

## **EFSPI regulatory statistics conference webinar “Data monitoring committees – evolving their role in a changing drug development landscape”, 12<sup>th</sup> October 2020**

### **Questions from the webinar chat addressed by the panelists**

The views expressed are the personal views of the panelists and members of the organizing committee and may not be understood or quoted as being made on behalf of or reflecting the position of the Agency or the company.

#### **General questions:**

Siva Prasad: Who will determine number of DMCs? How many DMCs per trial in general?

*Thomas: That decision is with the sponsor.*

*Steven: As per the DMC Guideline [https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-data-monitoring-committees\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-data-monitoring-committees_en.pdf), this is the Sponsor.*

*Paul: Interpreting “How many DMCs per trial” as “How many DMC meetings per trial”: This will be very case-by-case, and depend on particular ethical and strategic details of the trial, for example, accrual rate, study duration, presence of acute safety concerns, follow-up time to key outcomes, coordination with a group sequential scheme, etc.*

Weihua Cao: Can competent regulatory authorities approach DMC for unblinded data/results?

*Answered in panel discussion. And see Janet Wittes’ presentation.*

*Paul: As in Question 4 of the EMA Q&A as presented by Steven, this is not advised, and would require exceptional circumstances.*

*Janet: I am not sure what the question means. If Siva means, “How many trials should a DMC oversee”, I would respond that it is often useful for a DMC to oversee a set of closely related trials. It then serves as a “program-wide” DMC, but it needs careful discussion with the Sponsor and Exec Committee so that it understands its charge if the various trials show different results in safety, efficacy, or both. If the question means, “How many members should a DMC have”, I would answer, “This is a Goldilocks question – the DMC needs to be large enough to cover the necessary expertise but not so large that scheduling meetings becomes very difficult. Also, many people say it is important to have an odd number of members so that the vote isn’t evenly split. My view is that the DMC needs a strong, effective Chair who can forge a consensus. In fact, I don’t like voting on DMCs. If the goal is consensus, then it doesn’t matter if the size is odd or even.*

Sreekanth Gattu: Will these answers to questions be any different if it is a biosimilar clinical trials? Are there any special/unique aspects of DMC in the context of Biosimilar PK / efficacy studies?

*Thomas: The general principles are the same for biosimilar trials.*

*Steven: Typically not. Efficacy measures (like objective response or progression-free survival) and safety is compared in a sensitive patient population, much like in a ‘normal’ efficacy/safety trial. Thus, the principles (independence, protect safety, advisory role, maintain trial integrity and credibility) still hold and these drive the answers.*

*For studies only investigating PK, it could be that these are very short-term and a DMC cannot have its usual value. See also the DMC Guideline [https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-data-monitoring-committees\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-data-monitoring-committees_en.pdf) which acknowledges cases in which a DMC may not be useful.*

Sameera Govindaraju: Will all the trials need a DMC during the current times (pandemic)?

*Answered in panel discussion: Requirement for iDMC no different just because a trial deals with Covid-19. Requiring an iDMC for all trials would risk overburdening the system.*

Rama Sivasubramanian: How will the DMC be set up when the trial is an open label study?

Rui Qin: Is it necessary for an open-label randomized study to have a DMC? If yes, what are the additional considerations in open-label studies?

*Thomas: The necessity of a DMC does not depend on whether or not the study is open-label or not, but is based on other considerations (see section 2 of EMA guidance). Consequently, if the need is established, the operations of a DMC will be the same whether the study is open-label or not.*

*Steven: The need for an DMC is in principle the same for double-blind and open-label studies. Maybe implementing the blinding of the Sponsor against the results of analyses for the DMC needs more consideration than in a double blind trial, although I would not expect that in double-blind studies such blinding could be more relaxed. In any case the principles for the DMC remain the same.*

Unknown: Do we need to change the wording and terminology we use? Many would argue that stopping trials for futility may not be unfortunate - indeed this may well be a good thing and allow re-allocation of resources to other trials and other interventions?

*Thomas: Many people use "lack of benefit" instead of futility although I personally believe that these are different things. A study that cannot recruit sufficiently may be futile while a study with little evidence for benefit should be stopped for lack of benefit.*

*Paul: Regardless of terminology used, the DMC Charter should clarify what are the envisioned potential reasons why a trial might stop prematurely, and the basis on which this might occur.*

*Steven: I agree if 'unfortunately' only refers not reaching the success criterion of the trial (typically statistical significance of the primary endpoint). In the larger perspective, stopping for futility may be well be beneficial indeed.*

*Janet: I worry about overly rigid "rules" or even non-binding futility guidelines because once a DMC recommends stopping, it is very hard to restart. Often the results from the second half of a trial differ considerably from the first – perhaps such changes are due simply to variability; sometimes they may reflect changing populations entering the trial, or perhaps investigators learning how to carry out the protocol more effectively. In time-to-event trials, the hazards may not be proportional, so inference from a longer-duration trial may differ from that of a shorter-duration trial. In summary, a DMC should be extremely cautious in declaring futility.*

Kit Roes: Responsibility for adaptation decisions (e.g. dose selection decisions instead of only recommendations) is for me in potential conflict with independence: the advisory role is also instrumental to preserving independence.

*Thomas: I agree and hence would advise to use a DMC separate from a safety review committee (or whatever the term used is for the group that determines the next dose level in a dose finding study).*

*Steven: I agree, as the advisory role keeps the final responsibility for the trial clearly at the Sponsor. I can imagine for persons (such as the DMC) having to take decisions may influence their later recommendations and/or decisions or even the decision at hand.*

Kit Roes: Not mentioned - but we also see quite a few examples (also in COVID) that sponsors propose additional committees (sometimes also call ##DMC) with internal sponsor personnel being unblinded, in addition to independent DMCs. What are opinions there?

*Thomas: The default position should be not to have unblinded sponsor personnel, but as so often there might be exceptional cases where this could be considered. The example of dose-selection might be one of these areas.*

Emmanuel Zuber: How can we prepare DMCs to handle the "unexpected"?

*Thomas: Not very well, but experience, understanding of implications of multiple looks at data and clarity of the objectives of the study will help.*

*Steven: if it fully unexpected, then I think it would help if the DMC can consult external experts (see also next question). If the 'unexpected' can be foreseen, then the composition of the DMC can take that into account.*

Could the panel elaborate on the EMA Q&A suggestion to involve external experts?

*Answer: The iDMC should be careful reaching out to experts by itself, without involving the sponsor. Consider the risk of information leaking.*

How could that work and how much would that involve (or inform) the sponsor?

*Answer: Suggestion that iDMC first reaches out to sponsor before consulting external experts.*

*Paul: In general, the DMC is bound by confidentiality agreements and is not authorized to share the results further at their own discretion. If a need unexpectedly arises for an additional expertise not already included among its members, the preferred approach is for the DMC to make the request to the sponsor, and in a manner that conveys as little information as possible regarding the motivation or any comparative information.*

Marcus Millegård: How do the speakers see the role of the iDMC in Ph2 trials with no registrational intent?

*Thomas: As eluded before, I think the need for iDMCs is determined not by the study design or sponsor intent but more fundamental questions about safeguarding patients (see EMA guidance section 2).*

*Steven: First of all, some phase 2 studies are later used for registration in contrast of what was intended at planning stage. To the point: a DMC can play a useful role also in early phase studies, see for example Q9 of the Q&A, [https://www.ema.europa.eu/en/documents/scientific-guideline/questions-answers-data-monitoring-committees-issues\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/questions-answers-data-monitoring-committees-issues_en.pdf).*

Fanny Masson: Would you recommend consulting HAs first when we plan to have adaptation decisions lying with the Sponsor?

*Paul: If in a confirmatory trial sponsor representatives were to be involved in an adaptation decision, the case should be carefully made, e.g.: justifying the need for sponsor perspectives, conveying the least amount of information to the fewest number of individuals who can meet that need, insulating knowledge of results from personnel involved in trial operations and decisions, and documenting that secure firewalls are in place. Informing HAs in advance to get their reaction will often be advisable.*

*Steven: if I understand correctly, this concerns adaptations that are not (fully) preplanned in an algorithm. This may change the confirmatory nature and interpretation of the results of the trial. For example, when the involvement of the Sponsor in the adaptations involves unblinding of the results to Sponsor. Therefore, it could change chances of regulatory approval and thus, it would be wise to discuss this with regulatory authorities.*

Kit Roes: As a thought: the action on additional adjudication could very well have been advised without revealing anything about the treatment effect. Would for me (as a DSMB member) have been a very logical first step.

*Paul: The panel agrees, informing the sponsor that there were differences between the types of assessment that were important to reconcile in the interest of interpretability of trial results might have been a reasonable first step, without being explicit about the results themselves.*

NN: Very interesting scenario. Whilst the adjudication committee were reviewing potential discrepancy cases - was recruitment put on hold? Or did this continue for the trial?

*Answer: recruitment was already finished.*

NN: Could I ask hypothetically if recruitment were still to have been ongoing - what would be your thoughts on whether to continue or hold recruitment whilst data are being adjudicated?

*Answer: As a general rule, unless there's a burning ethical issue, I tend to be hesitant to pause enrollment too readily - that sort of tells everyone that "something's going on", and could set off speculation, whether right or wrong, that could have some subtle influence on trial conduct.*

Anh Nguyen: How has this been perceived by regulator(s)?

*Paul: The final data did not support registration of that specific indication, though it was part of the supportive package for a related situation, so it's not certain what the regulatory perception would have been.*

Baktiar Hasan: What bias the independent central review had and how was it possible if the review was (presumably) blinded?

*Paul: Most of the bias arose structurally from the informative censoring, since patients who the investigator felt had progressed, or who were switched to alternate neoplastic therapies, were censored, and these patients tended not to be representative of the full population.*

*Steven: it helps to clarify what is to be estimated (the effect if no one would have had subsequent therapy/switching, i.e. a hypothetical strategy // or: the effect including subsequent therapy as they occur, i.e. a treatment policy strategy). See the estimand framework ICH E9 revision 1 ([https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-sensitivity-analysis-clinical-trials-guideline-statistical-principles\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-sensitivity-analysis-clinical-trials-guideline-statistical-principles_en.pdf)).*

*For the hypothetical strategy, censoring could be an analysis method, but inverse probability of censoring weighting (IPCW) or rank-preserving-failure time models could be better suited.*

*For the treatment policy strategy, this censoring is informative and causes bias. This bias can be avoided if scans are still collected after investigator assessed progression, until the central review determines progression.*

## **Jaki**

Beth DiDomenico: Please elaborate on Simpson's paradox for those us not statistically oriented?

*Answer: Simpson's paradox is basically the phenomenon that, if you have (say) 2 different sources of data each of which you see something (some kind of trend) but when (naively) pooling, those trends disappears or even reverses when these sources are combined.*

## **Burger**

Lixia Pei: For a platform trial (containing multiple trials for a long duration), is it better to have one IDMC or multiple IDMC?

*Answer: Concerning the question to me on platform trials I would prefer to have one DMC to make things easy as the basis and then see if there would be real need for separate ones (may be different sponsors, different safety and benefit risk assessments etc.) But there should be for the study and the DMC a real benefit when going over to more than one.*

## **Wittes**

Maeva: Could you elaborate on the need of 2 statisticians for DMCs? Is it possible that the independent statistician and the DMC statistician would be the same person?

*Answer: I will elaborate. The problem I see is that the statistician on the IDMC has a central role and it's important that he or she has experience. The only way to get experience is to sit on committees. But the first time, the person will not have experience. I used to argue that sponsors should have an apprentice statistician as a "trainee" but most companies don't want to do that. (A shout out to Seattle Genetics, who has embraced that idea - many thanks!) So my new recommendation is to have two -one experienced person and one with no or very little experience. That will set us up so there will be lots of experienced statisticians in the future.*

*Paul: In general, the DMC statistician and the Independent Statistician serve very different functions, requiring different expertises and experience. While perhaps not impossible, this seems generally not advisable and should be very rare.*

*Kit Roes: I think the statisticians from the ISGR also learn a lot (and contribute a lot) in this setting - they attend all sessions...*

## **Fleming**

Reference of the 2011 paper about releasing conditional power to sponsor? That seems very relevant and interesting.

*Answer: <https://pubmed.ncbi.nlm.nih.gov/22024103/>*

Emmanuel Zuber: Can you elaborate on your proposal for starting with a closed session of the iDMC, and what would it be used for by the DMC members?

Florian Schirm: Yes, I would be interested as well about hearing a bit more on the Closed-Open-Closed Session Design proposed by Dr Fleming.

*Answer: If the iDMC starts with a closed session it can already have a look at the data and formulate questions that it would like to ask the sponsor in the open session. This also allows the chair / iDMC to remain on top of the situation. A final closed session can then be used to wrap up all the learnings from the earlier two session (closed + open).*