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GUIDELINE ON DATA MONITORING COMMITTEES

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INTRODUCTION

Clinical trials frequently extend over a long period of time. Thus, for ethical reasons it is desirable to ensure that for patients participating in such trials there is no unavoidable increased risk for harm. On the other hand it is also important to ensure that a trial continues for an adequate period of time and is not stopped too early to answer its scientific questions. An independent Data Monitoring Committee (DMC) as a group of experts external to a study that reviews accumulating data from an ongoing clinical trial might serve such tasks. While in general safety monitoring should be the major task for a DMC, other aspects of a clinical trial (e.g. study integrity, design aspects) might also be assessed by a DMC. However, it should be noted that a DMC is not needed for all clinical trials.

When monitoring a clinical trial a DMC might have to review accumulating data from an ongoing clinical trial in an unblinded fashion. Based on these reviews, a DMC has the capacity to make recommendations that might impact the future conduct of the trial. As access to unblinded treatment information during a clinical trial has the potential to introduce bias to future trial results, there are several aspects that require detailed regulatory consideration in order to ensure the scientific integrity of a clinical trial involving a DMC.

This Guideline document deals with independent Data Monitoring Committees. It is intended as an overview guide to highlight the key issues involved when sponsors include data monitoring committees as part of their trial management. While confirmatory, double blind, randomised clinical trials are in the focus of this guideline, the general principles outlined in this document also apply to other clinical trial situations.

The following regulatory guidelines make reference to independent Data Monitoring Committees. This guideline should be read in conjunction with:

- ICH Note for Guidance E3 (Structure and Content of Clinical Study Reports)
- ICH Note for Guidance E6 (Good Clinical Practice)
- ICH Note for Guidance E9 (Statistical Principles for Clinical Trials)
- Directive 2001/20/EC relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

1. GROUPS OVERLOOKING A CLINICAL TRIAL

Often there are different groups responsible for monitoring specific aspects of a clinical trial. However, the final responsibility for the conduct of a clinical trial is with the study sponsor and the investigators. Examples of groups overlooking various aspects of a clinical trial are:

Ethics Committees

According to Directive 2001/20/EC and ICH E6 Ethics Committees, constituted of medical and non-medical members, are mandatory in all clinical trials in human subjects. The responsibility of an Ethics Committee is to ensure the protection of the rights, safety and well being of human subjects involved in the clinical trial. For a more detailed description of the composition, function and operation of Ethics Committees refer to ICH E6.

Data Monitoring Committees

A Data Monitoring Committee is a group of independent experts external to a study assessing the progress, safety data and, if needed critical efficacy endpoints of a clinical study. In order to do so a DMC may review unblinded study information (on a patient level or treatment group level) during the

conduct of the study. Based on its review the DMC provides the sponsor with recommendations regarding study modification, continuation or termination. Data Monitoring Committees also go under different names like Data Monitoring Board or Data Safety Monitoring Committee (Board).

Steering Committees

Especially in large multicentre clinical trials often Steering Committees are set up. Usually these committees are appointed by the sponsor and comprise of investigators, (sometimes) clinical experts not directly involved in the clinical trial and staff from the sponsor. While blinded, such a committee often acts as a body that takes responsibility for the scientific integrity of a clinical trial. Among others a Steering Committee often takes responsibility for the scientific validity of the study protocol, assessment of study quality and conduct as well as for the scientific quality of the final study report.

Endpoint Adjudication Committees

In clinical studies where endpoints are complex to assess and/or include subjective components or the study cannot be blinded, an Endpoint Adjudication Committee, consisting of clinical experts in a specific clinical area, might be set up to harmonise and standardise endpoint assessment. In order to allow for an unbiased endpoint assessment the members of such a committee should be blinded to treatment assignment. Endpoint Adjudication Committees are, for example, widely used in the assessment of radiological endpoints.

Study Team

The Study Team consists of members from the sponsor's staff from different disciplines. Usually the aim of the Study Team is to overlook the daily work of a clinical study. Among others such a team has the responsibility to run a trial from writing the protocol, monitoring the trial and preparing the study report. External members (e.g. from a CRO) might participate in a Study Team. In double blind studies the Study Team is blinded until the blind is officially broken.

2. ASSESSING THE NEED FOR A DMC

During the planning phase of a clinical trial the sponsor - preferably in collaboration with the steering committee (if such a committee exists) - should assess the need for a DMC. Not all clinical trials need a DMC. In some situations a DMC may even be counterproductive.

When it comes to the decision whether a DMC should be set up or not aspects such as indication, study endpoint(s), study duration as well as study population should be taken into consideration. Also the available knowledge about a drug might trigger the need for a DMC.

In case of life-threatening diseases usually the implementation of a DMC is indicated from an ethical point of view. This might be regardless of whether the treatment under investigation aims to reduce mortality or morbidity or whether it is intended to relieve the patients' situation. There are only very rare situations when a DMC might not be considered necessary in such situations. Such a situation arises if a trial can be completed in a very short time, making the use of a DMC not feasible due to practical constraints. However, in case of long-term trials even in non-life-threatening diseases a DMC may be indicated for monitoring safety.

The patient population in a clinical trial might be another argument for setting up a DMC. For example, if a clinical trial is performed in a paediatric population even in a non-critical indication, a DMC might be needed considering that children are not capable to express themselves in the same way as adults do and in order to detect any potential harm to the patients as early as possible. Similar considerations are applicable for clinical trials in mentally disabled patients.

The implementation of a DMC might also be indicated in case of prior knowledge or strong suspicion that a treatment under consideration has the potential to harm patients (even though being eventually more effective than other treatments already available).

There are situations where besides indication and patient population the study design might give reason for setting up a DMC. Such situations arise e.g. in the context of preplanned interim analyses for early stopping (either for futility or for positive efficacy) or in case of complex study designs where a possible modification of the study design based on unblinded interim data is intended. In such a situation the use of an independent DMC gives more credibility to the process. However, major design modifications are considered exceptional and regulatory advice with respect to the acceptance of the planned procedure(s) should be sought in advance.

As noted above there are situations where a DMC might not add or not add much to a study. Usually the set up of a DMC as well as the preparation of DMC meetings take some time (up to a few weeks). Thus in case a clinical study can be performed in a short time frame that does not allow for appropriate preparation of information for a DMC the use of a DMC might not be beneficial for the study but might even delay the finalisation of such a trial. Other situations where a DMC might not add much to a study are clinical studies in non-critical indications where patients are treated for a relatively short time and the drugs under investigation are well characterised and known for not harming patients.

3. RESPONSIBILITIES OF A DMC

When assessing the responsibilities of a DMC one should keep in mind that the sponsor and the investigators participating in a clinical trial bear the final responsibility for the conduct of the trial. This responsibility cannot be transferred to a DMC.

Quality of study conduct is essential to allow a DMC to reach valid conclusions. Thus in performing its task a DMC should consider essential parts of study conduct like e.g. protocol adherence and patient withdrawal. These aspects might be of great importance as high numbers of protocol violations/deviations or high numbers of patients who withdraw from a study often are early indicators for possible problems with respect to safety or efficacy, or the feasibility of study procedures. Imbalances between treatment groups with respect to these aspects directly impact the study outcome. If major problems with the study conduct are observed, a DMC should consider possible recommendations to the sponsor to improve the quality of the study.

In most cases, safety monitoring will be the major task for a DMC. Even if the safety parameters monitored are not directly related to efficacy, a DMC might need access to unblinded efficacy information to perform a risk/benefit assessment in order to weigh possible safety disadvantages against a possible gain in efficacy. Other reasons for monitoring efficacy might be for futility, checking the assumptions for sample size calculation or whether criteria for early stopping are met. Regardless the kind of monitoring performed, the possible impact on the Type I error has to be taken into consideration when setting up the monitoring guidelines used by the DMC. It is also a responsibility of a DMC to apply appropriate statistical methods (e.g. group sequential methods). Consistency between monitoring guidelines related to efficacy and the statistical methods used for efficacy evaluation as outlined in the study protocol has to be ensured. Thus, if DMC monitoring activities are expected to have relevant impact on the conduct of a clinical trial (e.g. stopping the trial for efficacy, sample size adjustment) the circumstances under which a DMC is expected to consider such recommendations have to be pre-specified not only in the working procedures of the DMC, but also in the study protocol.

As the release of study results from other clinical trials in the same area as an ongoing trial monitored by a DMC might impact this trial, such information might be taken into consideration by the DMC. However, such external information should be assessed very carefully and a decision to stop or modify a clinical trial on external information should be taken under exceptional circumstances only.

Based on the results of the monitoring activities, a central responsibility of a DMC is to make recommendations on further study conduct. Such recommendations include continuing or terminating a trial or modifications to the trial. With regard to the latter such modifications should not violate the concepts behind the original study protocol. The proper communication of its recommendations is a major responsibility for a DMC. If changes in the study conduct are recommended by a DMC, sufficient information should be provided to allow the sponsor to decide whether and how to

implement these recommendations. The implementation of any DMC recommendation is solely the responsibility of the sponsor who is also free to neglect (in whole or in part) recommendations of a DMC.

A critical point in all DMC activities is to ensure the integrity and credibility of the ongoing trial. Thus, it is within the responsibilities of the DMC and the sponsor to have appropriate policies in place to ensure the integrity of the study. As an example, policies to avoid the dissemination of interim study result prior to unblinding have to be in place.

4. ESTABLISHING A DMC

The preparations for setting up a DMC should be finalised parallel to finalising the study protocol as DMC activities might interfere with study procedures and consistency of DMC working procedures and the study protocol should be assured. A DMC has to be fully functional before enrolment into the study starts to enable it to respond to any safety signal.

There are three major aspects with respect to membership to be considered when establishing a DMC: composition of the DMC, qualifications needed by DMC members and independence of DMC members.

As DMC work is a multidisciplinary task, usually a DMC needs expertise from different scientific areas. Clearly there is a need for qualified clinicians to assess the clinical aspects of safety and/or efficacy monitoring. But, as often statistical methods will be applied in the monitoring process, biostatistical expertise should also form part of a DMC. Furthermore, as ethical aspects are important especially in safety monitoring, the inclusion of a member with expertise in ethical questions might be appropriate. For practical reason the number of members of a DMC should be limited.

Experience is essential for DMC members to perform their task in a proper way. Potential DMC members should not only have scientific expertise relevant to the indication being studied, but they should also have practical experience with conducting clinical trials and a good understanding of the problems and limitations of clinical trials. In order to facilitate the work of a DMC it is helpful that some of the members, at least the DMC chair, have served on a DMC earlier.

While a DMC completely independent from the study sponsor would be desirable, this is not always possible. Usually DMC members will be appointed by the sponsor, often in cooperation with the principle investigator(s) of the study or the steering committee. Furthermore, the sponsor will not only pay for the expenses of the DMC members, but often will also pay an honorarium to account for the time DMC members have to spend. So there are some unalterable relations between sponsor and DMC members, but when it comes to the appointment of DMC members possible conflicts of interest should be taken into account. Potential candidates for a DMC membership should have no financial interest in the outcome of the study. Thus, it is obvious that e.g. employees of the sponsor who naturally have an interest in the trial outcome should not serve on a DMC. Besides financial interests other aspects should also be taken into consideration when assessing a possible conflict of interest. For example the planned authorship of DMC members in publications on study results might impact the independence of the DMC and is a non-financial conflict of interest. Furthermore, in order to allow for an unbiased assessment of study data and not to bias the further conduct of a clinical trial, any person (not only employees of the sponsor) involved in the conduct of the clinical trial (e.g. investigators) should not serve on the DMC. Another problem might arise in case a potential DMC member serves in parallel on the DMC of a clinical trial in the same indication area but with a different sponsor. This constitutes a conflict of interest that should be avoided.

5. WORKING PROCEDURES OF A DMC

A DMC might access unblinded treatment information of an ongoing trial. This implies the potential to introduce bias to future trial results. Thus transparency is important when it comes to the workflow and procedures used by the DMC. Operating procedures describing how the DMC works and how it communicates with other study participants (e.g. with the data centre or the sponsor) should be in place at the start of the trial. Such operating procedures should also describe how the integrity of the study with respect to preventing dissemination of unblinded study information is ensured.

The working procedures of a DMC should cover administrative as well as methodological aspects of the DMC work. As internal DMC activities as well as communication with other study participants form part of the DMC responsibilities both should be covered. In this context the following aspects should be documented:

- Description of the responsibilities of a DMC in the specific study (e.g. monitoring tasks)
- Members of the DMC including their qualification
- Declaration of possible conflicts of interest of DMC members
- Frequency and format of closed DMC meetings
- Description of communication procedures including data flow between the data centre and DMC and procedures to interact with the sponsor or other relevant parties
- Responsibilities, timelines and format (e.g. templates) for analyses to be assessed by the DMC, including methodological aspects
- Frequency and format of open DMC meetings (i.e. meetings with other study groups)
- Documentation of the DMC meetings (open as well as closed meetings).

If analyses of unblinded data are not prepared by a DMC member but by a third party, the working procedures should clearly describe who performs these analyses and the measures foreseen to avoid dissemination of unblinded treatment information. This is especially critical if the analyses are performed by an employee of the study sponsor or a CRO in charge of data analysis at the end of the study. In such a situation, there might be concerns with respect to a possible personal conflict of interest or a possible dissemination (directly or indirectly) of unblinded study information to individuals responsible for the further conduct of the study or future analyses.

The section on methodological aspects in the working procedures should describe the amount of information expected to undergo DMC assessment as well as the statistical methods planned to be applied by the DMC. It should include consideration whether and to what amount DMC analyses impact the final analysis of the study results.

In case of a submission the working procedures of a DMC as well as all DMC reports (open and closed sessions) should form part of the submission.

6. METHODOLOGICAL IMPLICATIONS OF DMC ANALYSES ON STUDY ANALYSES

Inflation of Type I error as well as a possible bias in the future conduct of a clinical trial are the major methodological problems in connection with DMC activities.

If a DMC monitors the primary parameter of the statistical analysis with the option to stop early, the impact on the Type I error is obvious and there are statistical methods (e.g. group sequential designs) available to account for this properly. In such a situation the DMC's working procedures should clearly describe the statistical methods to be applied for analysis. These methods have to comply with the statistical methods outlined in the study protocol. The study protocol has to describe the provisions planned to avoid an inflation of the Type I error.

If a DMC does not monitor the primary parameter of the statistical analysis, as is often the case when monitoring for safety, access to unblinded information on the primary analysis parameter might be necessary. For example, in order to weigh a possible safety risk against a possible gain in efficacy in an ongoing clinical trial a DMC might access unblinded efficacy information. Under such circumstances the impact on the Type I error should be properly taken into consideration. Any claim that no Type I error adjustment is necessary needs to be justified.

In situations where possible recommendations on a modification of the study design (e.g. sample size adaption) are within the scope of a DMC, intended modifications have to be described in advance not only in the working procedures of the DMC but also in the study protocol. Appropriate statistical procedures to avoid an inflation of the Type I error should be applied.

A slightly different situation might arise where a study is monitored for the feasibility of a positive outcome at the end of the trial. Such analyses (called 'futility analyses') mainly impact the Type II error and are usually of minor concern to regulators.

As mentioned several times a possible bias in the future conduct of the clinical trial might be induced by the dissemination of unblinded treatment information seen by the DMC. Proper working procedures not only have to be in place but adherence to these procedures is essential for all persons involved in DMC activities.

As interim analyses put an additional burden on those running a clinical trial, the number and extent of interim analyses should be limited. When performing interim analyses one should consider the time and amount of work needed to collect and clean the data used for these analyses, but one should also take into account that the data provided to a DMC should not be out of date - otherwise a DMC cannot fulfil its aim. Not only should the working procedures of the DMC, but also the whole organisation of a clinical trial account for these problems.