19 February 2018

Submission of comments on 'ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials' (EMA/CHMP/ICH/436221/2017)

Comments from:

Name of organisation or individual
German Region of the International Biometric Society (IBS-DR) German Society for Medical Informatics, Biometry and Epidemiology (GMDS) Network of coordinating centers for clinical trials (KKS-Netzwerk e.V.)

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 ICH E9 (R1) addendum stresses the importance of the detailed clarification of the scientific questions of treatment comparisons in the presence of intercurrent events before deciding on the analytical methods. Sensitivity analyses with regard to statistical methods and underlying assumptions for one estimand are distinguished from sensitivity analyses with regard to the choice of the estimand, i.e. the scientific question. This approach is much appreciated. The problem is that the five estimands are listed on the same level without giving explicit advice on preferred estimands in specific situations from the regulatory point of view. It would be helpful to discuss estimands for specific scenarios and reflect on the regulatory point of view resp. discuss the perspective of different stakeholders. There is little discussion on the feasibility applying specific strategies in given scenarios and the methodological challenges coming with it. However, this discussion is needed in order to establish the guideline in practice. Especially the role of the hypothetical estimand and of	

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	the principle stratum estimand for regulatory decision making has to be questioned as they rely on untestable assumptions. For this reason the ICH E9 (R1) addendum should provide • examples for the hypothetical strategy, including how to estimate the estimands in this scenarios with low risk of bias and including the extent and type of expected sensitivity analyses, • examples for the case the principle stratum strategy would be the preferred estimand and which methods are available for a robust estimation and advice on expected sensitivity analyses. Otherwise, the addendum can be perceived as providing a comprehensive framework without giving any recommendation for the application.	
	The described estimand framework seems to address efficacy analyses. Considerations on appropriate estimands for safety endpoints should be added.	

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)*
119–123 151-157		Comment: Why are intervention and comparator not mentioned in the list of attributes defining an estimand as it is usually required when to fully describe a clinical study for answering a scientific question (e.g. well known PICOS approach)? Proposed change (if any): Include intervention and comparator in the definition of an estimand.	
154-155		Comment: “how to account for intercurrent events” suggests reference to how the intercurrent events should be handled during analysis. However, analysis cannot be part of the definition of an estimand. The estimand needs to be defined on the population level, while analysis refers to estimation of the estimand from study data. Proposed change (if any): Wording should be changed accordingly.	
198		Comment: One would expect “estimator” instead of “estimate” since the planning stage view is assumed here. Proposed change (if any): Change estimate to estimator.	

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210-212		Comment: It might be possible to implement the treatment policy strategy “when values for the variable after the intercurrent event do not exist for all subjects". For example, imputation techniques can be used to include also subjects with missing data after the intercurrent event. Proposed change (if any): Change the statement that the treatment policy strategy cannot be implemented to the statement that the treatment policy leads to problems when values for the variable after the intercurrent event do not exist for all subjects.	
223		Comment: It is unclear what is meant by “area-under-the-curve” (which curve?) Proposed change (if any): Please specify.	
248-263		Comment: It is unclear whether in practice the principal stratum strategy would be considered adequate in situations where members of a principle stratum cannot be identified in advance, which will typically be the case. What claims could be derived for a treatment with superiority proven by analysis using a principle stratum strategy and adequate methods to address confounding, sensitivity analysis etc., given that in practice it cannot be told whether or not the patient falls into the	

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		principle stratum? Proposed change (if any): Please provide considerations and examples on the applicability of the principal-stratum strategy.	
264-271 743		Comment: For the while on treatment strategy, the use of the “average of the designated measurements while on randomised treatment” can lead to problems in case of different follow-up times. Proposed change (if any): Please comment on how to deal with the case of unbalanced times on treatment when the while on treatment estimand is considered.	
303		Comment: “in particular those that are estimated using the observed data”. All estimations will make some use of observed data, so maybe “using exclusively observed data” may be more appropriate. Proposed change (if any): Clarify and revise accordingly, e.g. “using exclusively observed data”.	
370-375		Comment: The meaning of this paragraph is unclear.	

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		Proposed change (if any): Please reword for clarification.	
391		Comment: Typo: should probably spell trial design Proposed change (if any): Please correct.	
412-413		Comment: The example confuses cessation of study treatment with premature end of recording study data. There is no inherent reason to stop documentation when the treatment is discontinued, as it is correctly emphasized in lines 403-407 in the same section. (The document is unclear in lines 85-87 in that regard.) Proposed change (if any): An example which directly relates to a plausible reason why data couldn't be collected would be desirable here.	
464-465		Comment: It is correct that "Estimation for an estimand … will require stronger and untestable assumptions if measurements are not collected following intercurrent events." Proposed change (if any): Add a statement about the importance of collecting relevant data after occurrence of intercurrent events in order to avoid this situation.	

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614-624		Comment: This part is repeated by L652-L661 (ending "…the treatment groups."). The paragraph L614ff seems to be the one that is in the wrong place since the section considers the case where no intercurrent events occur, however, intercurrent events and rescue switchers are mentioned in L621 and L623. Proposed change (if any): Consider inserting a headline "A.7.0 No intercurrent event" between lines 603 and 604, and suitable adaptation of L614ff.	
615, 652, 682		Comment: The given examples for recommended statistical methods (analysis of variance and logistic regression) are trivial for the respective situations. Instead of giving recommendations for trivial situations, recommendations for statistical methods should be given for situations where the choice of appropriate methods is really unclear (hypothetical strategy, principal-stratum strategy). Proposed change (if any): Recommendations for the choice of statistical methods for complex situations as the hypothetical strategy and the principal-stratum strategy should be given.	
688		Comment: The prospective planning of sensitivity analyses should be standard and is contributing to the validity of the interpretation of results. However, it is nearly impossible to	

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		pre-empt all possible situations of missingness. Rather than planning all sensitivity analyses in the protocol upfront it might be considered to explain the analyses strategy. Proposed change (if any): Please change accordingly.	
708-711 735-737		Comment: For the hypothetical and the principal-stratum strategy, the choice of the appropriate statistical methods for the main analysis and the extent and type of expected sensitivity analyses are unclear. Proposed change (if any): Advice on appropriate methods for analysis and examples for situations where these estimands are regarded as suitable should be given.	
748-750 813		Comment: There is usually interest in objectives requiring collecting data after switching to rescue medication. Proposed change (if any): Reformulate the statement that in general the collection of data after switching to rescue medication is required.	