17 September 2020
EMA/CHMP/470185/2020
Committee for Medicinal Products for Human Use (CHMP)

Questions and answers on Data Monitoring Committees issues

Draft agreed by Biostatistics Working Party	June 2018
Adopted by CHMP for release for consultation	26 July 2018
Start of public consultation	01 August 2018
End of consultation (deadline for comments)	31 July 2019
Agreed by Biostatistics Working Party	August 2020
Adopted by CHMP	17 September 2020

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

Background

The aim of this question-and-answer (Q&A) document is to supplement the CHMP Guideline on Data Monitoring Committee (EMEA/CHMP/EWP/5872/03 Corr) by providing clarification on (i) the role and necessity for a Data Monitoring Committee (DMC) in different phases of drug development and throughout the product lifecycle, and (ii) the responsibilities for implementing DMC decisions. This Q&A document should be read in conjunction with this guideline using the same definitions and considerations contained therein.

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Table of contents

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 or not to follow DMC recommendations. 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 substantially (as per the definition 3.3. in Communication from the Commission 2010/C 82/01) 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 Committee(s), as well as the competent regulatory authority(ies).

Question 2. Can a DMC stop a study?

As mentioned in Question 1, 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)?

The role of the DMC 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, as far as possible, be pre-planned and should also be clearly described and justified in the study protocol to ensure credibility of study outcome and trial integrity. In most cases, criteria should be devised upfront so that the DMC can provide recommendations without unblinding the Sponsor or affecting the integrity of the trial, allowing it to maintain its advisory role. 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, while the DMC can propose unplanned changes to the Sponsor, the integrity of the trial must be protected.

The Sponsor should refrain from trying to draw information on results in the ongoing trial by asking questions to the DMC as this poses a risk to trial integrity. However, if the questions can be addressed without knowledge of the trial results, then the Sponsor can seek advice from experts outside the DMC and those involved in the trial.

Ultimately, the Sponsor decides whether changes are implemented. Changes not foreseen at the planning stage must be implemented via protocol amendments. A protocol amendment introducing changes affecting the confirmatory nature of the study is substantial (as per the definition 3.3. in Communication from the Commission 2010/C 82/01*)* and requires approval from the competent regulatory authority and the Ethics Committee. Where such amendments may affect the chances of regulatory approval of the medicinal product, the Sponsor may also wish to discuss the amendment with the competent regulatory authority and/or Ethics Committee during a scientific advice and/or ethical advice consultation before implementation. Urgent safety measures are implemented immediately, e.g. if the DMC recommends terminating a particular treatment group due to safety issues; however, a substantial protocol amendment would need to be submitted subsequently (as outlined in Communication from the Commission 2010/C 82/01).

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, communication with competent regulatory authorities on all matters related to data monitoring is conducted by the Sponsor

of a clinical trial. The DMC has an advisory role for the Sponsor and therefore, as a general rule, communications primarily take place between the DMC and the Sponsor's personnel who serve as the DMC point of contact (e.g. Sponsor Committee), 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 further conduct of the trial at hand or other trials. The Sponsor should be involved in such justified requests and related communications to ensure that its respective roles and responsibilities are not undermined. Nevertheless, as long as there is the option to continue the trial, it is essential to preserve the integrity of the trial. To this end, any exchange of information from the DMC to the competent regulatory authorities is best operationalised via the DMC. Of course, if the competent regulatory authorities only want to inform the DMC about safety concerns, then this would go through the Sponsor, as the Sponsor has the obligation to inform the DMC of all relevant external information.

Question 5. Is a direct communication between Ethics Committees and a DMC possible?

In some EU Member states, national legislation and/or regulations may require Ethics Committees to play a specific role while a trial is ongoing, e.g. monitor Suspected Unexpected Serious Adverse Reactions (SUSARs) or risk/benefit, and decide to stop a trial early. As Ethics Committees may have the power of decision to make changes to the trial locally and usually have significant knowledge of the trial sites, the risk of introducing bias should be considered carefully in communications between Ethics Committees and DMCs. Therefore, the same principles as laid out for communication between competent regulatory authorities and DMCs apply.

Question 6. Should trial Investigators be informed about the outcome of DMC meetings?

In general, the recommendation of a DMC is either to continue the trial with no changes, to change aspects of the trial and then continue the trial, or to stop the trial. The underlying principle in communication of DMC recommendations to investigators is to preserve the trial's integrity as much as possible. Thus, no objections exist to informing the investigators that the DMC has met (e.g. after an interim analysis) and recommends the trial to continue as planned. Similarly, no objections exist to communicating DMC recommendations to improve data quality. Important DMC recommendations pertinent to patient care or patient recruitment regarding safety or negative benefit-risk should be immediately communicated. The same holds when the Sponsor adopts the DMC recommendation to stop the trial. In the case that the Sponsor (or representative) receiving the DMC recommendation disagrees with the DMC, see Question 8.

Question 7. When shall competent regulatory authorities be notified of DMC meeting outcomes?

Unexpected (in terms of presence or frequency) safety findings should be communicated to competent regulatory authorities as soon as possible. Other DMC meeting outcomes should be reported together with required or planned safety or interim analysis reporting such as Periodic Safety Update Reports (PSURs). As described in Question 3, important changes in design that are not preplanned would usually be discussed with the competent regulatory authority in advance.

Question 8. How should the DMC proceed when contemplating the recommendation to stop the trial?

The guiding principle in this situation is to minimize the impact on trial integrity should the trial subsequently continue. This should be considered in the degree of involvement of the Sponsor and in the communication to investigators. Therefore, when the DMC encounters issues for which it lacks requisite expertise or when it is contemplating a recommendation to stop the trial, it should first involve external experts to help resolve these issues. In closed sessions, the DMC and the external experts can consider all available evidence in the trial and any relevant external evidence. The trial recruitment may meanwhile be put temporarily on hold. Should the DMC subsequently recommend stopping the trial but the sponsor's representative (typically the trial's steering committee) disagrees, then in the interest of the trial, every effort should be made by both sides to reconcile their opposing views. A further step could be that DMC, external experts and sufficiently senior sponsor personnel with decision power and independent of the trial (typically higher management), convene in a closed session and reach a common decision. This is important, as providing two opposing views on proceeding the trial to the investigators will leave them in an impossible situation and will introduce operational bias (e.g. investigators withdrawing from the trial, selection bias in the recruitment of patients). Reaching reconciliation is also important, as otherwise the DMC may see no choice but to contact the Ethics Committee or competent regulatory authority to stop the trial.

Question 9. When is there a need for a DMC in early development phases?

Safety or risk/benefit monitoring is of large importance in early drug development as much less knowledge of the medicinal product has been acquired than in later phases. Therefore, knowledge of relevant and possible safety issues related to the medicinal product should guide the selection of the committee that performs safety review. The inclusion of members external to the Sponsor increases the credibility of such a 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 or the conduct of the trial which may impinge on objective decision making. However, in-depth knowledge of the medicinal product under evaluation might also be necessary. For early phase trials, such information might mostly be available within the Sponsor's organisation, or the manufacturer's organisation for trials where the Sponsor is a non-commercial institution. Moreover, where the nature of such studies is not confirmatory but exploratory, the need for internal members may be greater.

If safety review is implemented by a DMC in the definition considered in this Q&A, then by definition all members have to be independent from the Sponsor (see Guideline on Data Monitoring Committees (EMEA/CHMP/EWP/5872/03 Corr)). Otherwise, the committee should be called differently, e.g. a safety review committee (see Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07 Rev. 1)). Even if safety overview in early development phases is implemented via a non-(fully) independent committee, it is still in the interest of the Sponsor to (also) have a DMC in place. For example, in case of unexpected or critical findings that bear the risk of controversial, less urgent decision-making, a DMC should be considered to provide independent (additional) assessment and advice that enhances credibility of the decision-making process.