EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 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
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 the opportunity to comment on the planned ICH E9 (R1) revision and has provided specific comments below in order to increase its usefulness to sponsors and other parties involved in clinical trials. ACRO also has a number of general concerns with the proposed guideline. These are as follows:	

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	• The stated aim of the guideline is “to facilitate the dialogue between disciplines involved in clinical trial planning, conduct, analysis and interpretation, as well as between sponsor and regulator, regarding the treatment effects of interest that a clinical trial should address”. However, we think it would be difficult to use this document as guidance as it is currently written. We recommend that the document should be reduced in size, be less repetitive, and that some of the text is simplified to make it more accessible to a wider audience, given that consideration of estimands will involve multi-disciplinary teams. The current draft document is a difficult read and we recommend that it would benefit from stating the key points once rather than repeating them. In ACRO’s view, a document comprising key recommendations illustrated with more practical/real examples would be more suited to achieve the stated aim. • The terminology around estimand/estimate/estimator is hard to follow. Vague language is used too often: ‘might’ and ‘may’, for example. While ‘must’ and ‘mandatory’ may be too strong, ‘should’ or ‘it is advised’ would provide clearer direction.	

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	• Throughout the document, the notion of “intercurrent event” seems to be the major driver for this draft guideline, and it seems like the estimand approach has been introduced only or mostly to deal with intercurrent events. If so, ACRO recommends that it would be simpler and clearer to develop a guideline on handling intercurrent events, with specific recommendations for data collection and useful sensitivity analyses (instead of introducing all the complex terminology around estimands). • It is difficult to see how the estimands approach will enhance the way in which data are currently reported, analysed and understood. For example, (1) it is not clear how the principal stratum strategy differs from a per-protocol or subgroup analysis, (2) if the intake of rescue medication forms an intercurrent event, it is not clear how this is different from presenting those who take rescue medication while evaluable for the primary endpoint separately from those who did not. It would be helpful if more parallels were to be drawn with existing methods or explain why this is different (if it is) from what is currently being done.	

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	• There is inconsistent use of the glossary terms. Sometimes the quantity is defined (e.g., line 121), other times the glossary is referred to (e.g., line 70). ACRO recommends cross-referencing the glossary in all cases and within the text of the document to identify terms which are available in the glossary using bold and/or italics. • ACRO recommends re-ordering the contents of the document to make it more easily readable, e.g., starting with section A1 and then providing worked examples to introduce the different types of estimands. • Guidance is not included on how the use of estimands will fit into reporting in public clinical trial databases (e.g., clinicaltrials.gov): it is not clear whether estimands be used in place of endpoints (so that the entry is restricted to a maximum of 10) or up to 10 endpoints could be reported, with multiple estimands created, based on these. ACRO recommends that such guidance be included in the final version of the document. • In the descriptions, line 154 defines C as “The specification of how to account for intercurrent events to reflect the scientific question of interest”. However, ACRO recommends that it would be helpful for each time to define in C, the intercurrent event and how to account for it. In	

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	the general example, the “C. Intercurrent event:” seems to switch between describing what the intercurrent event is and describing the handling of the intercurrent event, without specifying the intercurrent event. For example, line 609 (“No intercurrent events to be taken into account”), line 637 (“regardless of whether or not switching to rescue medication had occurred)” and line 696 (“had rescued medication not been made available to subjects prior to month six”), define the intercurrent event; however, line 669 (“the intercurrent event is captured through the variable definition”) and row 719 (“the intercurrent event is captured through eh population definition”) specify the handling of the intercurrent event. ACRO recommends that both the intercurrent event and its handling should be included in the specification, and that this should be made clear in the final guidance document.	

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)*
58		Comment: ACRO recommends the following addition, for consistency and clarity. Proposed change (if any): Add “(see Glossary)” after … intercurrent events, as done elsewhere in the document (e.g., line 70).	
60		Comment: ACRO recommends replacing “The correct order is the reverse” (which fits strangely in the sentence) with the text proposed below. Proposed change (if any): Replace the current test with “Therefore, the treatment effect to be estimated and the impact of intercurrent events should be considered prior to defining the efficacy and safety variables”.	
82		Comment: ACRO recommends the following addition, for consistency and clarity. Proposed change (if any): Add “(see Glossary)” after … intercurrent events, as done elsewhere in the document (e.g., line 70).	
94		Comment: ACRO recommends amending the statement ”…..collected, present a missing data problem to be	

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		addressed. In turn methods to address…..” to read as follows. Proposed change (if any): Replace the text with ”…..collected, leads to a missing data problem that needs to be addressed. In turn, methods to address…..”	
113-116		Comment: For clarity, ACRO recommends replacing the last sentence of the paragraph as follows. Proposed change (if any): Replace the sentence with “With a precise specification of an estimand and with a pre-specified statistical analysis defined to a level that it can be replicated precisely, and that is aligned to the estimand, then regulatory interest can focus on sensitivity to deviations from assumptions and limitations in the data in respect of a particular analysis.”	
126		Comment: There is a missing “the” at the end of the line. Proposed change (if any): “… should be conducted in **the** …”	
135-136		Comment: For clarity, ACRO recommends deleting the phrase “hence the” from the sentence. Proposed change (if any): Delete “hence the” from the sentence.	

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159, 163, 170, 183		Comment: In ACRO's view, it would be more helpful if these paragraphs explicitly identified the particular component of the estimand that is referenced. Proposed change (if any): Add text to identify the the particular component of the estimand that is referenced.	
178-180		Comment: For clarity, ACRO recommends rewording this sentence as proposed below. Proposed change (if any): Reword the sentence as follows: "Taking use of rescue medication as an example, two different specifications could include 1) The combined effect of treatment and rescue medication (the intercurrent event) and 2) the effect of the treatment in the potentially hypothetical absence of taking rescue medication (the intercurrent event).	
188		Comment: The four components of the estimand have been given in the previous paragraphs but then the document immediately talks about intercurrent events (which is component C, third on the list). ACRO recommends that A and B should be mentioned at least beforehand, even if no extra detail is given (even just to say these are equivalent to population/endpoint definitions in E9), or point out why they are slightly different here. Proposed change: Add appropriate text on A and B.	

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206		Comment: For clarity, ACRO recommends rewording this sentence as proposed below. Proposed change (if any): Reword the sentence as follows: "For example, when specifying how to account for rescue medication as an intercurrent event, occurrence of the intercurrent event is ignored and the observations on the variable of interest are used regardless of rescue medication intake".	
222		Comment: For clarity, ACRO recommends replacing "ascribed" with "assigned". Proposed change (if any): Replace "ascribed" with "assigned".	
225		Comment: For clarity, ACRO recommends rewording this sentence as proposed below. Proposed change (if any): Reword the sentence as follows: "Sometimes an event being considered as intercurrent is itself the most meaningful variable that can be measured for quantifying the treatment effect of interest. This can be the case with death: the fact that a subject has died may be much more meaningful than observations before death, and observations after death will not exist."	
232-247		Comment: This section talks about the hypothetical event	

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		being 'if rescue medication had not been available'. Conceptually, it is possible to see why it would be useful to answer this question but, practically, it is very difficult to understand how the analysis would look. ACRO recommends referencing a different intercurrent event which can be addressed via the hypothetical strategy.	
248-263		Comment: The sentence in lines 254-255 talks about the principal strata effect that should be distinguished from subgroups based on trial data, but the previous paragraph gives the example of adherence to determine the principal stratum. In ACRO's view, adherence is a component of trial data, therefore we are unclear what is meant by this sentence. Also, the meaning of line 260 "membership in a principal stratum must then be inferred, usually imperfectly from covariates" is unclear, as is the intended guidance to sponsors on this point. Proposed change (if any): Clarify this section to ensure the meaning and guidance to sponsors is clear.	
288		Comment: For clarity, ACRO recommends rewording this sentence as proposed below. Proposed change (if any): Reword the sentence as follows: "Trial reporting should then discuss not only the way unforeseen intercurrent events were handled in the analysis	

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		but also the effect on what the chosen analysis estimates."	
343-348 and 663-691		Comment: These sections recommend dichotomising the data but there is no mention of the loss of power that results from this approach. It is therefore not clear why this is recommended. Also, in the composite strategy example, if this strategy is used as a sensitivity analysis then it is likely to have less power than the primary analysis. ACRO recommends that it be made clear in the assessment of the strategy that, to conclude consistency between the continuous and binary approach, it is not required to reach significance for both but that the conclusions around the treatment effect estimate should be consistent. Proposed change: Clarify why the dichotomous approach is recommended and its effect on power, and that in the assessment of the composite strategy, to conclude consistency between the continuous and binary approach, it is not required to reach significance for both but that the conclusions around the treatment effect estimate should be consistent.	
379		Comment: The phrase "and he" should be "and the". Proposed change (if any): Change "and he" to "and the".	
391		Comment: The phrase "trial sign" should be "trial design".	

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		Proposed change (if any): Change “trial sign” to “trial design”.	
413		Comment: ACRO recommends that the phrase “treatment discontinuation due to lack of efficacy” should simply be “lack of efficacy” since it is likely that treatment discontinuation would be in the actual case record form (CRF) question. Proposed change (if any): Delete “treatment discontinuation due to”.	
498-536		It is unclear in the document whether sensitivity analyses are intended to serve a different purpose for estimands compared to the usual purpose of assessing the robustness of primary conclusions. If so, it would be useful to highlight the differences. Proposed change (if any): Clarify the purpose of sensitivity analyses with regard to estimands and highlight any differences from the usual use of a sensitivity analysis.	
519-536		Comment: ACRO recommends that it would be helpful to re-explain here how sensitivity analyses are used to assess the robustness of primary conclusions, e.g. clarify that not all sensitivity analyses have to reach significance but there should be consistency in the treatment effect estimate. It is unclear how tipping point analyses help to assess consistency	

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		of the conclusion on the effect size and more explanation would be helpful. Proposed change (if any): Add text to re-explain how sensitivity analyses are used to assess the robustness of primary conclusions, and provide more explanation of how tipping point analyses help to assess consistency of the conclusion on the effect size.	
567-569		Comment: The sentence should be expanded to explain whether sensitivity analyses are required for all secondary endpoints. Proposed change (if any): Explain whether sensitivity analyses are required for all secondary endpoints.	
584-585		Comment: It is not clear why “analyses introduced while the trial was still blinded” are referenced. Such changes should be pre-specified and taken into account in the statistical plan. Proposed change (if any): Delete “analyses introduced while the trial was still blinded”.	
589-627		Comment: ACRO recommends that, for consistency, it would be helpful to use the flow diagram on page 5 of the document to present this and the other examples.	

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		Proposed change (if any): Use the flow diagram on page 5 of the document to present this and the other examples.	
610		Comment: It is not clear why the term “treatment conditions” is used rather than “treatment groups”. If “treatment conditions” is retained, it should, for clarity, be added to and defined in the glossary. Proposed change: Replace “treatment conditions” with “treatment groups” or add and define “treatment conditions” in the glossary.	
626, 627		Comment: This sentence appears unnecessary given line 609 and details included in glossary. Proposed change: Delete the sentence.	
655-657 and 685-687		Comment: The sentence “For example, missing data may be imputed based on similar subjects who remained in the trial. Similarity may be established based on the same baseline covariates, the same randomised treatment arm, the same measurement history and information on the intercurrent event” is repeated again on the following page. Proposed change (if any): Cross-reference to reduce repetition within the document.	

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743 and 760-761		Comment: It would be helpful to include an explanation as it is unclear why the variable changes to be “average of the designated measurements while on randomised treatment” rather than simply using the change from baseline to last measurement on treatment. Also, lines 760-761 state that “considering alternative choices for the variable definition by focussing on the last measurement while being on treatment, leading to different estimands.” ACRO recommends that further explanation be given as to what the different estimand would be of u vs “last measurement on treatment>”sing “average” Proposed change: Include explanations on these points.	
755-756		Comment: It is not clear why interpolation is recommended if the analysis is based on average results on treatment, as any intermittent missing measurement would be populated with the average at the visits that are present. Proposed change: Explain why interpolation is recommended.	
773		Comment: The word “both” should be replaced with “two” for consistency with lines 762 and 797. Proposed change (if any): Replace the word “both” with “two”.	
847		Comment: ACRO recommends that it would be informative	

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		and helpful to add an example here. Proposed change (if any): Add an example.	
850-852		Comment: ACRO recommends that it would be informative and helpful to add an example here. Proposed change (if any): Add an example.	
853-856		Comment: ACRO recommends that it would be informative and helpful to add an example here. Proposed change (if any): Add an example.	
854		Comment: The term “not collected” might imply there is no field on the CRF, which should have been considered when designing the CRF. Proposed change (if any): Replace “not collected” with “not available”.	
863-865		Comment: It is not clear why “principal stratification” (the quantity being defined) is included within the definition. Proposed change (if any): Include further explanation.	
867		Comment: In ACRO’s view, different assumptions would	

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		result in a different estimand. We therefore recommend the change proposed below. Proposed change (if any): Replace “differing assumptions” with “differing model assumptions”.	
		ACRO thanks the EMA for the opportunity to provide comments on “ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials.” Please contact ACRO (knoonan@acrohealth.org) if we can answer any questions or provide additional details.	