<Date of submission>

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

Name of organisation or individual
International Society for Clinical Biostatistics: Statistics in Regulatory Affairs Subcommittee

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)*

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)*
Lines 5-6		TEG Comment: The title of the document is grammatically questionable Proposed change (if any): Could change to "Data Monitoring Committee issues" or "Data Monitoring Committees: questions and answers".	
39-46		CJW Comment: The key consideration is whether the DMC has viewed any summaries of data by treatment arm. Prior to this occurring, any suggested changes to the study design by the DMC could be implemented by the Sponsor without harming the integrity of the trial. Suggested substantial amendments from the DMC following any review of data split by treatment arm would almost certainly damage the integrity of the trial and should not be accepted by the Sponsor. The discussions with the competent regulatory authority proposed in the guidance (lines 45-46) should certainly consider this aspect. Proposed change (if any):	
Line 42		TEG Comment: We find the phrase "Introducing amendments to the confirmatory nature of the study.." unclear. It is not clear whether there is an assumption that the study is confirmatory (and that this is to change), or whether this statement is referring to changes as to whether or not the	

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		study is confirmatory. Since a focus of this document is on early phase trials, assuming all relevant studies are confirmatory may not be appropriate. Proposed change (if any): Clarify whether the document is assuming confirmatory studies.	
Lines 49-51		TEG Comment: This statement is quite categorical but it is then qualified in the paragraph below. Proposed change (if any): Anticipate in the first paragraph that there may be exceptions.	
Line 57		TEG Comment: This implies that only the regulatory authority should initiate any such contact, not the DMC. However, there could be circumstances where the DMC might wish to initiate the contact. Proposed change (if any): Could add a sentence on any exceptional circumstances in which the DMC may consider it necessary to communicate directly with the regulator.	
Line 62		TEG Comment: Why is "circumstances" plural? Proposed change (if any): Change "circumstances" to "circumstance"	

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Line 69		TEG Comment: This seems to suggest that sometime it would involve sharing unblinded data. This would seem to be exceptional, and would be worth clarifying. Proposed change (if any):	
Line 77; Lines 87-88		TEG Comment: The terminology "Safety Review Committee" is unfamiliar and the distinction between this type of committee and a Data Monitoring Committee is not very clear. Proposed change (if any): Make the distinction between the Safety Review Committee and Data Monitoring Committee more clear	
79-81		CJW Comment: This is a narrow description which discusses the need for a DMC in relation to only one type of early phase trial design. Proposed change (if any): Replace "dose escalation" with "changes to the dose to be allocated to the next enrolled patient(s)" and "proceed to the next higher dose" with "change dose, continue the current dose or stop the trial".	
Line 92		TEG Comment: The need for one or more Safety Review Committee members internal to the Sponsor in order to have in-depth knowledge of the medicinal product seems somewhat overstated. One might expect an external expert to have	

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		sufficient knowledge to assess safety aspects. Proposed change (if any):	