28 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
International Society for Pharmacoeconomics and Outcomes Research (ISPOR)

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)*
	ISPOR is the leading global scientific and educational not-for-profit organization for health economics and outcomes research and their use in decision making to improve health. With over 20,000 individual and chapter members worldwide, our mission is to promote health economics and outcomes research excellence to improve decision making for health globally. We appreciate the opportunity to respond to call for comments on ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials. While this addendum focuses on a specialized area of statistical principles for clinical trials, ISPOR has a vested interest in regulatory data which is used by reimbursement authorities, physicians, and patients for coverage and treatment decision making. From the opening sentence of this addendum: "To properly inform choices …by patients and prescribing physicians, clear descriptions of the effects of a medicine should be available," it is clear that our 'constituent' audiences and data needs overlap. Thus, we feel it is important to consider reimbursement authorities, and the health technology assessors who inform them, to be consumers of these data and analyses as well. ISPOR's response was formulated in coordination with leaders of several of ISPOR's Councils and Special Interest Group (Statistical Methods, HTA, Institutional, and Health Science Policy) along with input from interested members of these sub-groups. To solicit such input, we asked members to respond to an on-line survey. Recognizing the technical nature of this addendum, as we expected, most responses came from our statistical experts. We received 15 responses in addition to the comments from our sub-group leadership. We felt that this new guidance would have a positive impact on the way trials are conducted, particularly with respect to the transparency and applicability of estimates of treatment effect. However, there were some areas to clarify. One of the most often mentioned areas is the impact that proper estimand specification could have on the ability of efficacy estimates to more closely answer the research question relevant to a real-world setting (or not) depending on how they are defined. Healthcare decision makers often want to know how a treatment will	

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	perform outside of a well-controlled setting. There is some concern about how to apply estimands to a pragmatic or real-world trial setting as this was not mentioned in the current guidance. On one hand, if the estimands are defined such that they include the intercurrent events as they happen in real practice (i.e. treatment switching), it would give a better view of how the product may work outside of the randomized controlled trial (RCT) setting. However, the opposite can occur - the estimand could be defined so that it leaves out the intercurrent event and gives a much more narrow view of treatment effect, which is less relevant outside of the RCT setting, especially to payers. To that end, more examples or details regarding the handling of intercurrent events are needed in the guidance. The examples should be structured around categories such as disease area or type of endpoint (time to event, continuous, etc.) to give more clarity. Estimands, by providing a standardized framework for research questions, could increase transparency and usefulness of clinical trial outcome results. While it may increase the time (and cost) of upfront trial planning and the number of analyses needed to report the endpoints, this could be offset by a decrease in the probability of having a study that fails or is uninformative due to inappropriately defined endpoints, and thus in the end could save resources. However, this will require a multidisciplinary approach to the estimand/trial design from the very beginning. We suggest that such a multidisciplinary approach be reflected in this guidance more strongly. The guidance will have an important role in future dialogues between drug developers, regulatory bodies and health technology assessors on requirements for evidence generation. It will be essential to ensure that sufficient support is provided by clinical, regulatory, and HEOR/market access personnel, otherwise there is risk that the development process could be delayed or that the ultimate estimands may not be fit for purpose, especially outside the regulatory arena.	

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)*
237		Comment: Consider adding the term 'counterfactual' somewhere within this example (e.g. before the point on line 237, add, 'i.e., counterfactual event') since this is a well-known analysis strategy and enables the reader to tie the description in the paragraph with known methods Proposed change (if any):	
263		Comment: Principal stratum strategy line 263 - add as another caveat: generalizability of the trial results should be considered, this may be a challenge if the principal stratum does not make up the vast majority of enrolled patients.	
264-276		Comment: "While on treatment strategy" – One might consider that the "holy grail" is the modelling of a joint process of treatment discontinuation/modification and effect while on treatment. The "while on treatment" strategy by itself does not seem to further the goal of improving treatment choice unless discontinuation/modification is exogenous (which is not likely to be the case in any interesting circumstance)	
289-290		Comment: we agree with this statement, and it is essential. The construction of the estimand(s) in any given clinical trial is a multi-disciplinary undertaking including clinicians, statisticians and other disciplines involved in clinical trial design and conduct.	

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		Proposed change (if any): Is it worth also adding this at the top of the document, e.g., within section A.1. Purpose and Scope, so it is clear who this guidance is for (=not only clinical statisticians)?	
343-348		Comment: it's unclear here if this is the recommended or to be avoided. Proposed change (if any):	
377		Comment: the document doesn't really give any guidance on how such deviations should be handled, and what needs to be done in those cases. Proposed change: Could be complemented with some references to other sources if not adding a brief suggestion in the text itself.	
841 - 845		Comment: The definition of estimand not fully clear in this glossary (though the idea comes through in the text earlier). Proposed change: Modify the glossary definition as follows and link it to the other definitions: Estimand: Is an estimate that addresses the scientific question of interest posed by the trial objective, the question pertains to a specific population. Attributes of an estimand include the population of interest, the variable (or endpoint) of interest, the specification of intercurrent events reflected in the scientific question of interest, and the estimation method by which the estimate will be derived from the data collected during the trial	

Please add more rows if needed.