17 August 2017

Submission of comments on Draft Guideline for the notification of serious breaches of Regulation (EU) No 536/2014 or the clinical trial protocol (EMA/430909/2016)

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 and supports the planned guideline on the notification of serious breaches of Regulation (EU) No. 536/2014 or the clinical trial protocol. The draft guideline provides useful instructions and examples for the reporting of serious breaches, but ACRO believes that some points require clarification and has provided specific comments below in order to increase the	

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	usefulness of the guideline to sponsors and other parties involved in clinical trials. Additionally, ACRO is concerned that there is a key omission from the draft guideline and recommends that this be addressed in the final version; ACRO notes that the guideline stresses the importance of good communication processes between all parties involved in a clinical trial in order to ensure that serious breaches are reported within the 7 day timeline. ACRO supports this fully. However, the experience of ACRO member companies in the UK (where a legal requirement for serious breach reporting has been in place for several years) is that there can sometimes be a difference of opinion between the sponsor and CRO as to whether or not a particular case meets the criteria for reporting as a serious breach. ACRO therefore recommends that this situation be addressed in the final guideline, and further recommends that a serious breach report should be submitted if any relevant party considers that the reporting criteria have been met.	

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)*
57 – 61 (and 52, 61, 65, 66, 178)		Comment: In light of the clarification within the text of rows 55 – 57, which specifies that the 7 day timeline relates to sponsors and any parties with whom the sponsor holds a contractual arrangement, the reference to “third party” in rows 58 and 61 is confusing. For example, it may not be clear whether the reference in line 61 is a reference to third parties who are contractual partners of the sponsor, or more broadly to other parties with whom the sponsor holds no contractual agreements. More generally (lines 52, 61, 65, 66, 178), the terms "other parties", "third parties", "another party" and "site” have been used throughout the document. It is not clear if they all mean the same thing or if there is a difference between the terms. Additionally, (line 61), we suggest modifying “the date when the third party is first informed” to reflect the third party becoming aware rather than informed. This would account for scenarios where the third party learns of a potential serious breach on its own in addition to being informed of a serious breach by another entity. Proposed change (if any): Include a general definition around the terms “site”, “third party”, “other party” and “party”, and revise the statement to read “Contractual agreements between clinical trial (CT) sponsors and other parties should	

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		clearly stipulate that any non-compliance identified by any party are promptly reported to the sponsor in order for the sponsor to meet its legal obligations. In this circumstance Day 0 (i.e. the day of first awareness that a serious breach has occurred) would be the date when the sponsor, or any party with a contractual agreement with the sponsor, is first aware."	
68		Comment: The draft guideline states that serious breaches should be reported to the member states concerned with the trial. It would be helpful to add additional detail to the final guideline to clarify that this should be done through the EU clinical trials portal to all concerned member states rather than requiring notifications to individual member states. Also, there is a typographical error in that "to the" appears twice. This should be corrected. Proposed change (if any): Clarify that serious breach notification should be made through the EU clinical trials portal to all concerned member states, and correct the "to the" typographical error.	
77 - 83		Comment: It would be helpful if there was an option for the reporter (via an update process) to downgrade an initial reporting of serious breach notification to a competent authority, if further information and investigation reasonably reveals to the reporter that the breach would not meet the	

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		definition of a serious breach under Article 52. The ability to downgrade would help reconcile the expedited reporting requirements as covered in section 3.2 as a full investigation may not be tenable in the seven day reporting period. Reporters who report a 'downgrade' to a non-serious (or non-breach event) should be prepared to demonstrate the veracity of their assessments and CAPAs (referring to lines 226-235 for CAPAs of breaches irrespective of the seriousness of said breach). This proposal would also correlate to lines 215-217 on the extended time it may take to investigate a possible breach. Proposed change (if any): Clarify that a serious breach report can be downgraded via the update process to a non-serious event when subsequent investigation allows this conclusion to be reached. The information on which the conclusion is based, together with any corrective and preventative actions, should be submitted as part of the update.	
91 - 95		Comment: The requirement that "If a serious breach occurred outside the EU/EEA while the application for CT authorisation is under evaluation in the EU/EEA territory and the serious breach has an impact on the accuracy or robustness of data filed in an application dossier, the sponsor should withdraw the application and correct the aspects or data impacted, as applicable" contradicts lines 70 – 72, which state "If the sponsor receives information that provides reasonable	

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		grounds to believe that a serious breach has occurred, it is expected that the sponsor reports the breach first within 7 calendar days, investigate and take action simultaneously or after notification." At the time of reporting a serious breach, a sponsor may have "reasonable grounds to believe that a serious breach has occurred" but on subsequent investigation it may be concluded that this was not the case. Consequently, reporting of a serious breach that may potentially impact the accuracy or robustness of data filed in the application dossier should not automatically require withdrawal of the application. This should be necessary only when a relevant impact has been confirmed. Proposed change (if any): Revise the statement to read: "If a serious breach occurred outside the EU/EEA while the application for CT authorisation is under evaluation in the EU/EEA territory and the serious breach is confirmed to have an impact on the accuracy or robustness of data filed in an application dossier, the sponsor should withdraw the application and correct the aspects or data impacted, as applicable."	
119 - 148		Comment: As noted in the draft guideline, the judgement on whether a breach is likely to have a significant impact on the scientific value of the trial depends on a variety of factors, and experience in the UK (where a legal requirement for serious breach reporting has been in place for several years) shows	

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		that it is not always clear whether the criteria for reporting a serious breach are met. Consequently, ACRO recommends that the final guideline should include a description of a mechanism by which sponsors can seek advice from regulators on the need to report in specific cases. Proposed change (if any): The final guideline should include a description of a mechanism by which sponsors can seek advice from regulators on the need to report in specific cases.	
126		Comment: Additional guidance on the phrase “the reliability and robustness of the data generated in the clinical trial” would be helpful to reduce subjectivity around possible breaches related to data integrity. For instance, a data integrity issue that impacts one of five hundred subjects is undesirable but it may not be reasonable to infer that deviations in this subject’s data would be ‘likely to a significant degree’ to impact the reliability and robustness of the overall data generated in the clinical trial. Another example of a possibly over-broad extrapolation could be a general security issue impacting a computerized platform containing electronic clinical records. If the security issue had not been exploited (or if it was but no records were altered) no serious breach reporting should be needed (the underlying issue would still remain subject to corrective and preventative action, irrespectively).	

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		Proposed change: Emphasise that in relation to data integrity issues, serious breach notification is required only when there is an impact on the overall data collected in the clinical trial.	
205 - 206		Comment: The referenced document, “Procedure for the management of serious breaches by the EU/EEA Member States including their assessment and the appointment of a lead Member State”, should be published so that all parties involved in a clinical trial can understand the process. Proposed change (if any): Publish the “Procedure for the management of serious breaches by the EU/EEA Member States including their assessment and the appointment of a lead Member State”.	
207 Appendix I - IMP		Comment: In lines 135 and 136 it is stated that overdose(s) would meet criteria for serious breach regardless of whether or not the subject suffered an adverse reaction. However, in Appendix I, the example given of overdose states that the subject experienced a severe adverse event and it was reportable as there was an impact on safety and scientific value. ACRO considers that the relationship between the sentence in the appendix and lines 135 - 136 is unclear and should be clarified. Proposed change (if any): Clarify the relationship between the sentence in the Appendix and lines 135 - 136.	

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207 Appendix I - Emergency unblinding		Comment: In this case the root cause of the breach is actually more important. The Pharmacy does not generally have the right to unblind any patient because the Pharmacy team includes people who are not treating Physicians and who are only dispensing a treatment prescribed by a Medical Doctor. Unblinding is a very important step in a clinical trial and generally the credentials to perform unblinding are given to the Principal Investigator (PI) and perhaps a small number of Sub Investigators (Medical Doctors). The emergency card should not have listed the Pharmacy number but a number from where the PI and treating Physician could have been contacted immediately for making this decision. The error stays with sponsor/CRO in this case and depending on the error spread, the impact on patients' safety and data quality (unblinding, either in excess or too little puts data at risk) can be important or significant. Proposed change (if any): Please clarify that the Pharmacy was not responsible for unblinding and that it is the investigator's decision.	
207 Appendix I – Protocol compliance		Comment: One of the examples given is "Minor visit date deviation. A common deviation in clinical trials", for which reporting is stated not to be required. ACRO agrees that visit date deviation is a common and generally minor deviation. However, there may be situations where (a) it is critical for	

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		the scientific integrity of the trial that assessment visits are within the window stated in the trial protocol and/or (b) where a significant number of deviations from the visit date cast doubt on the reliability of the data or GCP compliance of the trial. ACRO recommends the following addition in the column headed "Is this a serious breach?" Proposed change (if any): In the column headed "Is this a serious breach?" add the following text: "Yes if this is a systematic issue and (a) it is critical for the scientific integrity of the trial that assessment visits are within the window stated in the trial protocol and/or (b) where a significant number of deviations from the visit date cast doubt on the reliability of the data and GCP compliance of the trial."	
207 Appendix I – SAE reporting		Comment: Under the heading SAE Reporting, one of the details of breach reported is "The investigator was not clear on the reporting requirements for the trial and was incorrectly classifying events as expected, as they were common events seen with that particular disease." The investigator classifying events in this statement as "expected" is misleading since, although as per the Regulation EU 536/2014 the investigator can provide information on expectedness of the event to the sponsor, the sponsor is ultimately responsible for determining the expectedness of the event. Proposed change (if any): Revise the statement to read: "The	

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		investigator was not clear on the reporting requirements for the trial and was incorrectly classifying the serious criteria of the adverse events as they were common events seen with that particular disease."	
218 - 219		Comment: The statement "If the breach is caused by a third party confirmation should be obtained of any other trials that might be affected – whether open or closed" requires clarification. An individual sponsor/CRO would be able to do this only for their clinical trials that involve the third party, who may well be working with other sponsors and CROs. The expectation in this regard for the sponsor/CRO reporting a serious breach should be more clearly defined, as that individual sponsor or CRO will not have knowledge of trials for other sponsors and CROs involving the third party. Proposed change (if any): Define more clearly the expectation for a sponsor/CRO reporting a serious breach with regard to confirming other clinical trials that might be affected.	
		ACRO thanks the EMA for the opportunity to comment on this draft guideline. Please contact ACRO (knoonan@acrohealth.org) if we can provide additional information or answer any questions at all.	

Please add more rows if needed.