EUROPEAN MEDICINES AGENCY (EMA) CONSULTATION

Guideline for the notification of serious breaches of Regulation (EU) No 536/2014 or the clinical trial protocol' (EMA/430909/2016).

In August 2017, the UKCRC Registered CTU Network submitted the following comments on the draft guideline on behalf of its members.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22nd August 2017

Submission of comments on '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
UKCRC Registered Clinical Trials Unit Network

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)*
	We welcome the opportunity to comment on the guidelines, and note that they are based on the MHRA's 'guidance on notification of serious breaches' document in use over many years within the UK.	
	We note that the EMA guidelines do not include two useful elements from the MHRA guidance, namely: information on a channel of communication with the regulator (if the Sponsor is uncertain whether a breach should be notified as a serious breach or not), and some insight into the actions that the regulatory authority may undertake following a notification. These are important topics for sponsors, and we would request consideration of their inclusion in the EMA guidelines.	
	In the appendices the guidelines provide some useful scenarios of potential serious breaches, however some of the examples are very broad and we would suggest are open to interpretation. More detail may help to clarify. (See also later comments)	
	Some investigation is needed before a sponsor decision can be made that there are 'reasonable grounds' to believe that a breach may potentially be a serious breach. It would be helpful to acknowledge (in section 4) that such investigations would therefore by definition be before day '0' – rather than within the 7 days (as	

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	currently referenced at lines 75-76). As currently worded over-reporting of potential serious breaches that do not become actual serious breaches could be significant. A decision tree included in the guidelines would be welcomed.	
	Within the Regulation it is the responsibility of the Sponsor to report serious breaches, however the guidelines as worded appears to include investigators in this responsibility (lines 62-64). Whilst it is important that investigators report all breaches to the sponsor, assessment as to seriousness should be conducted by the Sponsor (unless the Sponsor formally delegates this function). Clarity on who is responsible for assessment also impacts on Day 0 and reporting timelines. (See also later comments)	
	The requirement for 'root cause analysis' is introduced, it would be very helpful for guidance on expected content and/or a template to be available in, or with, the guidelines.	

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)*
55-60		Comment: 'Within 7 calendar days' needs to relate to sponsor awareness 'that a serious breach has occurred' (as in line 60) rather than awareness of 'the breach' (as in line 55). Awareness of a breach would not necessarily result in a serious breach, therefore the calculation of 'Day 0' needs to be clear. It also needs to be made clear that Day 0 only starts when those who have the delegated authority to notify the authorities of the serious breach have been made aware of a serious breach. There is also some confusion/contradiction within the guideline (e.g. in lines 55 to 57) where it references 'anyone that has contractual agreement with the sponsor' becoming aware of the breach, rather than 'anyone who has a *contractual arrangement with (or delegated authority from) the sponsor to notify the authorities'.* Proposed change (if any): Suggest change from: "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." To: "Notifications should be made within 7 calendar days of the	

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		sponsor (or any third party that has a contractual agreement with the sponsor to assess the breach and submit notifications of serious breaches) becoming aware of the serious breach."	
62-64		Comment: As per general comment above, the evaluation and classification of a serious breach should lie with the Sponsor (or delegate), rather than the investigator. The investigator's responsibility is to report any breach promptly to the Sponsor (or delegatee). Proposed change (if any): "If a principal investigator is aware of the occurrence of a serious breach, then processes…." To "If a principal investigator (or other member of clinical trial site staff) becomes ~~is~~ aware of the occurrence of any breach of Regulation EU 536/2014 and/or the protocol during the course of the trial, then processes…."	
65-69		Comment: there is overlap between this section and the section covered by lines 55-61. Proposed change (if any): Suggest delete paragraph 65-69. If further detail is needed regarding the delegation function, suggest it is included in paragraph 55-61.	

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70-76		Comment: As per comment in general section and section 55-61, greater clarity on definition of Day 0 is needed. Furthermore, in this paragraph, there is no difference in actions or timelines if the Sponsor has reasonable grounds to believe the breach is a serious breach or not (i.e. for "other cases"). The wording in the last sentences is therefore largely redundant. Proposed change (if any): Suggest delete the last sentence of the paragraph.	
85-105		Comment: For clarity, re-ordering of section is proposed, so that line 96 appears earlier. Additionally other elements of the section can be made clearer with removal of redundant text, and clarification of the different scenarios. Proposed change (if any): Proposed change to lines 85-90: • "Serious breaches ~~of the Regulation or of the protocol of an EU/EEA authorised clinical trial occurring in the EU/EEA that are likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data~~ should be ~~reported~~ notified through the EU portal according to Article 52. All relevant fields must be completed. For serious breaches that are likely to affect the benefit-risk balance of the trial, in addition to the reporting requirement under Article 52, the sponsor has to	

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		consider the reporting requirement under Article 53, as an expected event, or Article 54, as an urgent safety measure, as applicable." Proposed replacement for lines 91-105: • Different actions may be applicable dependant on the location of the occurrence of a serious breach: ○ If a serious breach occurs in the EU/EEA for an EU/EEA authorised clinical trial protocol, the notification process described above will apply (Article 52 and, as applicable Article 53 or Article 54). ○ If a serious breach occurs exclusively outside the EU/EEA for an EU/EEA authorised clinical trial protocol, the notification process described above will apply (Article 52 and, as applicable Article 53 or Article 54). ○ If a serious breach occurs exclusively outside the EU/EEA and might have an impact on reliability or robustness of the data of a CT already authorised or being conducted in the EU/EEA territory, the notification process as per Article 52 will apply. ○ If a serious breach occurs exclusively outside the EU/EEA while the application for CT authorisation in under evaluation in the EU/EEA territory and the serious breach has an impact on the reliability or robustness of data filed in an application dossier,	

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		the Sponsor should withdraw the application and correct the aspects or data impacted, as applicable (in case for example the serious breach resulted from the problems in the design of the CT). No separate notification of the serious breach is needed.	
107-108		Comment: substantial modification is required to restart trial after halt, not to halt. Proposed change (if any): Suggest change: "…for example if a substantial modification is required due to a temporary halt in the trial." To: "…for example if a substantial modification is required to restart the trial after ~~due to~~ a temporary halt ~~in the trial~~."	
111 (and 192)		Comment: Elsewhere in the guidelines the reference is to a breach of 'the Regulation' or the protocol (as per Article 52), however in these lines (111 and 192) reference is made to 'GCP'. Proposed change (if any): Suggest change: 111 "Deviations from clinical trial protocols and **the Regulation** ~~GCP~~ may occur in clinical trials"	

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		192 "If persistent or systematic non-compliance with **the Regulation** ~~GCP~~ or the protocol…"	
111-113		Comment: Different criteria are used in this sentence from those in the definition of serious breach, i.e. wording is from MHRA guidance definition rather than definition in lines 125/6 of the EMA guidelines (and Regulations). Proposed change (if any): Suggest change: "The majority of these instances are technical deviations that do not result in harm to the trial subjects or significantly affect the scientific value of the reported results of the trial." To: "The majority of these instances are technical deviations that do not affect the safety or rights of ~~result in harm to~~ the trial subjects or significantly affect the reliability and robustness of the data generated in ~~scientific value of the reported results of~~ the trial."	
113 - 115		Comment: The wording implies that formal CAPA should be undertaken for all breaches. This would be required for serious breaches, but for example for minor protocol deviations. Proposed change (if any): Suggest change from: "These cases should be documented (for example, in the trial case report form or the trial master	

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		file) in order for appropriate corrective and preventative actions to be taken." To: "These cases should be documented (for example, in the trial case report form or the trial master file) and appropriate remedial actions implemented where necessary."	
133-136 and 182-184		Comment: The examples of overdoses as serious breaches in these two paragraphs appear to be contradictory. Lines 133-136 in particular imply that *all* overdoses, regardless of impact on subject safety, which we would not expect to be the case. Proposed change (if any): Request deletion of sentence at 134-136, and inclusion of clarification on when an overdose might constitute a serious breach in the guidelines.	
141-142		Comment: There is no description of the process that the Member State will follow after notification of the serious breach. However it is implied that a serious breach will trigger inspection. The wording at line 141 does not encourage communication and openness from the sponsor. Proposed change (if any): Request clarification of "…any process triggered…".	
151		Comment: Reference to 'Sponsor' in section 6.1 should include any third party delegated notification responsibilities by the sponsor.	

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162-165		Comment: As per general comment, it is not anticipated that an investigator would undertake assessment/classification as to whether a breach meets the classification of a serious breach. If the role of the investigator/third party (not delegated to notify serious breaches by the sponsor) is to be included in the guideline, the responsibilities should be confined to prompt reporting of protocol and regulatory deviations to the sponsor. Proposed change (if any): Suggested replacement of section 6.2: "6.2 Investigator/clinical trial sites~~/third parties~~. The investigator and clinical trial sites (and other third party not delegated by the sponsor to assess and report serious breaches) should also have a process in place to identify and notify the sponsor of the occurrence of any ~~serious~~ breach of the protocol and/or the Regulation of which they become aware. This may be a formal standard operating procedure or a process detailed in the protocol or study-specific guidance."	
Section 7 – title – line 176 (and line 143)		Comment: Reference is made in line 143 to Section 7 as the: 'section on general expectation for serious breaches reporting', which does not match the actual title of Section 7 ('General expectation for serious breaches'), which is intended/correct?	
Section 7 - general		Comment: The general purpose/intention of section 7 is unclear. If it is intended to provide a summary, this is not	

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		achieved, not least as the section introduces new concepts, e.g. clinical trial fraud. If the intention is to provide 'help when deciding on whether to submit a serious breach notification' (as suggested in lines 143-4), we would recommend referencing the examples at Appendix 1 and providing greater clarity in the wording and order. Proposed change (if any): Recommend referencing the examples at Appendix 1 and providing greater clarity in the wording and order of section. .	
178 - 180		Comment: The guidelines states: 'The term "site" refers to any site or party involved in the trial, for example, a CRO (such as laboratories analysing samples from subjects)…and not solely to investigator sites'. It is unclear whether this is a comment on the wording of the Regulation itself, or applicable only to the guidelines (or applicable only to the reference to clinical trial fraud? – as the statement appears between two sentences dedicated to fraud). In addition the Regulation refers to 'clinical trial sites' rather than 'investigator sites'. Proposed change (if any): Clarification requested	
192		Comment: (see comment under line 111) Proposed Change (if any):	

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		192 "If persistent or systematic non-compliance with **the Regulation** ~~GCP~~ or the protocol…"	
196		Comment: Clarification requested, what is intended by "…notified accordingly"? Proposed change (if any): Suggest amend "…notified accordingly." To: "…notified <u>within the serious breach report</u> ~~accordingly~~."	
197-199		Comment: This appears to be a repeat of the content of lines 100-105 Proposed change (if any): Suggest combine the paragraphs	
Appendix 1 – **general comment**		Comment: **The wording of several examples relates to the MHRA's definition of a 'serious breach', rather than the definition in the Regulation e.g. references are made to 'physical and mental integrity', rather than 'safety and rights' of patients, and references made to 'scientific value' rather than the 'reliability and robustness' of the data.** Also, request example(s) demonstrating an impact on 'rights of a patient'. Proposed change (if any): Ensure terminology in guidelines consistent with Regulations.	

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Appendix 1 – **general comment**		Comment: **It would be helpful to have further clarity on whether the assessment of a breach is being made against the hypothetical 'potential' for harm to have occurred, or the actual result of the incident.** **Several examples in Appendix 1 refer to 'potential', however the term 'potential' is not used in the guidelines.**	
Appendix 1 – Category – 'Potential fraud' page 9		Comment: This example refers to "issues" concerning consent and recruitment which were considered to be reportable as they "led to enforcement action". The example provided as it stands, is not helpful. We would welcome further detail and clarification here, as issues with consent/recruitment are not uncommon, however they would rarely be considered as fraud or deemed reportable.	
Appendix 1 – Category – 'source data' page 9		Comment: The 'source data' row states the following in the 'is this a serious breach' column: "**Yes**, and this needs to be reported when the concerns were raised." We wondered why immediate reporting would be required for this example but not for others? This situation would still need at least some further investigation before reporting, even if	

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		fraud suspected. (Additionally, the example describes 'monitoring visits' and a subsequent 'audit' – so the statement implies that the serious breach should have been reported after the first monitoring visit, which would seem premature?)	
Appendix 1 – Category – SAE reporting 1 (page 11)		Comment: The wording of the first SAE reporting example is ambiguous. As worded it could be interpreted that the investigator didn't report any SAEs at all (which would be likely to constitute a serious breach). Proposed change (if any): Suggest change from: " The investigator failed to report a single serious adverse event (SAE) as defined in the protocol" To: "One unreported serious adverse event (SAE) as defined in the protocol was identified at a site during monitoring"	
Appendix 1 – Category – SAE reporting 2 (page 11)		Comment: The "details" column of the second SAE reporting example refer to errors in 'expectedness' assessment, whereas the "is it a serious breach" column refers to errors in 'seriousness' assessment. Under-reporting of SUSARs (due to expectedness assessment errors) and incorrect classification of SAEs as AEs (due to errors in seriousness assessments) are different issues.	

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		Proposed change (if any): Clarification needed	
Appendix 1 – Category – 'randomisation/ stratification errors' (page 12)		Comment: Some of the examples would benefit from further detail to contextualise the situation, in particular in the 'randomisation/stratification errors' example, 1-2 incorrectly randomised patients would not have a significant impact on reliability/robustness of the trial data if there was a very large sample size, however 1-2 patients out of a sample size of 20 would be serious. Proposed change (if any): More detail needed	
Appendix 2 – 212-217		Comment: Guideline seems to imply potential serious breaches under investigation should be reported, however this bullet contradicts this? Proposed change (if any): Suggest amend from: "Does the breach meet the definition of serious breach? Has there been an assessment of whether the breach affects to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial? If not, then this is not a serious breach and should not be reported. However, this may be difficult to determine initially and may take some time to investigate, but the incident remains as serious breach whilst this is investigated and therefore should be reported." To:	212-217

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		"Does the breach meet the definition of serious breach? Has there been an assessment of whether the breach affects to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial? **Did the assessment confirm this?** If not, then this is not a serious breach and should not be reported. However, **if from the assessment it remains a 'potential' serious breach but it** ~~this may be difficult to determine initially and~~ may take some time **for investigation to confirm this** ~~to investigate~~, ~~but~~ the breach ~~incident remains as serious breach whilst this is investigated and therefore~~ should be reported **while investigations are on-going**."	
Appendix 2 – 218-219		Comment: It is unclear why the confirmation of impact on other trials is only required when the breach is identified 'by a third party'? The requirement to confirm whether or not additional trials have been affected by the breach is applicable to issues 'caused by' the Sponsor as well as by third parties. Additionally, it is suggested that the value of investigating closed trials is limited. If wording is to be retained, it should refer to 'trials ongoing or closed after the Regulation came into force'. Proposed change (if any): Suggest amend bullet point from: • "If the breach is caused by a third party confirmation should be obtained of any other trials that might be	

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		affected – whether open or closed." To: "The Sponsor should assess directly, or via third parties, the impact of a breach on other trials"	
Appendix 2 – line 227		Comment: Request strengthening of this statement to confirm that human error is considered as an acceptable root cause (as long as a full root cause analysis has excluded other causes). We have experience of trial sponsors being unwilling to accept human error as a root cause based on a belief that it is unacceptable to regulators in all cases. This has led to requests for disproportionate actions, without consideration of the lack of risk to patient safety or data integrity. This has the potential to harm the overall trial delivery, especially in the case of large pragmatic trials. However, failure to follow a procedure is not a root cause in itself. The root cause could be lack of training, for example. Proposed change (if any): Suggest add comment/examples of acceptable/possible 'root causes', with inclusion of 'human error'.	
231		Comment: Preventative action can never truly '*ensure that it will not happen again*'; consider rewording. Proposed change: Suggest amend from: "Does the preventative action address	

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		the breach and ensure that it will not happen again" To: "Does the preventive action address the breach and **provide assurance** that it will not happen again'	

Minor – typographical errors

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Throughout		Comment: Some terms used interchangeably within the guidelines e.g. 'trial' and 'CT' and 'clinical trial are all used in the guidelines. Proposed change (if any): Consistency of terms.	
Throughout		Comment: Inconsistency Proposed change (if any): Suggest replacement of "patient" with "subject" to mirror Regulation.	
58		Comment: Typographical error Proposed change (if any): Change from: '…identified by third parties, are promptly reported' To: '..identified by third parties **is** promptly reported'	
72		Comment: Typographical error. Plural verbal forms where the subject is singular (i.e. sponsor) Proposed change (if any): Change from: "investigate and take action simultaneously" To: "investigates and takes action simultaneously".	
191		Comment: Typographical error Proposed change (if any):	

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		Change from: "prior to re-start the clinical trial" To: "prior to re-start**ing** the clinical trial".	
195		Comment: Typographical error Proposed change (if any): Suggest change from: 'If a serious breach occurred at one investigator site leads to the removal of data from the trial analysis, then this should be notified accordingly' **To:** 'If a serious breach **occurring** at one investigator site leads to the removal of data from the trial analysis, ~~then~~ this should be notified accordingly' **Or:** 'If a serious breach **that occurred** at one investigator site **led** to the removal of data from the trial analysis, ~~then~~ this should be notified accordingly'	
Appendix 1 – access to data section – page 11		Comment: Typographical error - Missing apostrophe Proposed change (if any): Change from: "access to the patients notes" To: "access to patient**s'** notes".	
Appendix 1 – randomisation /stratification errors – page 12		Comment: Typographical error Mixture of use of US spelling and UK spelling – "randomisation" and "randomize" used. Proposed change (if any):	

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		Use consistent spelling	
Appendix 2 – line 222		Comment: Typographical error Proposed change (if any): Remove question mark contained within brackets.	