20 June 2017

Submission of comments on ' Guideline on multiplicity issues in clinical trials' (EMA/CHMP/44762/2017)

Comments from:

Name of organisation or individual
ACRO (Association of Clinical Research Organizations)

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 Association of Clinical Research Organizations (ACRO) represents the world's leading, global clinical research organizations (CROs). Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices – from discovery, pre-clinical, proof of concept and first-in-man studies through post-approval and pharmacovigilance research. With more than 130,000 employees engaged in research activities around the world (including 57,000 in Europe), ACRO advances clinical outsourcing to improve the quality, efficiency and safety of biomedical research. Each year, ACRO member companies conduct more than 7,000 clinical trials involving 1.3 million research participants in over 100 countries. On average, each of our member companies works with more than 700 research sponsors annually. ACRO welcomes and supports the proposed revisions to the guidance on multiplicity concerns, acknowledging this important issue in both the design and analysis of clinical trials. While recognizing that the draft guideline	

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	goes some way to achieving its stated aim of providing guidance on how to deal with multiple comparisons and control of type I error in the planning and statistical analysis of clinical trials, ACRO recommends that the value of the guideline to users would be enhanced greatly with the following general changes: a. The scope of the document should be rephrased to state clearly that it discusses when issues of multiplicity arise, and not how to address them from a technical point of view. The topic of multiplicity in sub-groups is not addressed. b. Sample size calculation guidance is not addressed; this exclusion should be stated up front in the scope statement. c. The addition of appropriate references would be extremely helpful. d. Adding some examples would enhance the document to be more of a guidance versus a commentary. e. Adaptive design multiplicity issues are not covered and the guideline should explain where appropriate guidance on this topic is available. f. The section on multiplicity on safety variables should be clearer. For example, no multiplicity correction	

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	is required. Additionally, the revised document offers limited new information over that included in the current CPMP Points to Consider document. There are some important recent developments that are not discussed, e.g. • Estimands • Competing risks • Adaptive designs (e.g. for dose or endpoint selection) • Multiple Comparison Procedure – Modelling (MCP-Mod) for dose-response testing and estimation ACRO recommends that clarifying the Agency's position with regard to multiplicity in these settings would be appropriate and useful additions to this guideline.	

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 77		Comment: The statement allowing 'protocol or SAP' is misleading since statistical procedures should be documented in the Statistical Analysis Plan, which may or may not be part of the protocol. They may also be documented in the protocol even when a separate SAP is provided, although the SAP is not typically included in a clinical trial application dossier. Proposed change (if any): In order to ensure assessors are able to review what is proposed, the phrase "protocol or SAP" should be changed to "protocol and SAP".	
Line 86		Comment: The distinction between 'endpoint' and 'objective' is not clear. Also, it is stated that secondary endpoints or subgroups are tested only after primary endpoints. It is recommended to replace 'only' with 'usually'. Proposed change (if any): Distinguish between "endpoint" and "objective", and replace "only" with "usually".	
Lines 98 - 111		Comment: The section should include a statement addressing operationally seamless study designs where inference may be based on the primary endpoint results from all phases (i.e., inferentially seamless). Proposed change (if any): Include a statement addressing	

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		operationally seamless study designs where inference may be based on the primary endpoint results from all phases (i.e., inferentially seamless).	
Lines 107 - 108		Comment: ACRO recommends that it would be very helpful to include a discussion of other gatekeeping procedures in addition to the hierarchical procedure, and inclusion of examples of when techniques such as Bonferroni, Holm, Hochberg or graphical models could be used. At the very least, ACRO recommends that the sentence “A number of methods are available for controlling the rate of false positive conclusions, the method of choice depending on the circumstances” is accompanied by references to published literature where information on additional techniques and their use can be found. Proposed change (if any): Include a discussion or references to published literature where information on additional techniques and their use can be found.	
Lines 136 - 141		Comment: ACRO recommends that this paragraph should include a statement on where appropriate guidance on inferentially seamless adaptive designs is available. Proposed change (if any): Include a statement on where appropriate guidance on inferentially seamless adaptive designs is available.	

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Lines 167 - 170		Comment: While it is true that multiple conditions/endpoints that all need to be successful do not inflate Type I errors, there is still an issue with Type II multiplicity. This is later referenced in lines 222-224. Proposed change (if any): Acknowledge the multiplicity impact on Type II errors, even if only to clarify that dealing with this multiplicity is outside the scope of this guidance.	
Lines 226 - 228; 240 - 242 (Section 5.1.2)		Comment: It is possible that lower ranked variables could still claim significance if the Fallback Method was utilised and sufficient alpha was allocated to the lower ranked variable at the outset. Proposed change (if any): Clarify that this conclusion ("*However, no confirmatory claims can be based on endpoints that have a rank lower than or equal to that variable whose null hypothesis was the first that could not be rejected*") assumes the Fixed-Sequence Method, and that there are other strategies where this would not apply. A discussion of the other strategies would be welcome, also.	
Line 273		Comment: The sentence "It is also important in this case that there is no inflation in the type I error" is ambiguous. It could be read as meaning "there *should be* no inflation" (and thus steps need to be taken to control the inflation), or as meaning	

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		that this case already controls the inflation (“in this case there is no inflation”) and thus no further actions are necessary. Proposed change (if any): Amend the wording to better reflect the true intended meaning of this sentence.	
406		Comment: It would be helpful for the guideline to include some examples of the “more complex methods” referred to, if only by providing references to relevant literature. Proposed change (if any): Include some examples of the “more complex methods” referred to and/or provide references to relevant literature.	
Lines 498 - 527 (Section 9.2)		Comment: In the current CPMP Points to Consider document from 2002, the corresponding section states “When defining a composite variable it is recommended to include only components for which it can be assumed that treatment will influence them similarly.” It is not clear whether the absence of this text from the present guideline implies that the similarity of the magnitude of effect on components is no longer necessary to be considered when defining composite endpoints (The similarity of direction of effect is confirmed in the text already.) Proposed change (if any): Clarify the Agency's position on this, and whether this interpretation was intended.	

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Lines 558 - 560		Comment: It would be helpful for the guideline to include an example of “different wording” for a product information labelling claim in this context that would be acceptable? Proposed change (if any): Include an example of acceptable wording.	
Lines 597 - 599		Comment: It would be helpful to distinguish situations in which multiple confidence intervals are used for testing (e.g., non-inferiority) versus estimation (e.g., showing the likely range of the estimate of treatment effect), and to include a statement to advise when corrected confidence intervals should be provided. Proposed change (if any): Add text to distinguish situations in which multiple confidence intervals are used for testing versus estimation, and include a statement to advise when corrected confidence intervals should be provided.	
		ACRO thanks the Agency for the opportunity to comment on this “Guideline on multiplicity issues in clinical trials (EMA/CHMP/44762/2017).” Please do not hesitate to contact ACRO (knoonan@acrohealth.org) if we can provide additional details or answer any questions at all.	

Please add more rows if needed.