1. INTRODUCTION

For ethical concerns, it is required to ensure that for patients participating in clinical trials that extend generally over a long period of time, there is no unavoidable increased risk for harm.
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 as a group of experts external to a trial team that reviews accumulating data obtained from an ongoing clinical trial might serve such tasks.
In order to assess the progress made in the clinical trial, the data related to the safety, and critical endpoints related to the efficacy, and to recommend the sponsor in certain intervals on the continuation, amendment, or interruption of the trial, independent data monitoring committee may be established by the sponsor. However, independent data monitoring committee may not be needed for all clinical trials. Turkey Pharmaceuticals and Medical Devices Agency or the ethics committee may request the formation of independent data monitoring committee with justification.
While general safety monitoring should be the major task for independent data monitoring committee, other aspects of a clinical trial such as study integrity, design aspects might also be assessed by independent data monitoring committee.
İndependent data monitoring committee might have to review the data obtained from an ongoing clinical trial in an un-blinded fashion. Based on these reviews, independent data monitoring committee may make recommendations that might impact the future conduct of the trial. As access to un-blinded treatment information during a clinical trial has the potential to introduce bias to future trial findings, there are several aspects that require detailed assessment in order to ensure the scientific integrity of a clinical trial involving independent data monitoring committee.
This Guideline is intended as an overview guide to highlight the key issues involved when sponsors include independent data monitoring committees as part of their trial management. While confirmatory, double blind, randomized clinical trials are in the focus of this guideline, the general principles outlined in this guideline also apply to other clinical trials. This guideline is parallel with the provisions of the related legislation, and should be assessed as in compliance with the provisions included in these. Moreover, when the assessment is performed, the statistical principles for clinical trials and the structure and the content of the clinical study reports should also be taken into account.

2. GROUPS RESPONSIBLE FOR THE FOLLOW-UP OF CLINICAL TRIAL

There are different groups responsible for monitoring specific aspects of the clinical trial. However, the final responsibility for the conduct of a clinical trial is with the trial sponsor, coordinator, principle investigator and other investigators. Some examples of groups overlooking various aspects of a clinical trial are as follows:

2.1. *Ethics Committees:* As required by the related legislation, the basic responsibility of ethics committees is to ensure the protection of the rights, safety and well-being of volunteers involved in the clinical trial.

2.2. *Independent data monitoring committees:* Independent data monitoring committee is a committee composed of independent experts, external to a trial, assessing the progress, safety data and, if needed critical efficacy endpoints of clinical trial. İndependent data monitoring committee may review un-blinded trial information on a

patient level or on treatment group level during the conduct of the trial. Based on its review the İndependent data monitoring committee may provide the sponsor with recommendations regarding trial modification, continuation or termination. independent data monitoring committee also goes under different names such as data monitoring group or data safety monitoring committee.

2.3. *Steering committees:* Especially in multicenter clinical trials, steering committees are often set up. Usually these committees are appointed by the sponsor and all investigators participating in the trail, sometimes clinical experts not directly involved in the clinical trial and staff from the sponsor. While blinded, such a committee often acts rather as a body that takes responsibility for the scientific integrity of clinical trial. Among others steering committee often takes responsibility for the scientific validity of the trial protocol, the assessment of trial quality and conduct, as well as for the scientific quality of the final trial report.

2.4. *Endpoint adjudication committees***:** In clinical trials where there is complexity or subjective components are included or the trial cannot be blinded, an endpoint adjudication committee, consisting of clinical experts in a specific clinical area, might be set up to harmonize and standardize 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.

2.5. *Trial team***:** The trial team consists of members from the sponsor's staff from different disciplines. Usually the aim of the trial team is to overlook the daily work of a clinical trial. The trial team has the responsibility to run a trial from the beginning until the end, from writing the protocol to monitoring the trial and to preparing the study report. People from contract research organization might participate in the trial team as external members. In double blind trials, the trial team operates blinded until the blind is officially broken.

3. ASSESSING THE NEED FOR INDEPENDENT DATA MONITORING COMMITTEE

3.1. During the planning phase of a clinical trial the sponsor, in collaboration with the steering committee (if any), should assess the need for independent data monitoring committee. Not all clinical trials need independent data monitoring committee.

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3.2. When it comes to the decision whether independent data monitoring committee should be set up or not, aspects such as indication, trial endpoint(s), trial duration as well as trial population should be taken into consideration.

3.3. In case of life-threatening diseases, usually the implementation of independent data monitoring committee is required 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 volunteers' situation. There are only very rare situations when independent data monitoring committee 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 independent data monitoring committee not feasible due to practical constraints. However, in case of long-term trials even in non-life-threatening diseases, independent data monitoring committee may be required for monitoring safety.

3.4. The volunteer population in the clinical trial might be another argument for setting up independent data monitoring committee. For example, if a clinical trial is performed in a pediatric population even in a non-critical indication, independent data monitoring committee 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 volunteers as early as possible. Similar considerations are applicable for clinical trials in mentally disabled patients.

3.5. The implementation of independent data monitoring committee might also be required in case of prior knowledge or strong suspicion that a treatment under consideration has the potential to harm volunteers, even though being eventually more effective than treatments already available.

3.6. There are situations where besides indication and volunteer population the trial design might give reason for setting up independent data monitoring committee. Such situations arise, for example in the context of preplanned interim analyses for early stopping of the trial, either for futility or for positive efficacy, or in case of complex trial designs where a possible modification of the trial design based on un-blinded interim analysis is intended. In such a situation the use of İndependent data monitoring committee gives more credibility to the process. However, major design modifications are considered exceptional and the advice of independent data monitoring committee with respect to the acceptance of the planned procedure should be sought in advance.

3.7. Usually the set-up of independent data monitoring committee as well as the preparation of independent data monitoring committee meetings take some time. Thus in case a clinical trial can be performed in a short time frame that does not allow for appropriate preparation of information for independent data monitoring committee, the use of independent data monitoring committee might not be beneficial for the study but might even delay the finalization of such a trial.

3.8. Other situations where independent data monitoring committee might not contribute much to a trial are clinical trials in non-critical indications where volunteers are treated for a relatively short time and the drugs under investigation are well characterized and availably known for not harming volunteers.

4. RESPONSIBILITIES OF INDEPENDENT DATA MONITORING COMMITTEE

4.1. When assessing the responsibilities of independent data monitoring committee, one should keep in mind that the sponsor, coordinator, principle investigator and other investigators participating in the clinical trial bear the final responsibility for the conduct of the trial. This responsibility cannot be transferred to independent data monitoring committee.

4.2. Quality of trial conduct is essential to allow independent data monitoring committee to reach valid conclusions. Thus in performing its task, independent data monitoring committee should consider essential parts of trial conduct such as protocol adherence and volunteer withdrawal from the trial, exclusion of the volunteer from the trial. These aspects might be of great importance as high numbers of protocol violations, deviations or high numbers of volunteers who withdraw or are excluded from a trial often are early indicators for possible problems with respect to safety or efficacy, or the validity of study procedures. Imbalances between treatment groups with respect to these aspects directly impact the trial outcome. If major problems with the trial conduct are observed, independent data monitoring committee should consider possible recommendations to the sponsor to improve the quality of the study.

4.3. Safety monitoring is the major task for independent data monitoring committee. Even if the safety parameters monitored are not directly related to efficacy, independent data monitoring committee might need access to un-blinded 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 termination met or not. Regardless the kind of monitoring performed, the possible impact on the Type I error has to be taken into consideration when preparing the monitoring guidelines used by the independent data monitoring committee. Moreover, it is also a responsibility of independent data monitoring committee to apply appropriate statistical methods (for example, group sequential methods).

4.4. Consistency between monitoring guidelines related to efficacy and the statistical methods used for efficacy evaluation as outlined in the trial protocol has to be ensured. Thus, if independent data monitoring committee monitoring activities are expected to have relevant impact on the conduct of the clinical trial (for example, stopping the trial for efficacy, sample size adjustments) the circumstances under which independent data monitoring committee is expected to consider such recommendations have to be pre-specified not only in the working procedures of the independent data monitoring committee, but also in the trial protocol.

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

4.6. Based on the results of the monitoring activities, the responsibility of independent data monitoring committee is to make recommendations on further trial conduct. Such recommendations include continuing or terminating the trial or modifications to the trial. Such modifications should not violate the concepts indicated in the original trial protocol. The proper explanation of its recommendations is a major responsibility for İndependent data monitoring committee.

4.7. If changes in the trial conduct are recommended by independent data monitoring committee, sufficient information should be provided to allow the sponsor to decide whether and how to implement these recommendations. The implementation of any independent data monitoring committee recommendation is solely the responsibility of the sponsor who is the right to neglect, in whole or in part, recommendations of independent data monitoring committee.

4.8. A critical point in all independent data monitoring committee activities is to ensure the integrity and credibility of the ongoing trial. Thus, it is within the responsibilities of the independent data monitoring committee and the sponsor to have appropriate policies in place to ensure the integrity of the trial. As an example, policies to avoid the distribution of interim trial findings prior to un-blinding have to be determined.

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5. ESTABLISHING INDEPENDENT DATA MONITORING COMMITTEE

5.1. Sponsor may form an independent data monitoring committee in order to assess in certain intervals the progress made in the clinical trial, including the safety data and critical efficacy endpoints, and to advise the sponsor for the continuation, modification, or termination of the trial.

5.2. The study procedures for independent data monitoring committee should be formed and independent data monitoring committee should keep and store the minutes of all meetings it has performed.

5.3. The preparations for establishing İndependent data monitoring committee should be finalized parallel to finalizing the trial protocol as independent data monitoring committee activities might interfere with study procedures and consistency of independent data monitoring committee working procedures and the trial protocol should be assured.

5.4. Independent data monitoring committee has to be fully functional before the initiation of the study to enable it to respond to any safety signal.

5.5. Three major aspects with respect to membership to be considered when establishing independent data monitoring committee are indicated as follows:

5.5.1. Composition of independent data monitoring committee,
5.5.2. Qualifications needed by independent data monitoring committee members,
5.5.3. Independence of independent data monitoring committee members.

5.5. As independent data monitoring committee work is a multidisciplinary task, usually independent data monitoring committee needs expertise from different scientific areas. There is a need for qualified physicians and those with doctorate or speciality degree in toxicology field when required to assess the clinical aspects of safety or efficacy monitoring. If statistical methods will be applied in the monitoring process, bio-statistical expertise is also required. 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 reasons, the number of members of İndependent data monitoring committee should be limited.

5.7. Experience is essential for independent data monitoring committee members to perform their tasks in a proper way. Potential independent data monitoring committee members should not only have scientific expertise relevant to the indication being studied, but they should also have experience with conducting clinical trials and a good training and experience on the problems and limitations of clinical trials.

5.8. In order to facilitate the work of independent data monitoring committee, it is preferred that some of the members, at least the independent data monitoring committee chair, have served on independent data monitoring committee earlier.

5.9. While independent data monitoring committee completely independent from the trial sponsor would be desirable, this is not always possible. Usually independent data monitoring committee members will be appointed by the sponsor, often in cooperation with the principle investigator(s) of the trial or the steering committee. Furthermore, the sponsor will not only pay for the expenses of the independent data monitoring committee members, but often will also pay an honorarium to account for the time independent data monitoring committee members have to spend. So there are some unalterable relations between sponsor and independent data monitoring committee members, but when it

comes to the appointment of independent data monitoring committee members possible conflicts of interest should be taken into account. Potential candidates for İndependent data monitoring committee membership should have no financial interest in the outcome of the trial. Thus, it is obvious that for example, employees of the sponsor who naturally have an interest in the trial outcome should not serve on independent data monitoring committee. Besides financial interests other aspects should also be taken into consideration when assessing a possible conflict of interest. For example the planned authorship of independent data monitoring committee members in publications on trial findings might impact the independence of the independent data monitoring committee and is a non-financial conflict of interest. Furthermore, in order to allow for an unbiased assessment of trial data and not to bias the further conduct of the clinical trial, any person involved in the clinical trial (for example, investigators) should not serve on the İndependent data monitoring committee. Another problem might arise in case a potential independent data monitoring committee member serves in parallel on the independent data monitoring committee of a clinical trial in the same indication area but with a different sponsor. This constitutes a conflict of interest that should be avoided.

6. WORKING PROCEDURES OF INDEPENDENT DATA MONITORING COMMITTEE

6.1. Independent data monitoring committee might access un-blinded treatment information of an ongoing trial. This implies the potential to introduce bias to future trial findings. Thus transparency is important when it comes to the workflow and procedures used by the independent data monitoring committee. Operating procedures describing how the independent data monitoring committee works and how it communicates with other study participants (for example, with the data center or the sponsor) should be indicated at the start of the trial. Such operating procedures should also describe how the integrity of the study with respect to preventing dissemination of un-blinded study information is ensured.

6.2. The working procedures of independent data monitoring committee should cover administrative structure as well as methodological aspects. In this context the following aspects should be documented:

6.2.1. Description of the responsibilities of independent data monitoring committee in the specific study (for example, monitoring tasks)

6.2.2. Members of the İndependent data monitoring committee including their qualification

6.2.3. Declaration of possible conflicts of interest of independent data monitoring committee members

6.2.4. Frequency and format of closed independent data monitoring committee meetings

6.2.5. Description of communication procedures including data flow between the data center and independent data monitoring committee and procedures to ensure interaction with the sponsor or other relevant parties

6.2.6. Responsibilities, timelines and format (for example, templates) for analyses to be assessed by the independent data monitoring committee, including methodological aspects

6.2.7. Frequency and format of open İndependent data monitoring committee meetings (i.e. meetings with other study groups)

6.2.8. Documentation of the independent data monitoring committee meetings (open as well as closed meetings).

6.3. If analyses of un-blinded data are not prepared by independent data monitoring committee member but by a third party, the working procedures should clearly describe who performs these analyses and the measures foreseen to avoid dissemination of un-blinded treatment information. This is especially critical if the analyses are performed by an employee of the trial sponsor or a contract research organization in charge of data analysis at the end of the trial. 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 un-blinded study information to individuals responsible for the further conduct of the study or future analyses.

6.4. The section on methodological aspects in the working procedures should describe the amount of information expected to undergo independent data monitoring committee assessment as well as the statistical methods planned to be applied by the İndependent data monitoring committee. It should include consideration whether and to what amount independent data monitoring committee analyses impact the final analysis of the trial findings.

6.5. In case of a submission, the working procedures of independent data monitoring committee as well as all independent data monitoring committee reports of open and closed sessions should form part of the submission.

7. METHODOLOGICAL IMPLICATIONS OF INDEPENDENT DATA MONITORING COMMITTEE ANALYSES ON STUDY ANALYSES

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

7.2. If independent data monitoring committee monitors the primary parameter of the statistical analysis with the option of early termination, the impact on the Type I error is obvious and there are statistical methods (for example, group sequential designs) available to account for this properly. In such a situation the working procedures of independent data monitoring committee should clearly describe the statistical methods to be applied for analysis. These methods have to comply with the statistical methods outlined in the trial protocol. The trial protocol has to describe the provisions planned to avoid an inflation of the Type I error.

7.3. If independent data monitoring committee does not monitor the primary parameter of the statistical analysis, as is often the case when monitoring for safety, access to un-blinded 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 independent data monitoring committee might access un-blinded efficacy information. Under such circumstances the impact on the Type I error should be properly taken into consideration. All claims that no Type I error adjustment is necessary need to be justified.

7.4. In situations where possible recommendations on a modification of the trial design (for example, sample size adaption) are within the scope of independent data monitoring committee, intended modifications have to be indicated in advance not only in the working procedures of the independent data monitoring committee but also in the trial protocol. Appropriate statistical procedures to avoid an inflation of the Type I error should be applied. A slightly different situation might arise where a trial is monitored for the validity 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.

7.5. A possible bias in the conduct of the clinical trial might be induced by the dissemination of un-blinded treatment information seen by the independent data monitoring committee. Proper working procedures not only have to be in place but adherence to these procedures is essential for all persons involved in independent data monitoring committee activities.

7.6. As interim analyses put an additional burden on those running the 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 İndependent data monitoring committee should not be out of date; otherwise İndependent data monitoring committee cannot fulfill its aim. Not only should the working procedures of the İndependent data monitoring committee, but also the whole organization of the clinical trial account for these problems.

8. SUPERSEDED REGULATIONS

"Guideline Regarding Independent Data Monitoring Committees", effective with the Authority Consent dated 23.08.2011 and numbered 7481, has been superseded.

9. EFFECTIVE DATE

This Guideline is effective as of date of approval.