EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 January 2017

Submission of comments on 'ICH guideline E17 on general principles for planning and design of multi-regional clinical trials - Step 2b' (EMA/CHMP/ICH/453276/2016)

Comments from:

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)*
	General comments: (1) The importance of the ICH-E17 guideline is acknowledged. The guideline does not only have importance for approval but also for benefit assessment of drugs in subsequent reimbursement decisions. If only one pivotal trial is available for benefit assessment, an adequate MRCT should offer the possibility to assess homogeneity among relevant subgroups within one trial. (2) A general critical point is the possibility to have different primary endpoints, if agreement cannot be reached regarding the primary endpoint among different authorities. As the whole study planning (sample size, expected heterogeneity, expected effect modification) depends on the primary endpoint, an adequate study planning is difficult or even impossible. The use of different primary endpoints can result in totally different required sample sizes, different effect modifiers, and large differences in the amount of heterogeneity between subgroups with the possible consequence that the recommendations of the guideline regarding evaluation of heterogeneity cannot be implemented. (3) We provide two references that may be of interest to the authors: i. Chen J, Zheng H, Quan H, Li G, Gallo P, Ouyang SP, Bimkowitz B, Ting N, Tanaka Y, Luo X, Ibia E. Graphical assessment of consistency in treatment effect among countries in multi-regional clinical trials. Clinical Trials 2013; 10: 842-851. ii. Alosh M, Huque MF, Bretz F, D'Agostino RB. Tutorial on statistical considerations on subgroup analysis in confirmatory clinical trials. Statist. Med. 2016. (wileyonlinelibrary.com) DOI: 10.1002/sim.7167	

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)*
Section 1.4, line 50		**Comment**: The description that the treatment effect should be "clinically meaningful" is too vague. It should clearly be stated that the treatment effect should be measured on the basis of patient relevant endpoints. **Proposed change (if any):**	
Section 1.3, Line 68		**Comment:** It would be useful to have some further explanation why MRCTs are important. For example this sentence that is found later on in the Guideline could be a good way to explain: "It is recognised that different drugs may be more or less sensitive to regional variability based on intrinsic factors, such as genetic polymorphism of drug metabolism or receptor sensitivity (described in ICH E5 Appendix D) which can impact PK/PD, and efficacy and safety of the drug. This applies not only to the investigational drug, but also to comparators and concomitant medications and should be taken into account during planning of MRCTs." **Proposed change (if any):**	
Section 1.4, lines 77 - 89		**Comment:** These paragraphs are not really basic concepts, as indicated in	

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		the section. It would be better to place them in their specific sections. **Proposed change (if any):**	
Section 1.4, lines 86-89		**Comment**: It should be added that the total sample size and the sample size allocation to regions should be performed in a way that potential analyses within regions due to heterogeneity have sufficient power. **Proposed change (if any)**:	
Section 1.4, line 104		**Commen**t: Please give a definition for "exploratory MRCT". **Proposed change (if any):**	
Section 1.4, lines 107-109		**Comment**: The extrapolation of study results to regions not studied at the confirmatory stage is critical. How can MRCTs serve as a "basis for approval in regions not studied at the confirmatory stage through the extrapolation of study results"? **Proposed change (if any)**:	
Section 2.1.1, Lines 144 - 154		**Comment:** With this wording it sounds that when we are conducting MRCT everything is easier, which is not the case. There are disadvantages, which the Guideline should state, in order to	

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		warn the researchers. It could be stated that MRCT should be considered carefully. Conducting small separate regional trials might increase the speed of the approval in specific regions, so patients can get the treatment earlier on in those regions. This might facilitate the company to get more funding/investment for obtaining further approvals in other regions. **Proposed change (if any):**	
Figure 1		**Comment:** The figure is rather simplistic. It is hard to believe that it represents the reality. Perhaps for large pharmaceutical companies but not for the vast majority. **Proposed change (if any):**	
Section 2.1.2, lines 159-160		**Comment**: Replace "clinically meaningful" by "patient relevant" (see above). **Proposed change (if any):**	
Section 2.1.2, Lines 160 - 167		**Comment**: This does not sound logical. What is the purpose of conducting exploratory trials to assess the differences between regions before the pivotal study? Why should this be done, instead of	

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		going straight for a simple study that covers only one ethnicity?	
Section 2.1.2, lines 163-164		**Comment**: Even if differences between regions are not expected to substantially impact safety and efficiency, it should clearly be described that it is inappropriate to neglect found evidence of heterogeneity due to a former homogeneity assumption (see CHMP 2014). **Proposed change (if any)**:	
Section 2.2.1, lines 235-236		**Comment**: It should be described how the sensitivity of drugs to regional variability based on intrinsic factors should be taken into account during planning of MRCTs. **Proposed change (if any):**	
Section 2.1.2, Lines 300 - 303		**Comment:** This text requires further explanation. How does one present the results if there are two regions with different dosage regimens? E.g., Region 1: 10 mg of experimental treatment vs placebo; Region 2: 15 mg of experimental treatment vs placebo. How do we test the overall effect in such a case? **Proposed change (if any):**	
Section 2.2.4, line 309		**Comment**: (Replace "clinically meaningful" by "patient relevant" (see above).	

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		Proposed change (if any):	
Section 2.2.4, lines 320-322		**Comment**: The statement that there is no need to adjust for multiple testing due to the fact that different authorities want to use different primary endpoints may be acceptable when the hypotheses regarding the different endpoints are considered as different research questions. However, the main problem is the difficulty in study planning if there are different primary endpoints for different regional authorities (see general comment 2). **Proposed change (if any):**	
Section 2.2.4, lines 358-359		**Comment**: It seems to be illogical that, on one hand, no adjustment for multiple endpoints is required if several primary endpoints are used (statement in lines 320-322) but, on the other hand, control of type 1 error across one primary and several secondary endpoints may be asked by some authorities. This would mean that different authorities can choose different ways to deal with multiple testing, which may have large effects on the required sample size. If no agreement on the primary endpoint can be reached and no unique way to deal with multiple testing across multiple endpoints is chosen, at the final end there will be no agreement on the required sample size for the whole MRCT. **Proposed change (if any)**:	
Section 2.2.5, line 380		**Comment**: Replace "clinically meaningful" by "patient relevant" (see above). **Proposed change (if any):**	

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Section 2.2.5, lines 401-404		**Comment**: The problem that different regulatory requirements regarding endpoints, heterogeneity, multiplicity, non-inferiority margins, effect sizes, etc. will impact the overall sample size is shortly mentioned, but no solution how to deal with this problem is given. This is a major issue and should be considered and discussed very thoroughly (see general comment 2). **Proposed change (if any)**:	
Section 2.2.5, lines 423-426		**Comment**: It is correctly stated that important effect modifiers have different distributions among regions and therefore, a proper planning for sample size allocation to regions is required. However, it is overlooked that the importance of effect modifiers may be different for different endpoints. If there is no agreement on the primary endpoint, a proper planning for sample size allocation to regions is impossible (see general comment 2). **Proposed change (if any)**:	
Section 2.2.5, lines 468-471		**Comment**: It would be useful to describe criteria, when regions or subpopulations are similar enough to justify pooling. **Proposed change (if any):**	
Section 2.2.7, lines 563-572		**Comment**: A reference to CHMP 2014 (DRAFT. EMA/CHMP/539146/2013) should be given. Again, an adequate planning of subgroup analysis and	

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		effect modifiers is only possible if there is an agreement on the primary endpoint (see general comment 2). **Proposed change (if any)**:	
Section 2.2.7, lines 626-627		**Comment**: Criteria and requirements should be given for an appropriate statistical model that allows – for small regions – a valid borrowing of information from large regions. **Proposed change (if any):**	
References		**Comment:** We suggest to cite the following reference in the ICH-E17 Guideline: Committee for Medicinal Products for Human Use (2014): Guideline on the investigation of subgroups in confirmatory clinical trials – DRAFT. EMA/CHMP/539146/2013. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/02/WC500160523.pdf. **Proposed change (if any):**	

Please add more rows if needed.