need for establishing a DMC in a clinical trial depends on the specific needs of the trial itself. For example, for most exploratory early phase trials and short-term studies without any important safety concerns, DMCs may not be required. However, for confirmatory clinical trials, especially those with large samples, high risk, complex designs with adaptive features, or clinical trials with longer observation periods, it is often necessary to establish DMCs.

Whether or not a DMC should be established, the roles and responsibilities of the DMC should be clearly defined in the protocol (including amendments) and the DMC charter. It is not acceptable if the DMC related content is not described in the study protocol or the DMC charter, or if the subsequent implementation of the DMC deviates meaningfully from the study protocol.

DMCs in clinical trials have mainly the following responsibilities: safety monitoring, efficacy monitoring, study conduct monitoring, recommendations for modification of trial designs, and evaluation of regional effects in multi-regional clinical trials, etc.

### **2.1. Safety Monitoring**

One of the important tasks of the DMC is to monitor the safety of subjects throughout the clinical trial. In particular, sponsors should consider establishing DMCs if there is pre-trial evidence that the study intervention may have significant safety concerns, such as potentials for having serious adverse reactions, serious toxicities, special safety concerns, or the intervention is for a life-threatening illness, or the study is performed with fragile patient populations (e.g., pediatric patients, pregnant women, very elderly, and terminally ill patients).

Prior to the start of the trial, the sponsor should discuss fully with the DMC members all potential adverse events and adverse reactions of special interest in the trial. Even so, there may be situations during the safety monitoring that have not been considered in advance, such as external safety information from other completed or ongoing clinical trials, for which the DMC will need to learn more details and additional information in order to make correct judgment.

If there are serious safety concerns during the clinical trial, DMC may consider recommending termination of the trial or suspension of the trial until the safety issues are further investigated.

### **2.2. Efficacy Monitoring**

Another important task for a DMC is to assess efficacy by reviewing the interim analysis results and assist the sponsor in making decisions on whether to terminate the trial early due to efficacy. Typically, the DMC, following an interim analysis of the unblinded data collected, determines whether the efficacy results meet the criteria for early termination of the clinical trial according to the statistical plan pre-specified in the protocol. Recommendations for early termination of the trial mainly include the following two situations: ① the interim analysis shows that the probability of eventually receiving positive outcomes is very small upon completing the trial as originally planned, hence it is meaningless to continue the trial. Therefore the trial may be terminated early due to futility; ② the interim analysis shows that the trial meets the prespecified

statistical criteria for early termination due to efficacy, so the trial is terminated early with positive results.

When recommending trial early termination due to efficacy, in addition to meeting statistical requirements, the DMC should carefully consider the reliability and validity of the interim analysis data, the adequacy of safety information, the internal and external consistency of the results, and regulatory requirements for such clinical trials.

### **2.3. Study Conduct Monitoring**

The DMC also monitors trial conduct by reviewing study data, including protocol adherence, recruitment status, subjects dropout, data completeness and so on. The DMC should recommend that the sponsor improve the quality of the study if serious problems are found in the conduct of the trial. For example, after DMC reviews the data collected and identifies randomization errors, a large proportion of missing data, or a serious imbalance in baseline characteristics between groups, it is necessary to promptly recommend that the sponsor identify and address the cause of the problem.

### **2.4. Recommendations for Modifications of Trial Designs**

During the course of the trial, accumulating data or emerging external information may suggest that some initial assumptions made at the study design stage, for example, dose regimen, study population, or effect size used for sample size estimation, are not reasonable. So without compromising the integrity of the trial, in accordance with the rules pre-specified in the protocol, the DMC can make recommendations on the modification of the ongoing trial design, which will help enhance the scientific rigor of the trial and reduce the risk of trial failure. For complex clinical trials, such as trials having adaptive designs, it is often necessary to modify procedures or statistical methods of ongoing trial based on accumulating data in which cases the involvement of DMC as an independent third party is particularly important.

### **2.5. Evaluation of Regional Effects in Multi-regional Clinical Trials (MRCTs)**

For a multi-regional clinical trial, a DMC should pay special attention to regional effects when performing the tasks stated in previous sections. If the patient populations from different countries or regions have large heterogeneity in baseline risk or treatment effect, the overall effect may not be consistent with a regional effect, especially when only a portion of data has been collected for the interim analysis. The more diverse the patient population is, the more important it becomes for the regional assessment of risk-benefit over the proposed indication. Different regulatory requirements in different countries or regions should also be considered. For example, in multi-regional clinical trial MERIT-HF study, recommended by the DMC, the study was terminated early due to substantial improvement in all-cause mortality, one of the primary efficacy endpoints. However, the mortality results for U.S. patients were neutral (not just because the US small size is small), which eventually led to the rejection of US regulatory agency for the mortality indication. Note that for multi-regional clinical trials that are

prematurely terminated due to established effectiveness, some regions with small sample sizes may not show regional efficacy. The participation of DMC members representing different regions in MRCTs can better help monitor the implementation of the trial in its entirety and in respective regions.

### **3. Establishment of DMC**

The purpose of establishing a DMC should be clearly stated in the protocol. The establishment of a DMC should focus on the composition and independence of members and should avoid potential conflicts of interest. The setting up of a DMC, including the selection of members and formation of DMC charter, should be completed by the sponsor prior to the enrollment of the first trial participant.

#### **3.1. Composition of DMC**

The work of DMC is multidisciplinary, so DMC members should be experts from different scientific areas. The inclusion of DMC members depends on the study objectives of data monitoring, the disease area under study and the requirement for the knowledge of the investigational products. Typically, DMC members are experienced clinicians with relevant disease expertise and statisticians familiar with study designs. But sometimes experts specialized in other related disciplines may be invited as needed. For example, some trials need to invite experts in toxicology, epidemiology, pharmacy, or medical ethicists to review the trial data. In large-scale MRCTs, special consideration should be given to the representation of DMC membership in each major participating country and region, e.g. including DMC representatives from countries or regions with large sample size contributions.

A DMC consists of a chair and general members. The DMC chair is generally appointed by the sponsor to oversee the operation of the DMC. A DMC may have as few as 3 members (including the chair) with the size varying according to the scope of work and the complexity of the trial. For a complex trial (such as a large MRCT), the size of the DMC can be larger.

DMC members should not only have expertise in the relevant areas of the study but also have extensive experience in clinical trial conduct. The DMC chair should have a deep understanding of the objectives and design of the participating trials, be familiar with the operation of the clinical trial and the DMC, and generally should have the experience in chairing or serving a DMC. The chair is usually a clinician or statistical expert experienced in clinical trial conduct, depending on the primary objective of setting the DMC. All members of a DMC have equal right to make recommendations and their opinions should all be taken into consideration. All recommendations made by the DMC should generally reach an internal consensus.

The appointment and replacement of DMC members must be in accordance with the DMC charter and well documented. DMC members should generally not come from the same affiliation as the study investigators.

Since a DMC may review the analysis results of unblinded data, an Independent Statistical Team (IST) needs to be established in parallel to support the work of the DMC (see Chapter VI, Section 2 for details). An assistant, who should be independent of the study-related parties and does not have voting right for DMC decisions, may be needed to undertake administrative work within the DMC. For clinical trials with complex designs such as adaptive designs or master protocol designs, the DMC may also invite external experts from relevant fields to provide advice, it should be noted that these experts must be independent of the ongoing clinical trials and will not have voting rights. Such activities should be described in detail in the DMC charter and reported in DMC meeting minutes.

### **3.2 Independence of DMC**

The independence of DMC is crucial. Objective review of the data will help protect the integrity of the study and reduce bias in the study results. DMC members may not play any role in or serve as consultants to the sponsor's study team. DMC members should maintain only necessary contact with the sponsor.

It is unrealistic to expect DMC to be completely independent from the sponsor. However, any negative impact on the clinical studies caused by DMC's connection with the sponsor should be minimized. In most cases, DMC members are appointed by the sponsor and will receive the service fees paid by the sponsor. DMC members are mostly senior researchers who likely have previously worked with the sponsor and/or the investigators. When the impact caused by these connections appears minor (e.g., prior DMC service for the same sponsor for a different product several years in the past), the experts concerned may be allowed to serve in the DMC after the disclosure of the information to the sponsor and other DMC members; if the impact is large (see next section), the member will need to be withdrawn from the DMC.

### **3.3 Avoiding Conflicts of Interest**

DMC members should avoid financial, intellectual and other conflict of interest.

**Financial conflicts of interest:** In general, those holding financial interests of the sponsor or competitors are considered to have potential financial conflict of interest and should not serve the DMC. In addition, there may be a concern of conflict of interest if the compensation for services received from the sponsor is beyond a reasonable range.

**Intellectual conflict of interest:** If some scholars have preset views on the relative merits of the interventions under study, it may not be possible to make an objective assessment of the data and therefore should not serve the DMC. The independence of the DMC may also be affected if the DMC member is or will be a lead author of a publication on the trial results.

**Other conflicts of interest:** If a DMC member is an external consulting expert of the regulatory agency, the conflict of interest may arise if the application the DMC member is reviewing is directly related to a study that the member supports.

Prior to the establishment of the DMC, all potential DMC members should report to the sponsor any information that could be perceived as a conflict of interest for the sponsor to determine the eligibility of their DMC membership.

Any potential conflicts of interests that develop during the course of the trial should be immediately disclosed to the DMC and the sponsor for appropriate action, including withdrawal, replacement, and cooptation of DMC members.

## **4. DMC Operation**

### **4.1. Developing DMC Charter**

To ensure the transparency of the DMC operating procedures, a DMC charter should be established before the start of the trial to clearly describe how the DMC works and how it communicates with other relevant parties. The charter is normally prepared by the sponsor and approved by the DMC. The main contents of the charter include:

- ① Overview of study objectives, study design, and purpose of establishing a DMC;
- ② Composition of DMC, rules of member replacement, scope of responsibilities, conflict of interest assessment rules and declaration of possible conflict of interest;
- ③ DMC meeting format, including meeting planning, schedule, quorum, and participants, etc.;
- ④ Methods of data analysis, including statistical criteria (to be consistent with the protocol);
- ⑤ The acquisition permission of interim analysis data and results
- ⑥ Procedures and timing of providing analysis results to DMC;
- ⑦ Communication between DMC and sponsor, independent statistical team, and other stakeholders, including the process and plan for communication of DMC recommendations;
- ⑧ Preparation and archiving of documentation (meeting minutes).

### **4.2. DMC Meetings**

In general, face-to-face DMC meetings are recommended. Teleconferences may be necessary in some situations, in particular when the purpose of the DMC meeting is only a regular trial status update, or DMC is composed of members from different countries for a multiregional trial or urgent issue arises in a trial. At the start of a DMC meeting, each DMC member is required to declare free of conflict of interest with the study, or the member must withdraw from the meeting.

- (1) Type of meeting

There are three types of DMC meetings: orientation meetings, scheduled data review meetings, and unscheduled ad hoc meetings.

### 1) Orientation meeting

The DMC orientation meeting is the first meeting held after the DMC is established. The purpose of the meeting is for DMC members to familiarize themselves with the context of the study, the DMC's workflow, and their respective responsibilities while reviewing and approving the DMC charter. The orientation meeting will normally take place in the final phase of the protocol development and should occur before the first subject is enrolled. Participants of the orientation meeting may include, but not limited to, all DMC members and administrative assistant (if available), sponsor's management team, the study team, and the Independent Statistics Team. The agenda for the meeting includes: understanding the investigational product(s); getting familiar with the study plan; reviewing the protocol(s); aligning the DMC responsibilities; discussing and finalizing the DMC charter; discussing the format and content of the interim analysis report(s); determining the timing of DMC meetings; determining the timeline for the interim analysis report(s) to be submitted to the DMC prior to the DMC meetings; maintaining meeting minutes; and other routine administrative work. A thorough discussion between DMC and the sponsor at the orientation meeting will help both parties to align on the data review plan, including criteria for early termination of the trial.

### 2) Scheduled data review meeting

The conditions, timing, and content of the scheduled data review meetings will normally be specified in DMC charter and determined at the orientation meeting. The frequency of the regular data review meetings depends on the study design, the purpose of establishing the DMC, and the expected operational characteristics of the trial (e.g., enrollment rate, event rate, follow-up period, etc.).

At the time of the scheduled data review meeting, the DMC will receive updated information about the trial provided by IST and the sponsor's study team. DMC may also request IST to provide un-preplanned analyses as needed. In addition, DMC should consider special information from external trials. The unblinded analysis reports provided to the DMC for review should be summarized by treatment arm.

### 3) Unscheduled ad hoc meetings

In addition to the scheduled data review meetings, the sponsor may request unscheduled DMC meetings to review the safety data and provide additional trial-related safety information to the DMC. Such meetings are particularly common when urgent safety concerns are identified by the sponsor.

The DMC may also request unscheduled meetings as deemed necessary, including meetings to review additional unscheduled statistical analyses. The DMC will determine whether the sponsor should be notified of any ad hoc meeting. If so, the DMC should explain to the sponsor the justification for the unscheduled meeting, but should not provide the sponsor with information that may bias the study results.

## (2) Format of meetings

During the operation of DMC, the DMC will receive periodic updates from the sponsor (e.g., status of ongoing study and external information which may have an impact on the study). In the meanwhile, the DMC will need to keep the confidentiality of the unblinded data and analysis results (e.g., results of interim analysis) from the sponsor. Therefore, DMC meetings are divided into two forms: open sessions and closed sessions.

**Open session:** At the open session, subject recruitment, data quality, compliance, drug safety, and other issues that may affect the conduct and outcome of the trial are discussed in the blinded setting. The sponsor may provide in-house blinded data from the ongoing trials, as well as relevant external information. In addition to representatives of the sponsor, DMC, and IST, open session participants may also include investigators and other relevant parties if needed. Open sessions are generally hosted by the sponsor or by DMC.

**Closed session:** Participation is limited to the DMC and relevant personnel from IST. At the session, IST statistician will provide the results of the unblinded data analysis. The DMC reviews the data and makes recommendations on the continuation of the trial, termination of the trial, or modification of the study design based on a pre-defined plan. The meeting will be hosted by the DMC chair or the designate.

Prior to the DMC meeting, DMC members should receive and review the analysis report, which is blinded for open sessions and often unblinded for closed sessions, i.e., the statistical report using codes that distinguish between treatment groups, at which time adequate confidentiality and security measures should be taken to ensure that unblinded data is not released to any parties outside the closed sessions. If the blinded and unblinded analysis reports are prepared by different teams, the two teams should align on each other's key analysis elements such as data structure and analysis programs before starting the formal interim analysis to ensure that the information submitted to the DMC meeting is accurate and consistent.

### **4.3. Making Recommendation**

One of the fundamental responsibilities of DMC is to provide the sponsor with recommendations concerning the safety, efficacy, and other relevant aspects of the trial conduct. These recommendations may include, but are not limited to:

- Continuation of the trial with no modification (as per existing protocol)

- Continuation of the trial with modification (e.g., adjust sample size);
- Suspension of enrollment until uncertainty is resolved (e.g., potentially serious safety concerns);
- Termination of the trial (e.g., observed efficacy, futility, or serious safety concerns).

Recommending early termination of a clinical trial is a major decision for clinical studies. The DMC must be very cautious about making such recommendations. In addition to the evaluation of internal and external safety and efficacy data, the results must be interpreted by considering other possible factors. This includes, but is not limited to:

- Serious quality issues with trial execution, such as poor data quality, randomization errors, protocol non-adherence, etc.;
- The reliability and the completeness of the interim data, such as the balance of baseline characteristics (especially baseline prognostic factors) between treatment groups, the impact of missing data on the interpretation of the primary results, etc.;
- Adequacy of safety information, such as newly emerging adverse events;
- The internal and external consistency of the results, e.g. data between primary and secondary endpoints, across subgroups, and between study data and results from similar external studies;
- Relevant regulatory requirements.

DMC recommendations should be clearly communicated to the sponsor's management team, usually through written documents signed by all DMC members. The sponsor's management team should then communicate the management decision to the study team in a pre-specified channel. The recommendations should not be delivered to the study team directly from the DMC. The recommendations of the DMC should be in strict accordance with the preset framework and follow the appropriate process, jointly determined with the sponsor. To minimize potential bias and its impact on the conduct of the trial, unnecessary contact between DMC and the study team should be restricted.

The DMC recommendations are not binding to sponsors. The ultimate responsibility for a clinical trial rests with the sponsor, and thus the sponsor may choose to accept or reject DMC recommendations. Should the sponsor refuse to follow DMC's recommendation, in particular, the recommendation to terminate the trial, it should respond with an explanation in writing to the DMC and inform the Ethics Committee as well as the regulatory authority.

#### **4.4. Meeting Minutes**

The meeting minutes, approved by all DMC members, should be provided after each DMC meeting. Meeting minutes and reports are typically prepared by the DMC chair, the DMC member designated by DMC chair, or the DMC administrative assistant (if available). The meeting minutes of the open session may be issued to all participants. The sponsor may determine whether to circulate meeting information to the Ethics Committee, investigators, and regulatory agencies, etc.; the minutes of the closed meeting are limited to the DMC members.

All meeting minutes and reports should be maintained confidential by the DMC or IST until the end of the study by which time all documents will be transferred to the sponsor. After the completion of the study, the sponsor should archive all documents of DMC activities and interim analysis datasets in case the regulatory authorities may request this information in the future.

## **5. Statistical Considerations during DMC Operation**

### **5.1. Interim Analysis Plan**

An interim analysis is a pre-planned data analysis that occurs when trial data are accumulated to a certain extent during the course of the trial. Decisions about the subsequent carry out of the trial will be made based on the results of the data analysis according to a preset procedure, such as whether the trial is to be continued or terminated based on safety or efficacy data, whether the sample size needs to be adjusted based on the observed effect size, whether the subject population needs to be enriched or expanded, etc. Some statistical methods for evaluating reliability and robustness need to be considered in the interim analysis plan, such as sensitivity analyses to provide a more adequate basis for DMC decision making. The interim analysis plan, typically prepared by the sponsor before the start of the trial, needs to be reviewed by DMC and should be completed prior to the first interim analysis. The interim analysis plan could be part of the study statistical analysis plan (SAP). However, if there is a risk for unbinding data to others, a separate interim analysis plan should be prepared.

Efficacy evaluations at interim analyses are usually performed using a group sequential analysis method. Under the theoretical framework of group sequential analysis, once the accumulating data are sufficient to make an inferential conclusion about the efficacy of the investigational product, the trial can be terminated and the conclusion can be that the investigational product is effective or ineffective. In addition, other commonly used methods, such as those based on Bayesian theory and those with emphasis on procedures of futility monitoring, e.g. futility rules based on conditional power, have been used as well.

An interim efficacy evaluation, special attention should be paid to the control of the overall Type I error rate. The DMC generally follows the statistical criteria pre-specified in the interim analysis plan to advise whether the study should be terminated. DMC should also consider other factors when making recommendations. For example, sometimes even if interim data show a convincing treatment effect and meet the statistical criteria for stopping the trial due to efficacy, the trial may still need to collect extra data to address safety questions. In this case, the recommendation for continuing the trial can be evaluated based on a risk-benefit assessment. The DMC generally does not recommend stopping a trial for interim data that does not meet the statistical criteria (e.g., a boundary is not crossed in group sequential analysis framework).

If the results of the interim analysis show that it is almost impossible to achieve the final objective of efficacy in accord with the pre-specified statistical criteria, the DMC may recommend that the trial be terminated early for futility. The DMC usually considers Type II

error rate or conditional power before recommending that the trial be terminated due to futility.

## **5.2. Role of Statisticians in DMC Operation**

DMC statistical work is jointly performed by the trial statistician, the Independent Statistical Team (IST), and the DMC statistician. Within the framework of DMC, the team of the statisticians from three sides must maintain adequate communication and coordination, while ensuring strict information blinding and confidentiality.

The trial statistician, who is usually employed or contracted by the sponsor, is most knowledgeable about the study. The trial statistician is also responsible for the statistical design of the trial and the development of the statistical analysis plan, including the interim analysis plan, the content, and format of the report submitted to the DMC, and performs the final statistical analysis at the end of the trial. The statistical methods used for data monitoring are often developed by trial statistician. Note however assigning the trial statistician the responsibility for performing interim analysis and especially reporting directly to the DMC can be problematic.

IST, typically composed of a statistician and statistical programmer(s), will perform statistical analyses on the collected data per pre-specified statistical analysis plan, prepare and present data analysis reports to the DMC. IST must be independent of the study-related parties (including the sponsor, investigators, contract research organization, the Ethics Committee, etc., except the DMC.), especially when data unblinding is involved. In principle, IST will provide unblinded data and the corresponding analysis results only to the DMC, and will not disclose unblinded information to any other person or organization. In general, IST should come from outside the sponsor and should not be from the same organization where the trial statistician or the DMC statistician works to maintain its independence and thus to protect the integrity of the trial. The trial statistician shall ensure that IST is familiar with the study design, data access, statistical methodologies associated with the interim analyses, and is able to perform the analyses independently. IST should report directly to the DMC and have full access to the data necessary to conduct the interim analysis and any additional analyses requested by the DMC.

The sponsor's trial statistician uses cumulative blinded data to write a report. In addition, the trial statistician will assist IST in preparing the statistical programming and generating report templates for the closed session of DMC meeting, using dummy treatment codes in accordance with the pre-specified interim analysis plan. The trial statistician may also assist IST by using blinded data to identify safety issues requested by the DMC, and IST may then independently analyze the data using the true codes that differentiate treatment groups.

The DMC statistician is primarily responsible for all statistically relevant aspects of DMC work, including, reviewing the interim analysis plan and reports submitted by IST, interpreting the interim analysis results to DMC members, adding the necessary data analysis, making recommendations based on the statistical analysis results, etc.

## **6. DMC Interaction with Relevant Parties**

In order to ensure that studies are conducted scientifically and in compliance with regulation, DMC should understand the roles and responsibilities of all relevant parties in the trials, which will help DMCs to fully communicate and interact with other stakeholders to ensure the smooth conduct and integrity of the trials.

In general, in trials using DMCs, the main parties that communicate with DMC include the sponsor, IST, and regulatory agencies, etc.

### **6.1. DMC Interaction with Sponsor**

While the independence of DMC from the sponsor is critical and can promote the objectivity of the assessment of DMC and increase the credibility of the trial's conclusion, sponsor's interaction with DMC provides value in many aspects, which helps the DMC to make full use of the resources and information the sponsor provides to better make recommendations.

The sponsor can provide important information to DMC regarding the sponsor's objectives, plans, resources, and external information that the DMC can leverage and later integrate into its subsequent monitoring. When the DMC faces difficult decisions based on interim data and the IST is unable to provide reasonable interpretations, the DMC may request the sponsor to provide appropriate information to further support DMC's monitoring of the current trial and to assist in decision making while ensuring the integrity of the trial.

To minimize the risk to the conduct of a trial, DMC recommendations should always be submitted directly to the sponsor's management team rather than the study team since the management team does not participate in the routine work of the trial. The management team makes decisions on trial continuation, design modification, or termination according to the recommendations from the DMC.

In addition, the sponsor shall appropriately address the relationship and/or interaction between the DMC and other committees involved in clinical trials. For example, the sponsor and investigators have the responsibility to ensure that the Ethics Committees are aware of important activities of the DMC, such as the meetings of the DMC and its recommendations; also members of the Endpoint Adjudication Committee cannot perform DMC duties in the studies, etc.

### **6.2. DMC Interaction with Independent Statistical Team**

IST directly reports to the DMC. It not only prepares the analysis results or other relevant material required by the DMC before DMC meeting but also provides the statistical support requested by the DMC at any time during the DMC meeting. In addition to the planned analysis, the DMC may request extra analysis based on the information obtained, requiring IST to provide timely feedback while keeping absolute confidentiality of unblinded information.

### **6.3. DMC Interaction with Regulatory Agencies**

Regulatory authorities generally do not interact with DMC directly. In some situations, the regulatory authority may wish to be sure that the DMC for the ongoing trial is aware of certain issues, e.g., the existing safety data contained in the application, and takes those data into consideration when evaluating interim safety data from the ongoing trial. In such cases, the regulatory authority may request the sponsor to arrange its communication with the DMC. The sponsor's safety summary of findings not specifically provided by the DMC will also often be reviewed by the DMC prior to submission to a regulatory authority.

When DMC recommends termination of the trial due to safety concerns, timely communication with regulatory authorities is required. The sponsor should discuss with the regulatory authorities before implementing the DMC recommendations on major changes to the trial design to ensure that these changes comply with regulatory requirements. Similarly, when the DMC recommends termination of the trial due to significant efficacy advantages, after accepting the recommendation and making corresponding decision, the sponsor may also communicate with regulatory authorities regarding new drug marketing applications.

At the time of filing a new drug marketing application, the DMC related activities should be described in the clinical study report, including information on open and closed, scheduled and unscheduled DMC meetings. Meeting minutes and reports at each DMC meeting (in particular those leading to study design modification or early termination) should be submitted as supplements to the clinical study reports. The database for the interim analysis should also be submitted.

In exceptional circumstances, regulatory authorities may accept requests for direct communication from DMC, e.g., in situations where the DMC discovers that there are significant safety concerns which are deliberately concealed by the sponsor.

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## **Glossary:**

**Multiregional Clinical Trial (MRCT):** A clinical trial conducted in more than one country/region under a single protocol.

**Non-blinded analysis:** also known as Comparative Analysis, refers to the analysis using actual trial grouping information (including the actual name of each group or distinguishable grouping code) at the interim analysis. The analysis involves comparison between groups.

**Blinded Analysis:** Also known as non-comparative analysis, refers to the analysis that does not use the actual trial grouping information at the interim analysis, or although the actual trial grouping information is known, no analysis involving comparisons between groups is performed, for example, a pooled analysis of data from both treatment groups is performed at the time of the interim analysis.

**Interim Analysis:** refers to the analysis conducted using cumulating data of the trial, such as the analysis to evaluate efficacy and safety, and the re-estimation of the sample size.

**Adaptive Design:** A clinical trial design that allows for prospectively planned modifications to trial design based on accumulating data in the trial.

**Conditional Power:** Conditional power is the conditional probability that a final analysis will achieve a statistically significant result, where the conditions refer to the efficacy data observed thus far, and specific assumptions about the pattern of the data to be observed in the remainder of the study, such as the expected efficacy of the original protocol design or the effect estimated from the current data.

**Statistical Analysis Plan (SAP):** A statistical analysis plan is a document that contains a more technical and detailed elaboration of the principal features of the analysis described in the

protocol (e.g. datasets definition, randomization, sample size estimates, statistical analysis criteria, statistics, statistical methodologies, and table/listing/figures, etc.) and includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

**Master Protocol:** A master protocol is a protocol designed with multiple sub-studies, which may have different objectives and involves coordinated efforts to evaluate one or more investigational drugs in one or more disease subtypes within the overall trial structure. Umbrella, basket, or platform trials are all designs under the master protocol framework.

