18 July 2019

Submission of comments on *Draft questions and answers on Data Monitoring Committees issues – EMA/492010/2018*

Comments from:

| Name of organisation or individual |
| --- |
| EFPIA |

*Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.*

*When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).*

1. General comments

| Stakeholder number  *(To be completed by the Agency)* | General comment (if any) | Outcome (if applicable)  *(To be completed by the Agency)* |
| --- | --- | --- |
|  | It would be useful to briefly clarify some terminology in the introduction to the document (lines 12-15), perhaps referencing the prior CHMP DMC guideline, to avoid confusion, especially in the later questions involving early phase trials. For example, what’s the distinction between a DMC and a safety review committee? The term “DMC” is in wide use in the field, but in some contexts refers to the *function*, not the *independence* (so that, for example, early phase groups could include sponsor members, as frequently occurs, and still be called a DMC). Thus, it would be better to clarify in advance the way the term is being used here. |  |
|  | The draft Q&A document should clarify that the use of an external DMC (or DMC at all) in early development phases may not be needed in many circumstances (e.g. in some first in human trials, or phase 1 SAD/MAD trials). These trials typically do not meet the published requirements for a DMC and requiring a DMC for early dose escalation would be prohibitive logistically and also quickly exhaust the community of experts qualified to sit on DMCs with the hundreds of ongoing dose escalation trials around the world.  Sponsors are responsible for safely making these decisions in partnership with clinical experts and study personal commonly deployed on dose-escalation committees to serve this purpose. |  |
|  | We suggest having a section to clearly define the scope of the document or situations covered by the Q&As. For example, it seems that the document is focusing on blinded studies. In the case of open label studies or studies without a control the practice is different and most of the Q&As are not applicable. |  |
| There is also a need to differentiate between Sponsor and study teams. They are different in many situations. In addition, a distinction should be made between the review committee that makes decisions about dose escalation, which typically includes study team members directly involved in study conduct and the Principal Investigator(s), and an independent SRC/Data Review Committee (which includes representatives from the Sponsor that are independent from the study team). The latter may also include an external expert who is independent from the Sponsor. |  |
| Reference is made in Questions 6 and 7 to early development studies. Clarification is requested regarding the scope of such studies, please define which studies are intended. |  |
| There are 7 questions in this document, only the answer to the first question has “No”. Suggest adding “Yes/No” to the other answers, if appropriate. This is particularly relevant for answers to Questions 6 and 7 which have some subtleties to them. |  |
|  | There are many important issues regarding DMCs, and the rationale for the choice of issues addressed in the Q&A document is unclear. Some examples of issues currently not addressed include: conflicts of interest; DMC membership; scope of DMC responsibilities; frequency/organization of DMC meetings; how DMC decisions are made; communication among DMCs, sponsors, and trial oversight bodies; DMC charters.  Please consider addressing these issues. |  |

1. Specific comments on text

| Line number(s) of the relevant text  *(e.g. Lines 20-23)* | Stakeholder number  *(To be completed by the Agency)* | Comment and rationale; proposed changes  *(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome  *(To be completed by the Agency)* |
| --- | --- | --- | --- |
| Line 23 |  | Comment: It is proposed that the guideline indicate where the documentation, justifying cases where DMC recommendations are not followed, should be sent or stored e.g. trial master file.  Proposed change (if any): |  |
| Lines 23-26 |  | **Question 1. Are DMC recommendations binding for a Sponsor?**  **Comment:** If the recommendation of minor modification of the trial is not followed, ethics committees (EC)/regulatory authorities may not need to be notified.  **Proposal:**  *However, in particular, if DMC recommendations to stop (in all cases) or* ***substantially*** *(as per the definition in Dir 2001/20/EC) modify the trial are not followed, the Sponsor is strongly advised to notify the Ethics Committees as well as the competent regulatory authority.* |  |
| Line 28 |  | In the answer to Q2, suggest adding the sentence “DMC can recommend, e.g., an early stop (generally due to efficacy according to pre-specified rule)” after “As mentioned above” |  |
| Line 30,  Question 3 |  | It is appropriate to state that the DMC can propose unplanned changes to the study. However, in certain circumstances, it may be appropriate to manage an amendment as an “urgent safety measure”, which is implemented immediately e.g. if the DMC recommends terminating a particular treatment group due to safety issues. However, a substantial amendment would need to be submitted subsequently (per “Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial”).  Proposed change: 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. **However, in certain circumstances, it may be appropriate to submit an amendment as an “urgent safety measure”, which is implemented immediately e.g. if the DMC recommends terminating a particular treatment group due to safety issues. However, a substantial amendment would need to be submitted subsequently (per “Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial”).** |  |
| Lines 30-46 |  | Changes to the study design for reasons other than safety should not be made by anyone with access to unblinded data, including DMCs. This might already be implied by the two statements about trial integrity in the existing text, but it should be stated explicitly. |  |
| Line 32 |  | Comment: It is proposed that the guideline clarifies the circumstances when the DMC can change an aspect of the study design.  Proposed change (if any): ~~Formally,~~ **With the exception of pre-specified design changes,** the DMC cannot change study aspects, because its role is to advise the Sponsor. |  |
| Lines 33-40 |  | **Comment:**  It would seem useful to add to this paragraph that if a DMC were to recommend unplanned changes to a study, it would most appropriately be to address an unexpected safety issue that arises. |  |
| Line 39 |  | This comment is in regard to Line 39, “In addition, the DMC can propose unplanned changes to the Sponsor but integrity of the trial must be protected”. It would be helpful if this section of the question-and answer document included examples of unplanned design changes in this context for reference. For example, this may be more applicable to new diseases that are less understood or rare diseases that are difficult to study. |  |
| Lines 41-42 |  | Comment: Note that when changes are made according to pre-specified adaptation rules in adaptive design studies e.g. change in randomisation ratio according to response adaptive randomisation, changes do not always result in a protocol amendment. Suggest making the sentence more inclusive.  Proposed change (if any): …the Sponsor decides whether changes are implemented ~~and if so, this has to be done via protocol amendments~~**. Unplanned changes are required to be done via protocol** amendments. |  |
| Line 52 |  | Proposed change (if any): Add “**and, as needed, efficacy**” after “continuous safety”, as described in the EMA DMC guideline. |  |
| Lines 53-55 |  | Comment: Rather than say “Sponsor” generically, reference to “Sponsor personnel who serve as the DMC point of contact e.g. Sponsor Committee” is suggested since the DMC should not be speaking directly to the Sponsor Study Team.  Proposed change (if any): **Thus,** 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 **personnel who serve as the DMC point of contact (e.g. Sponsor Committee)**, without direct communication between the DMC and any third party. |  |
| Line 53 |  | Comment: A DMC works to preserve the continuing safety of trial subjects (and those yet to be recruited) as well as the continuing validity and scientific merit of the trial. This is better captured as “benefit:risk” rather than just “safety”.  Proposed change (if any): “…in the interest of patient safety**(or, optionally, benefit-risk)** while the trial is ongoing” |  |
| Lines 56-62 |  | **Comment:**  Any approach to a DMC to request additional data should occur via the trial sponsor in every case rather than ‘preferably’ as responsible party. |  |
| Line 58 |  | Comment: Clarification is requested regarding the circumstances when the regulatory authority would be making a “decision” about the conduct of the study as well as the rationale for this. It is suggested that reference be made to the relevant clinical trial legislation and guidance (under both Directive 2001/20/EC and EU Regulation No. 536/2014, as appropriate).  Proposed change (if any): |  |
| Lines 59-62 |  | Comment: The term “Vice versa” is not considered to be appropriate. Also, it is considered that it is always appropriate for the regulatory authority to contact the DMC through the Sponsor.  Proposed change (if any): ~~Vice versa, e~~**E**xternal 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, t~~**T**he Sponsor **must** ~~should~~ be involved in such justified requests and related communications to ensure that their respective roles and responsibilities are not undermined. |  |
| Lines 62-64 |  | “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.”  Comment: Maintaining trial integrity is important for all trials. The scope of the answer could refer to more complex designs such as master protocols, multi-phase studies etc, where the competent authorities may be asking to see interim reports of data which may require some level of unblinding. Maintaining trial integrity may be best addressed in a new question.  Proposed change (if any): |  |
| Question 4  Lines 65-68 |  | **Is a direct communication and exchange of information between competent regulatory authorities and a DMC possible?**  **Comment:** Modified the sentence as the DMC is not implementing the changes itself.  Additional considerations which are not reflected in the proposed change: the needed communication between DMC and competent regulatory authorities and the modification of protocol/trial monitoring plan/statistical analysis plan are two different actions that can be carried out separately. It is also not clear why the recommendation comes from DMC to sponsors instead of directly from competent regulatory authorities to sponsors.  **Proposal:**  *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* ***recommend to have*** *implement****ed*** *to address the public health concern.* ***The impact from this type of communication on the trial integrity should be kept minimal and the*** Sponsor should be fully involved in any such communication ***without unblinding the sponsor.***  **Additional comments on this question:**  The text refers to the Competent Health Authority and the DMC communicating directly in exceptional circumstances related to a public health concern.  We are concerned about this suggestion because if there is a public health concern, it is the sponsor who can most efficiently provide additional analyses. Members of the sponsor’s safety team or team members not working on the project could have access to unblinded data to assist in the assessment if needed.  Finally, the sponsor should be involved in the discussion, planning and implementation of any subsequent actions in regard to the study or investigational medicinal product. If there is a public health concern, leaving the sponsor out may make the situation worse overall and not improve the outcome for patients. |  |
| Lines 72-73 |  | This section of the question-and-answer document pertains to notifying Investigators of overall DMC meeting outcomes. We recommend that these notifications would be for outcomes where there are important new recommendations to share that are pertinent for patient care, and that this document provides more definition around this topic of notifications. For example, a DMC may comment on certain statistical considerations that may not need to go to the Investigators. At other times, the overall outcome is just to continue and there are no new recommendations to convey to the Investigators.  We also recommend that this section add guidance as to when these notifications of overall outcomes may need to be submitted to regulatory authorities, as this is not covered in the question-and-answer document or in the main guideline (EMEA/CHMP/EWP/5872/03). |  |
| Lines 72-73 |  | Comment: It is considered that reference to “regarding safety” should include lack of efficacy. It is recommended that this be clarified.  Also, there is no need to inform the Investigators when the recommendation is to “Continue the Study as Planned”.  Proposed change (if any): **When a change in the study conduct due to safety or lack of efficacy is required** the Sponsor should ensure that theInvestigators in a clinical trial with an appointed DMC ~~are~~ are informed about overall DMC recommendations~~, i.e. regarding safety~~ in a timely manner. |  |
| Lines 72-73 |  | The document should emphasize that DMC recommendations to investigators should be limited to information that does not compromise the integrity of the study. |  |
| Lines 74-81 |  | The EMA guideline on Data Monitoring Committees (EMEA/CHMP/EWP/5872/03) covers the general concept that not all trials need a DMC and provides some general aspects that should be considered when it comes to the decision of whether or not a DMC should be set up. While the question-and-answers document continues this discussion of general aspects, we recommend that it be explicitly noted it is at the sponsors discretion to determine when a DMC or other safety review committee would be needed in early development settings and the way in which these concepts might apply specifically in the early development setting. |  |
| Question 6 |  | The question statement uses the term “DMC”, but the response does not. The response introduces the term “safety review committee” which it does not define. This terminology is not used in the EMA guideline on Data Monitoring Committees (EMEA/CHMP/EWP/5872/03), Is this SRC intended to be a committee distinct from the DMC, and if so, is a DMC relevant to the response to Question 6? |  |
| Line 74,  Question 6 |  | **When is there a need for a DMC in early development phases?**  **(See the General Comments for a similar point)**  **Comment:** Single dose and short term (<1 month) dosing in healthy volunteers or in a relatively healthy adult patient population may present logistical challenges for the timing of DMC reviews due to the short dosing intervals per cohort. Also, first in human studies typically have well defined protocol specified stop/pause criteria for individual subject dosing and dose escalation. In addition, for Phase 1 studies, treatment assignments may be unblinded to the sponsor if needed for safety decision making. Thus, data integrity concerns do not necessarily require confining unblinded safety data reviews to a DMC.  **Proposal:**  The above should be made clearer in the Q&A generally and in the question e.g. by addition text at the end such as:  *First in human studies typically have well defined protocol specified stop/pause criteria for individual subject dosing and dose escalation. In addition, for Phase 1 studies, treatment assignments may be unblinded to the sponsor if needed for safety decision making. Thus, data integrity concerns may not necessarily require confining unblinded safety data reviews to a DMC.* |  |
| Lines 75-81 |  | **Comment:**  Question 6 refers to the need for a DMC. However, in the subsequent response, line 77 appears to indicate that the need for a ‘safety review committee’ is usually higher in first in human clinical trials and other early phase trials. If this is a correct assumption, then while it is accepted that rigorous safety monitoring is required for early trials, the juxtaposition of question and response implies that the safety committee referenced is a DMC. However, any implied recommendation for use of a DMC in early phase trials is not consistent with the EMA’s Guideline on Data Monitoring Committees which does not make any specific reference to a need for DMCs for early phase studies and explicitly states that for clinical studies which can be performed in a short time frame, the use of a DMC might not be beneficial and may delay the conduct of the trial.  In fact, in very early phase dose escalation trials, it is not usually the case that a bureaucracy is set up where a “committee” (especially an external one) makes recommendations that have to be reviewed and decided upon – rather, some trial personnel have that responsibility. In this exploratory stage, confidentiality is not critical in the same sense as in confirmatory studies, so the best available expertise would typically be utilized, and in the most time-efficient manner, in the best interests of the patients and the program, which could involve sponsor and / or external experts.  It is proposed that the response is rewritten to more closely mirror the existing EMA guideline. |  |
| Lines 77-81 |  | “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.”  Comment: Clarify the safety review committee is an internal one for early phase studies. But for multi-phase studies, there needs to be a clear distinction between an internal safety review used to support dose escalation decisions versus an external DMC for monitoring safety in the confirmatory phase.  Q6 and Q7 focus on early phase only studies but increasingly such studies are multi-phase which is not recognised so much and should be.  Proposed change (if any): |  |
| Lines 79-81 |  | We recommend that this section on the early development phase includes the consideration that the sponsor, in consult with the investigators, can assess the data to make dose escalation decisions without the need for a DMC, and that this approach would be valid under various conditions. |  |
| Line 82 |  | Comment: Very often safety review committees in early development phases are internal within the Sponsor or include Sponsor personnel, especially in phase 1 studies. When there are qualified personnel within the Sponsor who are independent from the development team, credibility of the committee usually is not a concern. Questions 6 and 7 are closely related so it is better to address together. The current format, e.g., without distinguishing between Sponsor and the study team is confusing.  Proposed change (if any): |  |
| Line 82,  Question 7 |  | Two aspects of the response are confusing. (1) The first sentence states unequivocally that a DMC is external to the sponsor, but then the response discusses monitoring that includes the sponsor. This implies that the sponsor personnel are not part of the DMC. (2) Like the response to Q6, the response to Q7 mentions a safety review committee, which it does not define. Is the SRC distinct from the DMC?  In the end, the response to Q7 doesn’t answer the question.  Proposed change (if any): Clarify in this question or earlier in the Q&A document the difference between a DMC and a safety review committee, and ensure the response to question 7 is addressing the question. |  |
| Lines 82-95 |  | Comment: A safety review committee (if it is well understood that it is different from a data monitoring committee) might be used jointly externally and internally, comprising internal sponsor members and external study investigators – in this case it would be scarce to have truly independent members as part of the committee.  A data monitoring committee should comprise independent members, and as such, it should be clarified that those ‘external’ members part of the DMC are not study investigators, who are not independent to the study. This distinction should be made clear in the text, since ‘external’ does not necessarily mean ‘independent’.  Proposed change (if any): |  |
| Line 84 |  | **Comment:**  The statement that a DMC always refers to a committee independent of a sponsor is not consistent with the definition of a DMC in the EMA guideline which refers to a group of experts independent of a trial. This distinction is important, as ‘internal’ experts who are independent of the conduct of a trial may provide a more immediate and accessible route for decision-making to ensure patient safety. This is particularly important in the context of early phase trials where rapid decisions on dosing continuation may be required. |  |
| Lines 84-86 |  | Comment: Question 7 is addressing “Does safety monitoring in early phase studies need to be done by people independent from the Sponsor?” The first sentence of the response defines DMC as external to the Sponsor.  Proposed change (if any): Monitoring of an early phase study may be done by an external, internal, or blended (comprised of both internal and external members) committee. 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. |  |
| Line 85 |  | **Comment:**  In combination with Question 6, it seems strongly conveyed that safety monitoring has “more importance” in exploratory stages of development. This choice of wording seems ill-advised. While safety judgments and implications are different in the two stages as described, it does not seem appropriate to “order” them in importance, they’re both critical, but different. It’s certainly true as stated that there is more knowledge of the safety profile by the time of a confirmatory trial; however, a safety risk at that stage would affect more patients, and that will be a point at which crucial risk-benefit considerations can be better understood, and safety judgements can affect whether the treatment may be approved and become available to a very large population of patients.  Proposed change(if any): “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 k~~Knowledge of relevant … |  |
| Lines 88-91 |  | Comment: For larger sponsors, there may be knowledgeable committee members who have not been involved in the development of the medicine.  Proposed change (if any): The inclusion of members external to the Sponsor may increase 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. |  |
| Line 90 |  | Comment: It is recommended that the phrase “heavily involved” be changed to “directly involved” and this would allow for internal members to serve who are not on the study team.  Proposed change (if any): Therefore, this committee should have sufficient independent members so that decisions are not made solely by members who have been ~~heavily involved~~ **directly 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.~~ |  |

Please add more rows if needed.