EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19/08/2017

Submission of comments on

Guideline for the notification of serious breaches of Regulation (EU) No 536/2014 or the clinical trial protocol

Comments from:

Name of organisation or individual
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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).

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	EUCROF welcomes the opportunity to provide comments on the 'Guideline for the notification of serious breaches of Regulation (EU) No 536/2014 or the clinical trial protocol' which helps clarifying the procedures to be established at sponsor and third party organisations. Our general comment refers to the scope of this Guideline. Whereas Article 52 of the Regulation talks about serious breaches of the Regulation or of the version of the protocol applicable at the time of the breach, this Guideline occasionally is referring to serious breaches of the protocol or GCP. Clarification would be welcome as to whether the term "serious breach of the Regulation" is interchangeable with "serious breach of GCP". EUCROF suggests to place a respective sentence in section 1 (Legal requirement) or section 2 (Scope).	

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)*
51-53		"The sponsor or a person duly authorised by the sponsor to perform this function, if this function has been delegated by the sponsor to another party (for example, a legal representative or contract research organisation (CRO))." Comment: The sponsor will authorise a party (e.g., CRO), not necessarily an individual (a person) in the form of a contractual agreement. The sponsor is a "party" as well and not necessarily an individual. The requirement should remain on the "party" level. We also think that the "contract" should be mentioned in the sentence. In addition, the above text does not represent a full sentence. Proposed change (if any): "The sponsor or a third party duly authorised by the sponsor to perform this function, if this function has been delegated (for example, to a legal representative or to a contract research organisation (CRO)) via a contractual agreement."	
55-61		"Within 7 calendar days of the sponsor becoming aware of the breach or of anyone that has contractual agreement with the sponsor (CROs, contractors, co-development partners, etc.) becoming aware of the breach. Contractual agreements between clinical trial (CT) sponsors and other parties should	

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		clearly stipulate that any non-compliance identified by third parties, 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 third party is first informed." Comment: "are" should be "is" "first informed" should be "first becoming aware" The third party might not be actively informed but might find out through monitoring activities, for example. Again, the text does not represent a full sentence. Proposed change (if any): "Notification of a serious breach should be made within 7 calendar days of the sponsor becoming aware of the breach or of anyone that has a contractual agreement with the sponsor (CROs, contractors, co-development partners, etc.) for the notification of serious breaches becoming aware of the breach. Contractual agreements between clinical trial (CT) sponsors and third parties should clearly stipulate that any non-compliance identified by third parties, is 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 third party first became aware of the serious	

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		breach."	
57-59		"Contractual agreements between clinical trial (CT) sponsors and other parties should clearly stipulate that any non-compliance identified by third parties, are promptly reported to the sponsor in order for the sponsor to meet its legal obligations." Comment: EUCROF suggests to stick with the term "third party" throughout the whole document. Proposed change (if any): Contractual agreements between clinical trial (CT) sponsors and third parties should clearly stipulate that any non-compliance considered as potential serious breach identified by third parties, are promptly reported to the sponsor in order for the sponsor to meet its legal obligations.	
62-64		"If a principal investigator is aware of the occurrence of a serious breach, then processes should be in place to ensure that such information is promptly reported to the CT sponsor in order for the sponsor to meet the legal obligations." Comment: EUCROF encourages a respective clause in the contractual agreement with the investigator/institution in order to have more leverage in case a principal investigator is	

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		aware of a serious breach. Proposed change (if any): "If a principal investigator is aware of the occurrence of a serious breach, then processes should be in place to ensure that such information is promptly reported to the CT sponsor in order for the sponsor to meet the legal obligations. The obligation to notify the sponsor should be stipulated in the contractual agreement between the sponsor and the investigator/institution."	
65-67		"If the notification function has been delegated by the sponsor to another party, for example, a CRO, the 7-day timeline applies to the other party. Therefore, sponsors and CROs need to ensure that there is a documented process in place for timely communication on serious breaches between…." Comment: Use "third party" Proposed change (if any): "If the notification function has been delegated by the sponsor to a third party, for example, a CRO, the 7-day timeline applies to the third party. Therefore, sponsors and CROs need to ensure that there is a documented process in place for timely communication on serious breaches between…."	

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68		"…the parties, which results in the serious breach being reported to the to the Member States …" Comment: typo Proposed change (if any): "…the parties, which results in the serious breach being reported to the Member States …"	
72		"…days, investigate and take action simultaneously or after notification." Comment: typo Proposed change (if any): "…days, investigates and takes action simultaneously or after notification."	
77		"Reporters are not expected …"" Comment: The term "reporters" has not been used previously. Proposed change (if any): "The party notifying the serious breach is not expected …"	
83		"…completed and what follow-up reports will be submitted to the EU CT system and when."	

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		Comment: We think "through" would be the more appropriate wording (also used elsewhere in the guideline) Proposed change (if any): "…completed and what follow-up reports will be submitted through the EU CT system and when."	
106-108		" Organisations should also consider if there are any other relevant notifications that need to be undertaken to comply with the Regulation, for example if a substantial modification is required due to a temporary halt in the trial." Comment: We think that the above logic is not fully correct. A substantial modification is not required due to a temporary halt but due to a seriouch breach causing the temporary halt. Also, there are administrative notification requirements (like for a temporary halt) and required submissions (like for a substantial modification). Proposed change (if any): "Organisations should also consider if there are any other relevant notifications or submissions that need to be undertaken to comply with the Regulation, for example if a substantial modification is required as a consequence of a	

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		serious breach causing a temporary halt in the trial."	
85 - 109		Comment: EUCROF suggests to change the order of the different bullet points. Bullet point number 3 "Serious breaches are notified through the EU CT system. All relevant fields must be completed" would be better positioned as the last bullet point as it is true for everything mentioned above. Proposed change (if any): See above comment	
111		"Deviations from clinical trial protocols and GCP may occur in clinical trials." Comment: Most of the time the wording is "Deviations from the clinical trial protocol and the Regulation". The question is: is a deviation from the Regulation equivalent to a deviation from GCP? The wording is inconsistent. Clarification would be welcome. See also General Comment. Proposed change (if any): See comment above	
115-116		"In addition, these deviations should be included and considered when the clinical study report is produced, as they may have an impact on the analysis of the data."	

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		Comment: The wording is misleading as the analysis of data has already happened at the time when the clinical trial report is being written Proposed change (if any): "In addition, these deviations should be included and considered when the clinical study report is produced, as they might have had an impact on the analysis of the data."	
117-118		"However, not every deviation from the protocol needs to be reported to the EU CT system as a serious breach." Comment: The above sentence is incomplete as regards the Regulation/ GCP (whatever will be the final wording in this Gudieline). In addition, "to the EU system" should be "through the EU system". Proposed change (if any): "However, not every deviation from the protocol or the Regulation (or GCP) needs to be reported through the EU CT system as a serious breach."	
172-173		"However, it is also important that the breach is circulated/made available to staff for inclusion of relevant information in the clinical study report or a publication."	

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		Comment: EUCROF suggests to add "considerations regarding analysis sets" Proposed change (if any): "However, it is also important that the breach is circulated/made available to staff for considerations regarding the statistical analysis sets and/or inclusion of relevant information in the clinical study report or a publication."	
190		"would need to be submitted to the EU system ..." Comment: should be "through" the EU system Proposed change: "would need to be submitted through the EU system ..."	
192-194		"If persistent or systematic non-compliance with GCP or the protocol has a significant impact on the safety of trial subjects in the EU/EEA or on the scientific value of the trial, this will constitute a serious breach". Comment: As already mentioned (see also line 111 and General Comment) most of the references to "serious breaches" refer to "Deviations from the clinical trial protocol and the Regulation". Clarification is required whether or not a deviation from the Regulation is equivalent to a deviation from	

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		GCP. Proposed change (if any): See above comment.	
199		"…the EU/EEA, then this will require notification to the EU system." Comment: Should be "through" the EU system. Proposed change (if any) : "…the EU/EEA, then this will require notification through the EU system."	
205-206		"Procedure for the management of serious breaches by the EU/EEA Member States including their assessment and the appointment of a lead Member State" Comment: Above sentence seems to be incomplete – it is not clear to which document the reference is poining to. In addition, EUCROF suggests to add references to legal documents like the Regulation and ICH-GCP and maybe others. Proposed change (if any): See comment above	

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Appendix 1- Potential Fraud		"On two separate occasions the sponsor identified issues with the same organisation. …" Comment: We think "organisation" should be replace by "investigator/institution" as the example clearly refers to a clinical site. We suggest to use the same terminology for a clinical site as ICH-GCP, i.e. "investigator/institution". Proposed change (if any): "On two separate occasions, the sponsor identified issues with the same investigator/institution. …"	
Appendix 1- SAE		First example: The investigator failed to report a single SAE….. **No,** if this did not result in other trial subjects being put at risk, and if it was not a systematic or persistent problem. In some circumstances, failure of the investigator/institution to report a SUSAR could have a significant impact on trial subjects. Sufficient information and context should be provided for the impact to be assessed adequately. Comment: The text above is a bit misleading as it could be understood that it is an investigator obligation to report SUSARs.	

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		Proposed changes (if any): **No,** if this did not result in other trial subjects being put at risk, and if it was not a systematic or persistent problem. In some circumstances, failure of the investigator/institution to report an SAE and - as a consequence - failure of the sponsor to report a SUSAR could have a significant impact on trial subjects. Sufficient information and context should be provided for the impact to be assessed adequately.	

Please add more rows if needed.