EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

29 June 2017

The International Society for CNS Clinical Trials and Methodology, ISCTM, welcomes the opportunity to provide comment on the "**Guideline on Multiplicity Issues in Clinical Trials**" drafted by the Biostatistics Working Party of the European Medicines Agency.

The ISCTM was chartered in the fall of 2004 as an international society charged with providing a commercial free forum where key stakeholders from academia, industry and regulatory branches can discuss/resolve challenges specific to the design and methodological issues in CNS clinical trials. Recognizing the importance of this document for our constituency, the ISCTM convened a working group to review and comment on the guidance.

For this response, the group has provided general comments and some recommendations regarding the agency's proposal on managing multiplicity issues in clinical trials.

Below please find contributors to the ISCTM working group on "Guideline on Multiplicity Issues in Clinical Trials."

Chair: Atul Mahableshwarkar, MD, Blackthorn Therapeutics
Co-chair: Ibrahim Turkoz, PhD, Janssen Research and Development, LLC
Lawrence Adler, MD, University of Maryland School of Medicine
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Submission of comments on ' **Guideline on Multiplicity Issues in Clinical Trials** ' (EMA/…/…)

Comments from:

INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY (ISCTM)

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)*
	Please state in the guidance whether controlling for Type 1 error via simulation is acceptable. It would be valuable to see the Agency's position on this.	
	At multiple places within the document (e.g. Lines 238 -240, Lines 246 – 248), it states that statistical details should be defined in the study protocol. In practice, details of the statistical testing procedure may be provided in a separate document, such as the Statistical Analysis Plan, to prevent unnecessary protocol amendments or to prevent operational bias when a sample size re-estimation is being performed. Suggest flexibility in the statements to reflect that other documents that will be finalized prior to unblinding data may contain the details of the statistical testing procedure.	
Throughout document	Use the term "claim" specifically to refer to claim that would appear in the product labeling. Suggesting use of another term, such as "statement" or "conclusion" in other contexts.	
	Sections 5.2 and 5.3: Including these two sections as subsections of 5 is confusing since the type of subgroup analyses described or an appropriately-controlled evaluation of alternative models do not require multiplicity	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	adjustment. On the other hand, it would be helpful to include a discussion on multiplicity adjustment for a multiple doses scenario (separate from dose-response, section 5.5.3).	

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)*
Page3/ Line 60		Comment: In order for the sentence to be clear and not awkward "points to consider considering…" Proposed change (if any): Add the following, "Points to Consider on Multiplicity issues in clinical trials (EMA/286914/2012)	
Page 3/Line 72		Comment: It is "answers to more than a single question" Proposed change (if any): Change "a positive answer" to "positive answers"	
Page 4/Line 134		Comment: Please clarify what is being estimated in the scope section for clarity of guidance purpose Proposed change (if any):	
365-371, 381-382, 393-394, 477, 548, 559		Comment/Rationale: The guideline states that the Summary of Product Characteristics (label) is "governed by a separate regulatory guidance document", but then provides guidance about it anyway. A regulatory document creates uncertainty when it states or implies that a topic is out of scope and nevertheless provides guidance on that topic. Proposed change (if any): Should be consistent about whether the label is in scope or not.	

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)*
Page 4/ Lines 400-402		Comment: Additionally, it would be helpful to provide details on multiplicity adjustment methods other than hierarchy. Proposed change (if any):	
Page 12/Line 438		Comment: Should define number of subgroups that is considered to be "small". The statement as currently written is ambiguous. Proposed change (if any):	
474-476		Comment: Unless the study is powered for every component, it is almost inevitable that there will be different estimated effects on different components, even if the underlying truth is that all components are affected equally. Moreover, it would not be surprising if one or more components show a trend in the wrong direction. The stated position therefore creates regulatory uncertainty around composite endpoints. Proposed change (if any): Change "very difficult" to less strong language.	
498-519		Comment: It is not clear how this section 9.2 impact on multiplicity problem. Proposed change (if any): add some language on how the topic of this section (9.2) impacts on multiplicity problem.	
559		Comment: Should be able to suggest wording to use in this or similar situations	

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)*
		Proposed change (if any): Provide example of "different wording"	
576-577		Comment: In most cases, the dose selection in by not only efficacy but safety as well. Proposed change (if any): Suggest adding a cautionary to highlight that treatment selection can be based on safety as well.	
587		Comment: The term of "maximum bias" is not a commonly used terminology and its definition is not clear. Please clarify. Proposed change (if any):	