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To: Directors of Prefectural Health Departments (Bureaus)

Director of Evaluation and Licensing Division,
Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare
(Official seal omitted)

Guideline on Data Monitoring Committee

The activation of clinical studies and the advance of information technologies in recent years have allowed rapid accumulation of clinical study data. Against this background, consideration has been given to active use of interim analysis in order to judge, during the early stage after starting the clinical study, the feasibility of the subsequent development of drugs and medical devices. In exploratory clinical studies as well, attention has been given to the study design in which the study is continued with partial amendment of the study protocol based on the results of the interim analysis.

In light of these circumstances, there were deliberations on the necessity of monitoring of efficacy and safety data in clinical studies, including interim analysis, and on the necessity of adequate establishment and management of a data monitoring committee and, as a result, the “Guideline for Data Monitoring Committee” will be applied as specified in a separate attachment. Please inform the relevant manufacturers, sellers, and medical institutions under your jurisdiction about the application of this guideline.

* This English version of the Japanese Notification is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

Attachment

Guideline on Data Monitoring Committee

1. Introduction and background

This guideline intends to provide general guidance, at the current moment, related to the necessity, role, establishment, and management of a data monitoring committee (DMC) in a clinical study (trial) of a drug or medical device (hereafter referred to as “drug, etc.”) by a sponsor (including those who conduct clinical trials by themselves).

A DMC is an organization that consists of members with expertise knowledge required for evaluating clinical studies, and evaluates interim study data from a neutral position. Usually, it is independent from the sponsor, investigator, etc., and provides appropriate advice and recommendations necessary to the sponsor for ensuring the safety for subjects and for the ethical and scientific validity of study conduct.

During the course of the clinical study, it may become necessary to judge whether the study should be discontinued or continued, or whether or not the study design should be changed. For example, if a serious safety problem is noted while a clinical study is being conducted, the study must be terminated early or the study design must be changed, in order to ensure the safety for subjects. Also, if persuasive evidence is obtained that the objective of the clinical study has already been achieved or if it is expected with a high certainty that the objective of the study cannot be reached even if the study is continued, it may be necessary to terminate the study early from an ethical standpoint. In addition, the study design needs to be modified in order to achieve the objective of the study or to conduct the study in an appropriate manner. However, early termination of the clinical study may result in accumulation of only insufficient data for long-term safety evaluation or affect other clinical studies that are being conducted for similar therapies simultaneously. Therefore, in making a judgment on clinical study termination or on study design change as described above while ensuring the safety for subjects and the integrity of the clinical study as much as possible, it is critical that the DMC evaluates the data from a neutral standpoint, considering the necessity and the effect of such termination or change.

In contrast to those in the United States and European countries, relatively few large-scale and long-term clinical studies have been conducted in Japan using deaths or other serious events as endpoints and, except for clinical studies conducted in the development of some types of drugs such as those for anticancer drugs, there were few cases of interim analyses in which data accumulated up to a certain time point during the clinical study were analyzed and study continuation or termination was decided based on the results of comparison between treatment groups. In recent years, however, against the background of the active discussion on the early decision-making for the purpose of efficient development and on the clinical study design that allows the design modification while the study is being conducted, active implementation of an interim analysis during the clinical study is now drawing attention. Also, with the promotion of simultaneous global development and use of foreign clinical data, there are an increasing number of chances for Japanese patients to participate in large-scale and long-term clinical studies that are conducted in multiple countries or regions including Japan as global clinical trials. Against this

background, it was judged necessary to prepare, in Japan as well, a guideline on DMC that plays an important role in decision making during clinical studies based on interim data.

In the "Ministerial Ordinance on Good Clinical Practice for Drugs" (Ministry of Health and Welfare [MHW] Ministerial Ordinance No. 28 of 1997), the "Ministerial Ordinance on Good Clinical Practice for Medical Devices" (Ministry of Health, Labour and Welfare [MHLW] Ministerial Ordinance No. 36 of 2005), and the "Statistical Principles for Clinical Trials (PMSB/ELD Notification No. 1047 of the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, 1998), Data and Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC) is defined. DMC was proposed as an organization that aims to evaluate the data of an ongoing clinical study from a standpoint different from that of sponsors and investigators, who actually conduct the clinical study and does not necessarily have to be independent from the sponsor. However, in a clinical study aimed at confirming the efficacy of the investigational product, it is required to prove that conducting an interim analysis does not cause any bias in study results and, for this purpose, the organization in charge of the interim evaluation is required to be independent from the sponsor. Therefore, the term "Independent Data Monitoring Committee" (IDMC) has come to be used, particularly in studies intended to establish efficacy. This guideline assumes establishing DMCs not only in clinical studies for efficacy confirmation but also in a wider range of studies, and therefore uses the more common term "DMC" throughout to make the original purpose of DMC clear.

In general, the term "monitoring" refers to the examination of the implementation status of the entire clinical study or to the evaluation of efficacy and safety data accumulated while the study is being conduct. In this guideline, the latter monitoring activity is referred to as "data monitoring" to differentiate from the former activity. In this guideline, the term "interim analysis" refers to the analysis that is conducted under unblinded conditions during the course of the study in association with data monitoring in a controlled study, with the purpose of between-group comparison of efficacy or safety.

Matters related to DMC are described also in the following ministerial ordinances and guidelines, which should be referred to as appropriate.

- Ministerial Ordinance on Good Clinical Practice for Drugs" (MHW Ministerial Ordinance No. 28 of 1997)
- Ministerial Ordinance on Good Clinical Practice for Medical Devices" (MHLW Ministerial Ordinance No. 36 of 2005)
- Guidelines of International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)
  - E3: Structure and Content of Clinical Study Reports
    Guideline of Structure and Content of Clinical Study Reports (PAB/ELD Notification No. 335 of the Evaluation and Licensing Division, Pharmaceutical Affairs Bureau, MHW, dated May 1, 1996)
  - E8: General Considerations for Clinical Trials
    (PMSB/ELD Notification No. 380 of the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, MHW, dated April 21, 1998)
  - E6: Guideline for Good Clinical Practice

- E9: Statistical Principles for Clinical Trials
  (PMSB/ELD Notification No. 1047, dated November 30, 1998)

- International standards on clinical studies of medical devices established by the International Organization for Standardization (ISO) "ISO 14155:2011, Clinical investigation of medical devices for human subjects – Good clinical practice"

The guideline may be applied in a flexible manner without strictly following the details, if there is reasonable ground for that. For example, during the early stage of the development, DMC may be established as an independent organization for reflecting the objective opinions of experts to ensure the safety for subjects. Also, in many studies during the early stage of development, the confidentiality and statistical interpretation of interim data may not have to be as rigorous as those in confirmatory studies. Even in such cases, however, it is desirable to maintain and improve the scientific and ethical level in clinical trials/studies in Japan.

2. Necessity and roles of DMC

2.1 Consideration of necessity for establishing DMC

Whereas safety monitoring of subjects is essential in clinical studies, data monitoring by DMC is not required for all clinical studies. In general, necessity of DMC is determined by taking into account the objective of the clinical study, study design, endpoints, study duration, and patient population. A DMC is established by the sponsor if independent monitoring of efficacy and safety data is necessary during the course of the study period, for example, in the following studies: 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, and studies with a high expected risk as judged from the characteristics of the drug, etc., or subjects. Since establishing a DMC requires a certain amount of resources and results in more complicated study management, a thorough consideration should be given to its necessity.

2.2 Roles and responsibilities of DMC

The DMC evaluates the data of an ongoing clinical study in order to ensure the safety for subjects and assure the integrity of the clinical study as much as possible and, based on the results, provides appropriate advice and recommendations to the sponsor. Early 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, etc., to organizational influence by those involved in the development with different roles, to intellectual curiosity of persons concerned, and to market pressure. The DMC is required to provide advice and recommendations from a neutral standpoint by appropriately understanding and considering these effects, and also by examining the possible gain or loss of information by early study termination or protocol change. Although the criteria for study termination/continuation stipulated in the study protocol, etc., 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 members of a DMC should be knowledgeable about the methodologies of clinical studies and about the roles of the DMC, and be fully competent to bear the responsibilities. Also, the DMC members must be qualified to express unbiased opinions required for the DMC; they should not have any serious conflict of interest with the sponsor and not be in a position affected by the site of the clinical study.

Each of the DMC members must fully recognize the roles and responsibilities of the DMC and discuss issues from a neutral position based on the recognition of various factors that may possibly affect the judgment of the DMC, including societal demands. Also, they 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. In DMC, each member should express evidence-based opinions, respect the specialty and opinion of other members, and hold discussions based on their roles and responsibilities.

2.4 DMC activities

DMC activities are classified as follows.

- Safety monitoring

  In many cases, safety monitoring of subjects is an important role for the DMC. In a long-term controlled study using death or other serious outcome as the endpoint, if the test treatment is found to have a higher risk of the outcome compared with the control, the DMC may recommend early study termination for safety reasons. Comparison of the incidence of adverse events between the test treatment and the control and a detailed investigation of clinically significant adverse events are also important aspects of safety monitoring. In some cases, in addition to the safety results, benefit and risk balance of the test treatment is evaluated by taking efficacy data into account to decide whether or not to continue the study. Also, in order to minimize the risk of adverse events, the DMC may recommend study continuation with protocol revisions such as change in inclusion criteria and/or introduction of additional screening methods.

- Evaluation based on interim analysis

  In addition to safety monitoring, the DMC may recommend early study termination because of the efficacy, or futility, of the test treatment, based on the results of the interim analysis of efficacy at a time point when a certain amount of information has been accumulated from subjects. Performing the interim analysis should be specified in advance in the study protocol. If, as a result of the evaluation of study conduct status as described below, it is judged practically difficult to perform the interim analysis according to the objective, the sponsor may revise the study protocol.

- Monitoring of study conduct status

  In order to ensure the quality of a clinical study, the DMC may conduct periodical monitoring of data related to study conduct status, such as subject enrollment, eligibility of study subjects, incidence of drop-outs, and protocol compliance. For monitoring with this purpose, data need not be unblinded.
- Use of external information

  In addition to monitoring of safety and efficacy data, the DMC may be required to evaluate, from a neutral position, the effect of external data such as results of related studies on the ongoing clinical study, to the extent that it does not undermine the credibility of the study results. Also, there may be cases where information exchange between DMCs in ongoing related studies is useful. However, if a DMC with knowledge of interim data of the study recommends a study protocol change by taking external information into account, the type I error rate may be inflated. Also, the credibility of the study results may be damaged due to insecure independence of the pertinent study from other studies. These possibilities should always be kept in mind.

Based on the results of the data monitoring as discussed above, the DMC provides advice and recommendations to the sponsor regarding the necessity of termination of further study or of change in study design.

2.5 Relationship with other clinical study-related organizations

Multiple organizations, including DMC, are involved with different responsibilities in data monitoring in a clinical study in order to ensure the ethical and scientific validity of the study. Other study-related organizations, their roles, and relationship with DMC are as follows.

- Sponsor

  The sponsor plans the clinical study and bears the responsibility for the entire study. The sponsor is responsible for establishing and managing the DMC and for the decision making of terminating the study or changing the study plan following the advice/recommendations of the DMC.

  The sponsor may establish a steering committee (clinical trial steering committee) as necessary. In this case, the sponsor receives the recommendations of the DMC via the steering committee. The steering committee may include representatives of the sponsor, investigators, and experts who are not involved in the clinical study conducted.
- Institutional review board (IRB)

  The IRB is mainly responsible for reviewing the appropriateness of assurance of safety for subjects and scientific validity related to clinical study conduct in each clinical study site. Depending on the characteristics of the study and on the reason or purpose of establishing the DMC, the IRB may check whether or not a DMC is established and, if such is the case, the roles of the DMC, as part of the review of the clinical study plan and the study organizations. Also, the IRB may evaluate the

appropriateness of study conduct, based on the recommendations of the DMC to the sponsor.

- Event assessment (adjudication) committee
  The event assessment committee (or each event assessment committee member) assesses, usually under blinded conditions, significant events reported by the investigator to determine whether or not they meet the criteria stipulated by the study protocol, to ensure the consistency and objectivity of event assessment, thereby playing an important role in ensuring the scientific validity of the clinical study. The event assessment committee may be established to assess the appropriateness of event adjudication in a study in which an event based on subjective judgment is used as an endpoint or in a study with complicated definition of events, but does not share the monitoring works of clinical study data with the DMC.

3. Establishment and management of DMC

3.1 Structure of DMC

Usually, DMC members are appointed by the sponsor. The DMC is required to provide appropriate recommendations based on the monitoring of study data and, for this purpose, it is critical that the DMC consists of appropriately selected members. In most cases, the DMC consists of at least 3 members including clinicians with relevant specialty for the pertinent disease area and for safety characteristics expected for the test treatment and at least 1 statistician familiar with clinical study design, data, and statistical analysis. The members should be selected based on the specialty required, based on the objective and the design of the study to be conducted. It is also important, in selecting DMC members, to take into consideration the experience of involvement in clinical studies and the experience of serving as a DMC member in other clinical studies. DMC members thus appointed should be thoroughly aware of their roles and responsibilities (see “2.3 Roles and responsibilities of DMC members).

Since the DMC is required to objectively review the data, presence or absence of conflict of interest should be taken into consideration in selecting the members. Although there are various aspects to the extent of the 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. Specifically, the conflict of interest should be disclosed, and the process of the DMC reaching a conclusion should be available for post-hoc review by a third party (see section 3.3.4). In general, individuals with a serious conflict of interest should be excluded from DMC members. If there is a potential conflict of interest with a DMC member, disclosing the details to the DMC, etc., is the least requirement for the pertinent member. The extent of the conflict of interest that should be considered problematic in selecting the members, the procedure for selecting the members including the evaluation of conflict of interest in each candidate, and the method for disclosing the information related to conflict of interest should be discussed and

determined in advance, based on the study objectives and the conditions of the study conduct.

In establishing a DMC in a large-scale, global clinical trial, it is generally appropriate to select members from each of the participating regions or at least from a subset of regions. If Japanese subjects participate in a global clinical trial, it is desirable that Japanese experts join the DMC with knowledge of the healthcare environment and safety information available in Japan. If this is infeasible, methods for ensuring or evaluating the safety for Japanese subjects should be considered in advance. In cases where special safety monitoring for Japanese subjects is required, for example when there is scant experience or safety information of the study treatment in Japan compared with in other regions, the significance of Japanese experts joining the DMC increases further in order to closely monitor the safety in Japanese subjects.

From the practical aspect of DMC management, it is necessary to establish a secretariat to support the management and to appoint statisticians (including programmers) in charge of interim analysis. Secretariat works and statistical analysis may be outsourced to a contract research organization (CRO), etc. In this case, the sponsor should select an appropriate CRO together with selection of DMC members.

3.2 Handling of interim data

There is a possibility that, during the course of a clinical study, the sponsor, the investigator, etc., happen to know unblinded data, which may affect study conduct and/or analysis of data, causing bias in the study results. Therefore, 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 of comparison based on the interim analysis.

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

3.3.1 Preparation of DMC charter

The DMC works according to the procedure (DMC charter) agreed upon by the sponsor and the DMC. The DMC charter should specify the following: 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, procedure for 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, and preparation and storage of records. Also, requirements and procedures for holding an emergency meeting should be specified to cope with situations such as when there is a safety concern or serious external information becomes available.

3.3.2 Holding of DMC meeting

It is important to maintain the confidentiality of the interim data by holding a DMC meeting with closed doors in order to minimize the bias in the subsequent study. On the other hand, in order to check the appropriateness of the study implementation system and to share external data, it is sometimes useful for the DMC to exchange information with the sponsor or other study-related persons. Therefore, most DMC meetings consist of an open session and a closed session. In general, an open session meeting and a closed session meeting are held in this order and, based on the results, recommendations by the DMC are made to the sponsor.

- Open session meeting
  The participants of the open session meeting are 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. Data that are subject to open sessions include subject enrollment status, reason and frequency of ineligible cases, safety data not containing treatment assignment information, and other data necessary for evaluating the study progress status and data quality. The deliberation on these issues is expected to lead to improvement in the study management. The open session meeting provides an opportunity for the sponsor and the DMC to share external data related to the clinical study being monitored.
- Closed session meeting
  Only DMC members, the statistician in charge of the interim analysis, and the DMC secretariat participate in the closed session meeting. The meeting mainly deliberates based on the non-disclosed efficacy and safety-related monitoring data (which may include unblinded data and confidential information) submitted by the statistician in charge of the interim analysis or on the report of the results of the interim analysis. Based on the above deliberation, the meeting discusses what recommendations should be made to the sponsor.

Depending on the type of the deliberation topic, the DMC may be held as a written discussion instead of an actual meeting. In this case, it is necessary to specify, in the DMC charter in advance, the type of issues that can be discussed on a written basis and the method of the written discussion.

3.3.3 Recommendations

The DMC makes recommendations to the sponsor based on the results of the monitoring and the results of the interim analysis. The recommendations may be study continuation (no change in the study protocol, written information to subjects, informed consent form, study implementation system, etc.), study continuation with modification of study plan, temporary suspension of the study, study termination, etc. Details of the study results are not conveyed, as a general rule. The DMC's

recommendations to the sponsor should be made in writing while maintaining the blindness of the study. The sponsor, upon receiving the DMC's recommendations, makes a decision and communicates the decision to the institutional review board, the steering committee, the investigators, etc., and takes appropriate measures. The sponsor is responsible for the decision of study termination, change in the study plan, etc., in response to the DMC's recommendations, but it is possible to consult the regulatory agency in advance regarding the possible effect of such a decision.

3.3.4 Necessary records

The minutes of all meetings related to the DMC must be prepared and stored. The meeting minutes of open sessions and those of closed sessions are prepared separately. The meeting minutes of open sessions are circulated to the sponsor, the investigators, etc., as necessary. The meeting minutes of closed sessions are prepared by, and circulated among, the secretariat and the DMC members, and not disclosed to anyone other than the DMC members until the completion of the clinical study. 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. These records are valuable for confirming the independence of the DMC and the appropriateness of the conclusion.

Regarding the description related to DMC in clinical study-related records, the study protocol should in general describe the roles of the DMC and at least the name of the DMC chairperson and, for more details of the DMC, give reference to the DMC charter. The clinical study report describes the DMC members including the chairperson, the details of the data monitoring by the DMC, recommendations made by the DMC, the sponsor's decision in response to the DMC's recommendations, etc. It is desirable to attach the DMC charter, meeting minutes, written recommendations, etc., to the clinical study report as the appendices.

4. Independence of DMC

4.1 Independence of DMC

Establishment of a DMC as an organization independent from the sponsor allows highly objective data monitoring and minimize the risks of biases in the study. It is thus 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 is considered to be increased by the requirements for DMC members not to participate in the designing or conduct of the pertinent study except as responsibilities of DMC members and not to have any financial or other important conflicts of interest with the sponsor except receiving payment as DMC members. However, while ensuring its independence, the DMC should at the same time obtain detailed information from the sponsor on the study in order to have a thorough deliberation on the study. Consideration should therefore be given so that those necessary

information can be exchanged between the DMC and the sponsor, the investigators, under a certain restriction.

4.2 Relationship between DMC and sponsor

The sponsor is responsible for selecting and appointing DMC members and creating an environment that allows smooth management of DMC. The sponsor must ensure the independence of the DMC in decision making. In response to the recommendations by the DMC, the sponsor is to carefully make the final decision on the handling of the ongoing clinical study (e.g., study continuation, continuation with protocol modification, temporary study suspension, termination).

4.3 Independence of statistician in charge of interim analysis

As a general rule, unblinded data of the ongoing study should be accessible only to the statistician, except DMC members, who performs the interim analysis and prepares the report of the interim analysis to be submitted to the DMC. When performing the interim analysis, the unblinded data should be appropriately controlled so that the data are not accessible to anyone except the statistician in charge of the analysis. In order to minimize the bias in decision making based on the interim analysis and to ensure the confidentiality of the unblinded interim data, careful consideration should be given to the independence of the statistician in charge of the interim analysis and, for this purpose, 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, therefore, 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

In the interim analysis performed to judge the necessity of early termination for effectiveness based on the interim data of clinical study, there is concern about inflation of the type I error rate due to multiple testing. An appropriate statistical procedure should be employed to control type I error rate. Also, treatment effect may be overestimated in the interim data, and the extent of the overestimation is affected by the size of the information (information time) available at the interim analysis relative to the information of the entire study, such as the number of subjects or events subjected to the interim analysis. The DMC statistician should, by taking into account these statistical problems in the interim analysis, examine the validity of the statistical analysis plan (timing of the interim analysis, number of times of interim analysis, statistical analysis methods, etc.) at the planning of the clinical study, and make necessary recommendations to the sponsor. So that the DMC can make an appropriate decision, the method for presenting to the DMC the results of interim analysis on efficacy and safety should be specified in an appropriate manner. DMC members other than the statistician should make a decision with understanding of the statistical problems in the interim analysis as described above.