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Questions and answers on Data Monitoring Committees issues

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Comments should be provided using this template. The completed comments form should be sent to Biostatistics@ema.europa.eu

Keywords	Data Monitoring Committee (DMC); clinical trial; study design; trial integrity; early drug development phase; safety review committee; competent regulatory authority

The aim of this question-and-answer document is to supplement the CHMP Data Monitoring Committee Guideline (Doc Ref. EMEA/CHMP/EWP/5872/03) by providing clarification on the role and necessity for a Data Monitoring Committee (DMC) in different phases of drug development and throughout the product lifecycle as well as with regard to the responsibilities for implementing DMC decisions.

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Question 1. Are DMC recommendations binding for a Sponsor?

No, the ultimate responsibility for a clinical trial rests with the study Sponsor and thus the Sponsor must conclude whether to follow DMC recommendations or not. However, cases where DMC recommendations are not followed should be justified and documented by the Sponsor. In particular, if DMC recommendations to stop (in all cases) or modify the trial (e.g. in relation to safety considerations or the confirmatory nature of the trial) are not followed, the Sponsor is strongly advised to notify the Ethics Committees as well as the competent regulatory authority.

Question 2. Can a DMC stop a study?

As mentioned above, the final responsibility for conducting a study rests with the study's Sponsor. Of the Sponsor and the DMC, only the Sponsor has the capability to stop the study.

Question 3. Can a DMC change study design aspects (e.g. increase sample size, drop treatment arms)?

Formally, the DMC cannot change study aspects, because its role is to advise the Sponsor.

Regarding changes in study design, regulatory guidelines (e.g. ICH guideline E9: Statistical principles for clinical trials (CPMP/ICH/363/96), Reflection paper on methodological issues in confirmatory clinical trials planned with an adaptive design (CHMP/EWP/2459/02)) recommend that changes to the study design should in general be pre-planned as much as possible and should be clearly stated in the study protocol to ensure credibility of study outcome and trial integrity. Design changes that are pre-planned (e.g. implementation of rules for assessment of futility or efficacy) and that form the basis for DMC recommendations should also be described in the DMC charter. In addition, the DMC can propose unplanned changes to the Sponsor but integrity of the trial must be protected.
Ultimately, the Sponsor decides whether changes are implemented and if so, this has to be done via protocol amendments. Amendments introducing changes to the confirmatory nature of the study are usually substantial and require approval from the competent regulatory authority and the Ethics Committee. When such amendments may impact on the chances of regulatory approval of the medicinal product, the Sponsor may also wish to discuss the amendment with the competent regulatory authority during a scientific advice consultation before implementation.

Question 4. Is a direct communication and exchange of information between competent regulatory authorities and a DMC possible?

As the final responsibility for a clinical trial rests with the study Sponsor, the communication with competent regulatory authorities on all matters related to data monitoring is conducted by the Sponsor of a clinical trial.

A DMC is primarily established to provide continuous safety monitoring independently from the Sponsor in the interest of patient safety while the trial is ongoing. The DMC therefore has an advisory role for the Sponsor and therefore, as a general rule, communications primarily take place between the DMC and the Sponsor, without direct communication between the DMC and any third party. In exceptional circumstances related to a public health concern based on trial data or information from other sources than the trial at hand, competent regulatory authorities may consider it necessary to obtain more detailed information from the DMC before making decisions about the conduct of the trial. Vice versa, external data known to competent regulatory authorities but not to the DMC may be of importance to the DMC in respect to its roles and responsibilities. Preferably, the Sponsor should be involved in such justified requests and related communications to ensure that their respective roles and responsibilities are not undermined. Considerations should be given to the fact that requests which

may lead to unblinding of involved parties could potentially compromise the trial's integrity, the ability to proceed with the trial and with this the outcome of the trial.

Where direct communication and information exchange between DMC and competent regulatory authorities is needed, this should preferably be without breaking the blind, e.g. with additional statistical analysis plans, intensified monitoring, or modified stopping rules which the DMC can implement to address the public health concern. Usually the Sponsor will be also involved in these communications when it would not require sharing unblinded data.

Question 5. Should the Investigators be informed about the outcome of DMC meetings?

The Sponsor should ensure that the Investigators in a clinical trial with an appointed DMC are informed about overall DMC recommendations, i.e. regarding safety, in a timely manner.

Question 6. When is there a need for a DMC in early development phases?

Safety considerations related to indication, study population and knowledge of the treatment under consideration, may trigger the need for more intensive safety monitoring in early development phases, implemented via a safety review committee that monitors safety aspects. The need for such a safety review committee is usually higher in first in human clinical trials, and other early phase trials, as often there is only very limited information on the safety profile of a medicinal product. Such a committee often also has a role in assessing data before dose escalation in early phase trials, and to give recommendation to the Sponsor whether or not to proceed to the next higher dose.

Question 7. Do DMC members have to be external in relation to the Sponsor in early development phases?

The term DMC always refers to a committee independent from the Sponsor. Safety monitoring is of even more importance in early drug development than in later phases when already more knowledge of the medicinal product has been acquired. Therefore, knowledge of relevant and possible safety issues related to the medicinal product should guide the selection of members of a safety review committee. The inclusion of members external to the Sponsor increases the credibility of such a safety review committee. Therefore, this committee should have sufficient independent members so that decisions are not made solely by members who have been heavily involved in the development of the medicinal product which may lead to subjective rather than objective decision making. However, it might also be necessary to have an in-depth knowledge of the medicinal product under evaluation. For early phase trials, such information might only be available within the Sponsor's organization. Moreover, where the nature of such studies is not confirmatory but exploratory, having also internal members may be more needed.