Q<Date of submission>

Submission of comments on ´Questions and answers on Data Monitoring Committees issues' (EMA/492010/2018)

Comments from:

Name of organisation or individual
Association for Applied Human Pharmacology (AGAH), Hamburg, Germany

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).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	The objective of the document is to clarify the role and necessity for a DMC in different phases of drug development and throughout the product lifecycle as well as with regards to the responsibilities for implementing DMC decisions. The document should better address common and differing aspects in setting up a DMC in early vs. late clinical development (e.g. focus on either blinded or unblinded data reviews, focus on assessing exploratory safety aspects (by a SRC) vs. confirmatory efficacy aspects (by a DMC), assessments during the conduct of early phase clinical trials. We recommend to differentiate different subtypes of DMCs - or even better to use different names - depending on the different tasks: 1) **DMC in early phase clinical trials (proposed name: Safety Monitoring Board):** as this is primarily a medical and pharmacological case assessment, adequate clinical and pharmacological expertise is needed; statistical expertise is less pertinent. Furthermore, the PI(s) need(s) to be consulted or should participate; Such safety assessments can well be realised internally with qualified persons unless there are complex safety issues	

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	e.g. in first-in-class FIH trials. In the latter case external expertise is meaningful to be considered in the DMC. Safety Monitoring Board monitors the safety data in the blinded manner. 2) **DMC in later phases where the safety of the trial participants is in the focus of the assessment (proposed name Safety Review Board)**: here adequate measures are needed to ensure that the DMC recommendation is not influenced by the sponsor. Adequate clinical expertise in the indication and adequate statistical knowhow needs to be present in the DMC. To make sure that the sponsor does not influence the DMC recommendation and to ensure that no conflict of interest occurs, adequate measures are to be defined in the DMC charter and financial disclosure forms are to be applied. The safety data review may require unblinding of the data. In such case adequate measures need to be installed to assure that the integrity of the trial is not affected by the unblinding of the data. 3) **DMC in pre-planned interim analysis (possible name: Data Monitoring Committee):** This DMC requires medical expertise, expertise in the methodology of interim analysis and clinical trials as well as statistical expertise. The statistical expertise may be of higher importance than in other DMCs as often sample size and complex statistical questions like interference with type-I-error are of relevance.	

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	In case such DMCs are unblinded (e.g. fully adaptive designs) it is of utmost importance to establish adequate measures which ensure - especially if a representative of the sponsor has to be involved in the final decision - that in no case any influence on further trial decisions may occur.	

2. 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 20-26		Proposed change (if any): To add: This does not refer to the situation when the activities of the DMC are pre-specified in the protocol that may be a case in the context of pre-planned interim analysis for early stopping or in case of complex study designs where a possible modification of the study design based on unblinded interim data is intended.	
Line 27-29		Comment: The original guideline specifies the situation when the DMC monitoring activities are expected to have relevant impact on the conduct of the trial (e.g. stopping the trial) and these activities are pre-specified in the study protocol. Proposed change (if any): To add: if DMC activities are not otherwise pre-specified in the protocol.	
Line 84-95		Comment: The original guidelines indicates that completely independent DMC is desirable but not always possible. Proposed change (if any): To add: The possible conflict of interests should be avoided.	
Line 72-72		“overall DMC recommendations” is somewhat too general. The investigator should know about “relevant safety findings and DMC recommendations”	

Please add more rows if needed.