03 September 2010

Draft Revised Version of Detailed Guidance on the Collection, Verification and Presentation of Adverse Reaction Reports Arising from Clinical Trials on Medicinal Products for Human Use ('CT-3')

Comments from:

Name of organisation or individual
Pfizer; Contact Person: Maria Grazia Zurlo, EU Qualified Person for Pharmacovigilance (mariagrazia.zurlo@pfizer.com)

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)*
	Patient safety is Pfizer's highest priority and we are pleased to have the opportunity to provide comments that are intended to further protect subjects in interventional clinical trials. This public consultation document is a draft detailed guidance intended to replace these three documents that apply to clinical trials: (a) Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use (revision 2 of April 2006); (b) Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (Eudravigilance - Clinical Trial Module)Translations. (revision 1 of April 2004); and (c) Questions & Answers Specific to Adverse Reaction Reporting in Clinical Trials Version 1.0 (December 2009 We commend the European Commission for addressing widespread concerns of stakeholders regarding implementation of the Clinical Trials Directive 2001/20/EC. However, there are many aspects of the former documents that were more complete and better organized than the proposed draft detailed guidance. We urge the European Commission and the European Medicines Agency to adopt clarifying language, but in the format and more robust style of the more complete earlier version of 'CT-3.' For example, definitions would be	

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	more useful were they placed together in an Annex, similar to the April 2006 detailed guidance. Specific comments are below.	

2. Specific comments on text

Line number(s) of the relevant text ***(e.g. Lines 20-23)***	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)***
Page 3 Section 1.3 Definitions (7)	Priority: Low **Comment** The hyperlink for footnote 6 appears to be broken; message: "The requested page does not work." (accessed 12 August 2010) **Proposed change** Check, repair, and maintain all hyperlinks in the document.	
Pages 3 & 4 Section 2.2. 'Serious adverse event' (12, 14)	Priority: Low **Comment** Points 12 and 14 convey the same information, so are duplicative. **Proposed change** Combine these definitions into one paragraph and include in the proposed Annex for definitions of terms; otherwise, eliminate one of them.	
Page 3 Section 2.1.	Priority: Medium	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	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)*
Legal basis (11)	**Comment** It is accepted practise to NOT require immediate reporting of certain serious adverse events, e.g., progression of disease in oncology clinical trials. Such events should be identified in the protocol and serve as the set of instructions for the investigators to follow during the trial. This approach, however, has to be carefully evaluated and implemented in each therapeutic area under investigation. **Proposed change** **11.** The purpose of this obligation is to ensure that the sponsor has the necessary information to continuously assess the ~~risk-benefit~~ **benefit-risk** balance of the clinical trial, in accordance with Article 3(2)(a) of Directive 2001/20/EC. **Serious adverse events not subject to immediate reporting should be specified in the clinical trial protocol; this approach must be carefully evaluated and implemented in each therapeutic area under investigation.**	
Page 4 Section 2.2.2. 'Serious event' (16)	Priority: Medium **Comment** 16. "Medical events may jeopardise the clinical trial participant or may require an intervention to prevent one of the characteristics/consequences above. Those events (hereinafter referred to 'important medical events') should also be considered as 'serious' in	

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	accordance with the definition." The intended meaning of 'important medical events' in this context is not clear. What is the relationship between the events referenced here and the "Important Medical Events" (IME) list that has been developed by the EudraVigilance Expert Working Group? The MedDRA MSSO has developed the inclusion/exclusion criteria for this published IME list and it can be anticipated that the terms in such a list, if maintained by the MSSO in step with the MedDRA terminology, will change over time as new versions of MedDRA are released two times per year. For example, a new IME list was published based on MedDRA version 13.0 that is different from the IME list derived from MedDRA version 12.0. While we support the concept of consistently identifying events that are medically important to facilitate the classification of adverse events, the concept of an ever-changing list would provide challenges for doing so. Such a published IME list should provide conceptual reference rather than regulatory guidance. **Proposed change** Define 'important medical events.' Medical judgement, which reflects medical advances over time, should be central to the definition. Conclusions regarding 'important medical events' should not depend on a migratory list of terms.	
Page 4	Priority: Medium	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	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)*
Section 2.3.1. Immediate reporting and follow-up report (19)	**<u>Comment</u>** The investigator is obligated to "immediately" report all serious adverse events, except certain events specified in the protocol or Investigator Brochure or other written agreement between the investigator and the sponsor. The timeline for an investigator to report serious adverse events to the sponsor should be specified in the protocol. A 48-hour timeline was not specified in the previous version of CT-3 and should not be specified in the revision; indeed, in some instances a 48-hour timeline may not be adequate to protect patient safety. If such a provision is implemented, it will likely require wholesale amendments to ongoing clinical trials. **Proposed change** 19. The immediate reporting should allow the sponsor to take the appropriate measures to address potential new risks in a clinical trial. Therefore, the immediate report should be made within a very short period of time ~~and under no circumstances exceed 48 hours~~ following knowledge of the adverse event **by the investigator**.	
Pages 5 & 9 Section 2.4 Subject identification (21); and	Priority: Medium **<u>Comment</u>** While this detailed guidance document is not geared to	

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Section 4.7.1.2. Content of initial reporting (62)	data privacy requirements, the following statements appear contradictory: 21. In the report, the subject shall be identified by way of unique code numbers assigned to him. 62. Any one of several data elements is considered sufficient to define an identifiable subject (e.g. code number, initials, age, sex) or an identifiable reporter (e.g., initials, address, qualification). **Proposed change** Provide clarity on expectations for patient identifier(s) to be used.	
Page 6 & 8 Section 4.2.1. 'Adverse reaction - causality' (28) and Section 4.5. Adverse reactions not to be reported (48)	Priority: High **Comment** These sections define what is **not** a SUSAR for the purposes of expedited reporting and then cross refer to section 4.2.1 which does not actually give guidance on how to report such non-SUSARs, as implied. The section where some guidance **is** provided is in Section 4.11.3. (page 15). The various options provided, while certainly appropriate for a significant issue which may impact study subject safety, may not be appropriate for some individual SUSAR reports, e.g., for a non-IMP. The document also remains silent regarding the current	

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	provision for a sponsor to report spontaneous SUSARs from third countries where the IMP is marketed and which is still in the pre-authorisation phase in the EU. It is unclear if this was an inadvertent oversight or if such cases would now not be considered SUSARs. In addition, SUSARs occurring in an EU clinical trial are unlikely to come to the knowledge of another sponsor undertaking trials with the same IMP through spontaneous reporting. **Proposed change** We propose that: • Section 4.5 (48) be amended to cross refer to Section 4.11.3 and not 4.2.1 as the former section is more relevant; • 4.11.3 (101) be expanded to give guidance on how to report non-SUSARs from a solicited (interventional) source but which are not of sufficient concern to warrant an urgent safety restriction, termination of the trial or a substantial amendment to the protocol. For example, it may be appropriate to send a copy of the non-SUSAR report to the manufacturer of the non-IMP; and • Section 4.5 (48) should be amended to include an additional bullet point which covers SUSARs	

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	from spontaneous sources where an IMP is marketed in a third country by the sponsor but not yet authorised in any Member State; reference to spontaneous reports should be deleted from 48 (second bullet). Thus, the text would read as follows: *4.5 Adverse reactions not to be reported* *48. It follows from section 4.4 that there is no need for the sponsor to report :* • *Adverse reactions not related to the IMP……..This is addressed through the reporting and follow up measures outside SUSAR reporting (see section ~~4.2.1~~* ***4.11.3****); or* • *SUSARs occurring in a clinical trial performed……These SUSARs may come to the knowledge of the sponsor through ~~spontaneous reports,~~ publications (such as academic literature) or regulatory authorities* • ***SUSARs from spontaneous sources where an IMP is marketed in a third country by the sponsor but not yet authorised in any Member State*** ***4.11.3. safety issues not falling within the***	

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	definition of SUSAR – other ~~follow up~~ measures 101. These events/observations are not to be reported as SUSARs according to this detailed guidance. However, these events/observations may require other action during a clinical trial which may require action such as : • **Notification of individual serious and unexpected ADR reports which do not qualify as SUSARs, e.g., from non-IMPS to the original marketing authorisation holder**	
Page 6 Section 4.2.4. SUSARs occurring after the end of the trial (35)	Priority: Medium **Comment** Given that the protocol will specify the period for which adverse reactions will be considered related to study treatment, it should be clarified here if the obligations related to SUSAR reporting after the end of a trial rest with Ethics Committees, investigators, or both. **Proposed change** Clarify whether the obligations related to SUSAR reporting after the end of a trial rest with Ethics Committees, investigators, or both.	
Page 7	Priority: Low	

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Section 4.3.2. Causality (41)	**Comment** Point 41 could be strengthened by suggesting that, should the investigator's assessment of causality continue to remain unknown, the Sponsor should consider the SUSAR as "related" for purposes of evaluating the report. **Proposed change** Revise Point 41 to read as follows: 41. In the absence of information on the causality by the reporting investigator, the sponsor should consult the reporting investigator and encourage him to express an opinion on this aspect. The causality assessment given by the investigator should not be downgraded by the sponsor. If the sponsor disagrees with the investigator's causality assessment, both, the opinion of the investigator and the sponsor should be provided with the report. **Should the investigator's assessment of causality continue to remain unknown after follow-up attempts, the sponsor should consider the SUSAR as "related" for purposes of evaluating the report.**	
Page 7 Section 4.3.3. Expectedness (45)	Priority: High **Comment** We note the introduction of a new requirement which strongly advises the sponsor to obtain an expectedness	

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	assessment from the investigator for all serious suspected ADRs. We have significant concerns about this. We do not see a public health justification for changing this notion of separate determinations by sponsor and investigator. There should be no difference between sponsor and investigator determination of expectedness and this new provision seems to legitimise the thinking that there could be a difference. If an investigator does not provide a determination of "expectedness," would the sponsor's assessment be the final one plus an ongoing query? Otherwise, if a "blank expectedness" per investigator defaults to "unexpected," there would be a tremendous over-reporting of SUSARs. This is very different from "blank causality" per investigator. This will lead to confusion. The sponsor is in the best position to determine expectedness reliably and within the timelines. The Investigator makes his or her judgement based upon sponsor-supplied information and hence repeating the analysis of the sponsor by the investigator will lead to confusion. The unnecessary complications of this point should be considered very carefully.	

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	In addition: • This section conflicts with the guidance provided in section 4.2.3 (34), which states that "The unexpectedness of an adverse reaction is determined by the sponsor according to the reference safety information." • The sponsor is in a better position to understand the regulatory meaning of expectedness than the investigator, who is more likely to use their medical judgment of the patient's condition, disease and expected pharmacological effects of the IMP as opposed to what is in the reference safety information. • Practical issues in training and retraining all investigators every time the reference safety information is updated. • There are also concerns about consistency among investigators, and the fact that none of the internationally-accepted consensus guidelines (e.g., ICH or CIOMS) include the concept of investigator-supplied expectedness assessments. • It would appear that sponsors will need to record both investigator and sponsor opinion of expectedness. If this is the case, this will impact	

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	systems considerably (e.g., an additional data field not currently specified amongst the E2B electronic case reporting data elements). While we have no objection to 4.3.3 (44) with respect to the sponsor taking into consideration an investigator's assessment of expectedness when provided, but strongly suggest that the subsequent paragraph (45) be deleted. **Proposed change** We strongly recommend that item 45 be deleted so that the revision will remain the same as the present guidelines. *4.3.3 Expectedness* 45. ~~In the absence of information on the expectedness by the reporting investigator, the sponsor should consult the reporting investigator and encourage him to express and opinion on this aspect. The expectedness assessment given by the investigator should not be downgraded by the sponsor. If the sponsor disagrees with the investigator`s expectedness assessment, both the opinion of the investigator and the sponsor should~~	
Page 7 Section 4.3.3. Expectedness	Priority: Low **Comment**	

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(42, 43)	Note that the previous guidance regarding how to select the most appropriate SmPC has been removed. Suggest inclusion of this guidance to avoid confusion. **<u>Proposed change</u>** Revise Points 41 and 42 to read as follows: 42. The sponsor is responsible for ensuring that only unexpected adverse reactions are reported **to the competent authority concerned.** 43. The expectedness of a serious adverse reaction ~~is assessed in the light of the applicable product information (e.g. IB or SmPC)~~ **shall be determined by the sponsor according to the reference document, which is ordinarily:** **- the investigator's brochure for a non-authorised investigational medicinal product,** **- or the summary of product characteristics (for a medicinal product authorized for marketing in the European Union, which is being used according to the terms and conditions of the marketing authorisation). When the investigational medicinal product has a marketing authorisation in several Member States with different summary of product characteristics, the sponsor should select the most appropriate summary of product characteristics, with reference to patient safety, as a reference document for assessing expectedness. The reference document should be**	

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	the same for the whole clinical trial in all the Member States concerned.	
Pages 7 & 11 Section 4.4 SUSARs to be reported (46, 47) and Section 4.7.3.1.	Priority: Medium **Comment** There are 5 pages between SUSARs to be reported and the destination to which they should be sent. To better guide the reader, in Section 4.4 (46, 47), make parenthetical reference to Section 4.7.3., which details the addressee of the report. **Proposed change** Revise Point 47 to read as follows: 47. ~~While the transitional reporting procedures still apply, additional SUSARs should be reported to Member States (cf. Section 4.7.3.3).~~ **Information on reporting arrangements for SUSARs, e.g., addressees, are described in Section 4.7.3.**	
Pages 7 & 12 Section 4.4 (46) and Section 4.7.3.3 (78)	Priority: High **Comment** The final point on page 7 refers to SUSARs to be reported from trials …..*sponsored by another sponsor who is either part of the same mother company or who holds a development agreement with the sponsor.* This does not encompass the complexity of business	

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	development agreements and introduces the potential for duplicate reporting. **<u>Proposed change</u>** The text should be re-worded as follows: 4.4 SUSARs to be reported - sponsored by another sponsor who is part of the same mother company or ~~who holds a development agreement with the sponsor~~ **as stipulated in the safety data exchange agreement which must ensure that one party takes responsibility for notification of SUSAR**s. The same proposed change would also apply to the second point in 4.7.3.3 (78)	
Page 8 Section 4.5. Adverse reactions not to be reported (48)	Priority: Low **<u>Comment</u>** This section refers the reader to Section 4.2.1. ”It follows from section 4.4 that there is no need for the sponsor to report: • Adverse reactions not related to the IMP but to a non-IMP received by the subject and without interaction with the IMP: This is addressed through the reporting and follow-up measures outside SUSAR reporting (see	

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	section 4.2.1); " The reference to Section 4.2.1. is confusing because the referenced section does not provide reporting and follow up measures: "28. An untoward and unintended response to a non-IMP (e.g. concomitant medications, background treatments, rescue medications or challenge agents) which does not result from an interaction with an IMP is, by definition, not a SUSAR." **<u>Proposed change</u>** Revise Point 48 to read: 48. It follows from section 4.4 that there is no need for the sponsor to report: • Adverse reactions not related to the IMP but to a non-IMP received by the subject and without interaction with the IMP: This is addressed through the reporting and follow-up measures outside SUSAR reporting (see section 4.2.1). **Refer to Directive 2001/20/EC, Article 2(d), for the definition of an IMP**; or • SUSARs occurring in a clinical trial performed (partly or exclusively) in the EU for which he is not the sponsor. These SUSARs may come to the knowledge of the sponsor through spontaneous reports, publications (such as academic literature), or regulatory authorities.[10]	

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Page 10 Section 4.7.2.1. Timelines (63-66)	Priority: Medium **Comment** This section is especially important with respect to compliance calculations. As currently worded, however, this section is very confusing. "(1) Follow-up information received before the 15 days reporting timeline" **Proposed change** (1) Follow-up information received ~~before the 15 days~~ **after day 0 and up to and including the day 15** reporting timeline	
Page 11 Section 4.7.3.1. Introduction (71)	Priority: Low **Comment** The word "concerned" in the clause "Member State(s) concerned" should be defined here.	
Page 11 Section 4.7.3.2 (75)	Priority: High **Comment** This section introduces the option of either direct or indirect reporting to EVCTM, as determined by the	

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	Member States. In these circumstances : • It is inevitable that different Competent Authorities will oblige different options, in which case, for any multinational trial, sponsors would be submitting directly to EVCTM for some CAs but not others; • As Member States can oblige either direct or indirect reporting, it is difficult to see how the third option (leaving the sponsor to choose) can actually work for a SUSAR occurring in a MS in which the CA obliges the route of reporting which is not the sponsor`s choice; • As a practical matter, direct reporting would be the only option for third country SUSARs as, if many sponsors choose MSs which ensure indirect reporting, this would place an undue burden on the Competent Authority(ies) concerned. As a result, not only will complex procedures need to be put in place by sponsors (particularly for multinational trials) but there is the added problem that, if sent directly to EV by the sponsor, the ICSR could then be duplicated by another CA which chose indirect reporting, especially for third country reports. We believe only one route for reporting should be	

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	available. Our preference is for direct reporting by the sponsor as this is consistent with the proposed new PV legislation for spontaneous report submission to EVPM and allows for a single process for multinational studies. In particular, we consider that direct reporting should be mandatory for third country SUSARs. **<u>Proposed change</u>** Revise text as follows: Section 4.7.3.2 reporting Modalities and Use of the European database – direct ~~and indirect~~ reporting 75. As regards the input of information regarding SUSARs into EVCTM, Member States may ~~provide for one of the following measures~~ : • **~~Obliging~~ Oblige** the sponsor to report directly as individual case safety report (ICSR) to EVCTM only (hereafter referred to as direct reporting). The national competent authority of the Member state concerned is then informed through EVCTM • ~~Obliging the sponsor to report only to the national competent authority of the Member State where the SUSAR occurred who, in turn, enters this information into EVCTN(hereinafter referred to as indirect reporting)~~	

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	• ~~Leaving it to the sponsor to choose direct or indirect reporting~~	
Pages 11 & 12 Section 4.7.3 Addressee of report, reporting to EVCTM, reporting arrangements (73–81)	Priority: Medium **Comment** Although reform of the reporting route is to be welcomed this is less than clear and may cause confusion. It would be better to have a simple and clear single route of reporting. The transitional arrangements are not clear **Proposed change** Please clarify this confusing set of points. In addition, it would be useful to refer to point 46 explicitly in point 77 for clarity.	
Page 12 Section 4.7.3.2. Reporting modalities (76)	Priority: Medium **Comment** Some sponsors may not have the resources or experience for direct reporting so provision in the guidance is needed to address this situation. Nevertheless, we are concerned that, despite the fact that final accountability will always reside with the	

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	sponsor, commercial partners which assume SUSAR reporting from academic collaborators could become exposed from a compliance perspective. In an investigator initiated trial situation, whereby a commercial partner may provide some funding, it is inevitable that many academic centres will wish to take this option. **<u>Proposed change</u>** This option should be modified to contain the caveat that delegation can occur if offered by the commercial partner, documented in the letter of agreement between the sponsor and commercial partner and on the understanding that compliance with reporting requirements remains with the sponsor. Text could be re-cast as follows: 76. (second bullet point) Where a commercial partner is involved (e.g. the marketing authorization holder of the IMP), delegate the direct submission to the partner, **if offered by the commercial partner and fully documented in any letter of agreement. Accountability for reporting compliance remains with the sponsor, even if the responsibility for SUSAR reporting to EVCTM is delegated.**	

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Page 14 Section 4.9 Reporting of SUSARs to Ethics Committees (89)	Priority: Medium **Comment** 89. "Regarding all aspects of SUSAR reporting (reporting procedures, timelines) reference is made to sections 4.7.1, 4.7.2, 4.7.4.2 and 4.8. Regarding the addressee, this should be only the Ethics Committee issuing the 'single opinion' in accordance with Article 7 of Directive 2001/20/EC of the Member State where the event occurred." This guidance regarding ECs is now much briefer and does not mention national requirements etc., which we consider to be pro-public health and more efficient. **Proposed change** Add the following sentence to the end of point 89: "All concerned Ethics Committees should be provided with the same information on SUSARs relevant to the IMP."	
Page 14 Section 4.10. Informing the investigator (91)	Priority: Medium **Comment** "If appropriate, the information on SUSARs should be aggregated in a line listing of SUSARs in periods as warranted by the nature of the clinical development	

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	project and the volume of SUSARs generated. This line listing should be accompanied by a concise summary of the evolving safety profile of the IMP." This appears to give a much welcomed flexibility regarding Sponsor communication with investigators. It would be additionally helpful here to describe what "if appropriate" means and examples of the time period expected. **Proposed change** Define "if appropriate" and give examples.	
Page 14 Section 4.11.1 Blinded IMPs (94)	Priority: High **Comment** 94. "As regards the sponsor, when an event may be a SUSAR the blind should be broken by the sponsor only for that specific patient. The blind should be maintained for persons responsible for the ongoing conduct of the study (such as the study management, monitors, investigators) and those responsible for data-analysis and interpretation of results at the conclusion of the study, such as biometrics personnel. Unblinded information should only be accessible to	

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	those who need to be involved in the safety reporting to EVCTM, national competent authorities, investigators, ethics committees, and Data Safety Monitoring Boards[29], or persons performing ongoing safety evaluations during the trial." The underlined wording is stronger than the previous version, which said this was recommended where possible. We note that maintaining the blind for persons responsible for the ongoing conduct of the trial is not always possible, as investigators want to know whether an individual patient who may be compromised is on a placebo or the IMP, usually they keep notes on these findings, and these notes are read by study monitors. We recommend using the conditional statements in the former guidance. The unblinding process should capture the concepts in the ICH E2A guideline. In addition, the last part of the last sentence could be misinterpreted as allowing all investigators access to all unblinding information. This can easily be modified to prevent such unintended interpretation. **Proposed change**	

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	Thus, the following modifications are suggested: 94. **As a general rule, treatment codes should be broken by the sponsor before reporting a SUSAR to the competent authority and the ethics committee of the concerned Member State. The blind should be broken only for that specific patient by the sponsor.** Unblinded information should only be accessible to those who need to be involved in the safety reporting to EVCTM, national Competent Authorities, ~~investigators~~, ethics committees, and Data Safety Monitoring Boards, or persons performing ongoing safety evaluations during the trial. **Investigators may have access to unblinded information if directly pertinent to assure the safety of individual clinical trial participants. The blind should be maintained for other investigators and for those persons, such as biometrics personnel, responsible for analysis and interpretation of results at the study's conclusion.**	
Page 16 Section 5. Yearly Reporting of Suspected Serious Adverse	Priority: Low **Comment** Reference should be made to the status of the EMA guideline on DSURs, not only the ICH E2F guideline.	

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Reactions by the Sponsor (105)	**<u>Proposed change</u>** Delete the black box "Note to reader" as to the status of ICH DSUR guideline because the status will change over time.	

Please add more rows if needed.