Guideline on Using Clinical Trial Data Monitoring Committees

(Trial Version)

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1. INTRODUCTION

In clinical trials, it is paramount to ensure that the subjects in the trial do not bear unnecessary risks. 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 periodically review accumulating data from one or multiple ongoing clinical trials in order to ensure the safety of subjects in clinical trials, the reliability of the trials, the validity of the outcomes for trials. The DMC is also known 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. This guideline is mainly applicable to the pivotal clinical trials for the purpose of supporting drug registration, but can also be used as the reference for the clinical trials for non-registration purposes.

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, to protect the interests of trial subjects and improve the integrity and reliability of the trial, the DMC can use the efficacy and safety data collected during the course of the trial, to perform periodic or ad hoc risk-benefit assessment and make recommendation to the sponsors.

The responsibilities of DMC may include the following aspects: safety and efficacy monitoring, quality monitoring of trial operation, recommendation on trial design modification, etc. A primary role of the DMC is to provide recommendations to the sponsors, however it is up to the sponsors to decide whether to accept the recommendations.

Whether or not to establish a DMC in a clinical trial depends on the specific needs of the trial. For example, for most exploratory early phase trials and short-term studies without 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. Even for an open-label trial, including a single-arm trial, the sponsor should consider setting up a DMC if it is necessary to assess accumulating data during the trial.

If a DMC is required in a trial, the roles and responsibilities of the DMC should be clearly defined in the protocol (including amendments) and the DMC charter.

2.1 Safety Monitoring

One of the most 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, during the safety monitoring, there may be situations 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 trial according to the statistical plan pre-specified in the protocol. Recommendations for early termination of the trial mainly include the following two situations:

- The interim analysis shows that the probability of eventually receiving a positive outcome 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.
- The interim analysis shows that the trial meets the pre-specified statistical criteria for early termination due to superior efficacy, so the trial is terminated early with a positive result.

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.

For a multi-regional clinical trial (MRCT), when recommending early termination of the trial due to strong efficacy, the DMC should pay attention to the regional efficacy. Especially when only part of the trial data is collected for interim analysis, the regional efficacy is likely to be inconsistent with the overall efficacy. The participation of DMC members who represent different regions in MRCTs can better help monitor the implementation of the trial in its entirety and in respective regions.

2.3 Study Conduct Monitoring

The DMC also monitors trial conduct by reviewing study data, including adherence to protocol, recruitment status, subject 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 the sponsor to identify and address the cause of the problem.

2.4 Recommendations for Modifications of Trial Designs

For clinical trials with complex designs such as adaptive design, it is often necessary to modify the ongoing trial design features based on the accumulating data, such as intervention dose, study population, or effect size and standard error for sample size estimation. The involvement of DMC as an independent third party is essential in this situation. The DMC may make recommendations

for modifying the ongoing trial design based on the rules specified in the study protocol and DMC charter in advance and on the premise of ensuring the integrity of the trial, which will help to improve the integrity of the trial and reduce the risk of trial failure.

The DMC should implement the plan pre-specified in the study protocol, rather be directly involved in modifying the protocol, especially the modification related to the efficacy evaluation. When it comes to adjusting the trial design based on external data, it is the sponsor, not the DMC, that often proposes the trial design changes (such as modifying the endpoint, changing or adding the subpopulation).

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 representativeness, 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 in general 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 who are familiar with study designs. However, 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 ethics 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 other members. The DMC chair is generally appointed by the sponsor to oversee the operation of the DMC. A DMC may have as few as three 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 trial, be familiar with the operation of the clinical trial and the DMC, and generally should have prior experience in chairing or serving a DMC. The chair is usually a clinician or statistical expert who is 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. DMC has a voting mechanism, and relevant decisions need to be made through the voting of members. However, all recommendations made by the DMC should generally reach an internal consensus, instead of being determined through voting.

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. An assistant, who should be independent of the study-related parties, may be needed to undertake administrative work within the DMC. The IST and the assistant do not have voting right for DMC decisions. Sometimes, 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.

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

3.2.1 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 DMC services received from the sponsor is beyond a reasonable range.

3.2.2 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.

3.2.3 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 drug application being reviewed by the DMC

member is directly related to a study which the member works on, in which case, the member should not join the DMC.

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 DMC member withdrawal, replacement and adding new members.

4. DMC Operation

4.1 Developing DMC Charter

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

- The purpose of establishing DMC and the main responsibilities of DMC, sponsor and independent statistical team.
- DMC members: including composition of DMC, determination and declaration of conflict of interest.
- DMC meetings: meeting objective and planning, including orientation and data review meeting, planned or ad-hoc meeting, etc.
- The process to ensure confidentiality and the process of communication, including the open and closed sessions, blinded or unblinded reports, meeting minutes, as well as the communication between DMC and sponsor, independent statistical team or other relevant parties, etc.

- Statistical criteria assisting decision making, including methods of data analysis (to be consistent with the protocol).
- The content of blinded and unblinded DMC report.

4.2 DMC Meetings

In general, face-to-face DMC meetings are recommended. Teleconferences may be necessary in some situations, such as 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.

4.2.1 Type of meeting

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

4.2.1.1 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 trial subject is enrolled. Participants of the orientation meeting may include, but not limited to, all DMC members, 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.

4.2.1.2 Scheduled data review meeting

The conditions, timing, and content of the scheduled data review meetings are normally specified in DMC charter and determined at the orientation meeting. The frequency of the scheduled 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 unplanned interim analyses as needed to further understand the safety and efficacy of the drug. In addition, the DMC will consider any specific items brought to its attention from external trials.

4.2.1.3 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 unplanned statistical analyses. The DMC will determine whether the sponsor should be notified of any information from ad hoc meeting. If such a notification is needed, the DMC should provide the sponsor with the justification for the unscheduled meeting but should not provide the sponsor with any information that may bias the study results.

4.2.2 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 that 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 often consist of two types of sessions: an open session and a closed session.

- 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 can be chaired by the sponsor, but may also be chaired by the DMC chair or someone designated by the chair.
- Closed session: Participation is limited to the DMC and relevant personnel from IST. At the session, IST statistician provides the results of the unblinded data analysis. The DMC reviews the data and result, making 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 designee.

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. The unblinded report uses codes to distinguish between treatment groups, so security measures should be taken to ensure that the unblinded data is not released to any parties outside the closed sessions. If the blinded or 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 the

accuracy and consistency of the information brought to the DMC meeting.

4.3 Making Recommendation

One of the fundamental responsibilities of DMC is to provide the sponsor with recommendations concerning the safety, efficacy, the quality of trial operations and other relevant aspects of the trial conduct. The DMC shall document its recommendations and the rationale for these recommendations. The recommendation should be specified in the trial protocol and DMC charter, and should not include specific interim analysis data. 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., sample size adjustment).
- Temporarily suspension of enrollment until uncertainty is resolved (e.g., potential serious safety concerns).
- Termination of the trial (e.g., due to 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. These include, but are 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., consistency between the results of primary and secondary endpoints, consistency among the results of across subgroups, and consistency between study data and data from similar external studies.
- Relevant requirements from regulatory agencies.

The recommendations of the DMC should adhere to the pre-defined framework The communication of the recommendation to the sponsor should follow a process decided in conjunction with the sponsor in advance。To minimize potential bias and its impact on the conduct of the trial, unnecessary contact between DMC and the study team should be restricted. DMC recommendations should be clearly communicated to the sponsor's management team as specified in the DMC Charter via a written report signed by the DMC Chair. In addition to basic information such as meeting dates, the report briefly states DMC recommendations, such as the continuation of the trial as planned, and should not release any unblinded results (such as interim analysis effect sizes or P values, etc.). To avoid compromising the integrity of the trial, DMC members must not privately disclose results to the sponsor management team or study project team.

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’s recommendations. If the sponsor decides to not follow DMC’s recommendation, in particular the recommendation to terminate the trial due to safety concern, the sponsor should respond with an explanation in writing to the DMC and inform the Ethics Committee.

4.4 Meeting Minutes

The meeting minutes should be approved by all DMC members after each DMC meeting. The meeting minutes and reports are typically prepared by the DMC

chair, or a DMC member designated by the chair, or the IST. The meeting minutes of the open session may be provided to all open session participants. The sponsor may determine whether to circulate meeting information to the Ethics Committee, investigators, and regulatory agencies. The minutes of the closed meeting are limited to the DMC and the IST.

The minutes from open sessions can be maintained by the sponsors. All closed session meeting minutes should be maintained confidential by the DMC or IST. After the completion of the study, the sponsor should archive all documents of DMC activities and interim analysis datasets in case the regulatory authorities request this information.

5. Statistical Considerations during DMC Operation

5.1 Interim Analysis Plan

An interim analysis is a data analysis that occurs when trial data are accumulated to a certain extent during the course of the trial. Decisions about the subsequent execution 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, or 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.

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. Another situation may occur where the interim analysis shows that the primary efficacy analysis meets the statistical criteria for terminating the trial due to efficacy, but the opposite results occur for the important secondary endpoint analysis. 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.

The trial statistician, who is usually employed or contracted by the sponsor, is most knowledgeable about the trial. 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. Note however assigning the trial statistician the responsibility for performing interim analysis and reporting directly to the DMC can be problematic. During the course of the study, except for DMC and IST members, others should not generally have access to the unblinded data and interim comparative analysis results.

IST, typically composed of a statistician and statistical programmer(s), will perform statistical analyses on the interim accumulating data per pre-specified statistical analysis plan, prepare and present analysis reports to the DMC. IST must be independent of the study-related parties. 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.

In principle, for any clinical trial with the requirement to maintain the blindness of data, the IST provides unblinded data and its analysis results only to the DMC, and it shouldn't disclose unblinded information to any other person, institution and organization. The trial statistician should ensure that the independent statistical team is familiar with the study design, data access, and statistical methods related to interim analysis, and is able to perform the analysis independently. IST should report directly to the DMC and have full access to the data, which is necessary to conduct the interim analysis and any additional analyses requested by the DMC. For unplanned analyses requested by the DMC, the IST generally does not need to communicate with the sponsor team on every analysis and inform the sponsor about the purpose of the analyses.

The trial statistician will assist IST in preparing the statistical programming and generating report templates for the closed session of DMC meeting, based on dummy treatment codes in accordance with the pre-specified interim analysis plan. The IST performs the analysis using codes that distinguishes treatment

groups to produce the results. Care should be taken to prevent the trial statistician from obtaining unblinded data.

The DMC statistician is primarily responsible for all statistically relevant aspects of DMC work, including but not limit to reviewing the interim analysis plan and reports submitted by IST, interpreting the interim analysis results to DMC members, requesting for unplanned data analysis, and making recommendations based on the statistical analysis results.

6. Interaction with Relevant Parties

In order to ensure that a study is conducted scientifically and in compliance with regulation, the DMC should understand the roles and responsibilities of all relevant parties in the trial, 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 made from DMC and increase the credibility of the trial's conclusion, DMC's interaction with the sponsor provides value in many aspects, which helps the DMC to make full use of the resources and information so 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's recommendations should 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 continuation, design modification, or termination of trial 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 has the responsibility to ensure that the Ethics Committees are aware of the DMC's recommendation for modification, suspension, or termination of the study. Also note 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 meetings but also provides the statistical support requested by the DMC at any time during the DMC meetings. 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 communication with the DMC.

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 that are deliberately concealed by the sponsor.

6.4 Sponsor's Interaction with Regulatory Agencies

When a sponsor plans to establish the DMC in a study, it is encouraged that the sponsor communicates with the regulatory authorities regarding the setup of the DMC during the study protocol discussions, which includes the DMC charter and interim analysis plan, etc. Prior to the communication, the sponsor should provide the regulatory authorities with the study protocol, DMC charter, interim analysis plan, and other relevant documents.

During the course of the trial, after the DMC recommends termination of the trial due to safety concerns, it is necessary for the sponsor to inform regulatory authorities in a timely manner. The sponsor should discuss with regulatory authorities prior to implementing DMC's recommendation for significant modifications to the trial design to ensure that these changes meet regulatory requirements. In addition, when the sponsor accepts DMC's recommendation on terminating the trial due to the superior efficacy advantage of the drug, it is recommended that the sponsor communicates with regulatory authorities regarding the new drug application.

In the package of new drug marketing application, DMC activities should be a part of clinical reports, which includes meeting minutes of all blinded and unblinded, scheduled and unscheduled DMC meetings held. DMC meeting minutes and reports reviewed at the meeting should be provided as attachments to the clinical summary report. It is recommended that the sponsor submits the DMC charter (including the interim analysis plan) to the regulatory authorities

before any interim data unblinding (preferably before the start of the trial).

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Appendix 1: Glossary

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

Unblinded 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 carried out during the trial using cumulating data of the trial, such as the analysis to evaluate efficacy and safety, and the re-estimation of the sample size, etc.

Adaptive Design: A clinical trial design that allows for prospectively planned modifications to trial design based on the analysis of 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.

Appendix 2: Chinese-English Vocabulary

中文	English
适应性设计	Adaptive design
方案依从性	Adherence to protocol
不良事件	Adverse Event
盲态分析	Blinded analysis
盲态数据	Blinded data
终点事件判定委员会	Clinical Endpoint Committee/Clinical Event Committee, CEC or Event Adjudication Committee
条件检验效能	Conditional power
确证性临床试验	Confirmatory clinical trial
合同研究组织	Contract Research Organization, CRO
数据监查委员会	Data Monitoring Committee, DMC
数据安全监查委员会	Data Safety Monitoring Board, DSMB
DMC 章程	DMC Charter
效应量	Effect size
外部数据	External Data
整体 I 类错误率	Global type I error rate
成组序贯分析	Group sequential analysis
独立数据监查委员会	Independent Data Monitoring Committee, IDMC
独立统计团队	Independent Statistical Team, IST
期中分析	Interim analysis
缺失数据	Missing data
多区域临床试验	Multi-Regional Clinical Trial, MRCT
新发不良事件	Newly emerging adverse event
非盲态分析	Unblinded analysis
招募状态	Patient recruitment status
基线预后因素	Prognostic factors at baseline
样本量估计(重新估计)	Sample size estimation (re-estimation)
统计分析计划	Statistical Analysis Plan, SAP

中文	English
项目统计师	Trial/study statistician
非盲数据	Unblinded data