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')

Public consultation document

Name of Organisation	Country
EUCROF European CRO Federation **Secretariat** 60, Rue Carnot F-92100 Boulogne-Billancourt Tel: +33 1 46 99 94 54 Email : info@eucrof.eu Representative on this matter : **Ramona Daniela Bobeica, MD** Tel: +31 10 48 55 177 Mobile: +31 65 5708 353 Email: r.bobeica@sticares.org Date Comments submitted: **10 September 2010**	**CRO Associations of EU Member States:** **Belgium** **Czech Republic** **France** **Germany** **Italy** **Spain** **The Netherlands** **Norway** **UK**

1. Specific comments on text

Comment number/ organization	Chapter	Section Paragraph Line	Page no.	Comment	Proposed change
1. *WG-CTL*	**2**	**2.3** **18**	**4**	Despite the scope it would make sense to add to whom the investigator has to report	"The investigator has to immediately report all SAE with ….**to the Sponsor."**
2. *WG-CTL*	**2**	**2.3** **20**	**5**	No deadline is mentioned for the follow-up information	
3. *WG-CTL*	**2**	**2.3.2.**	**5**	"… taking into account of the specificities of the trial and of the serious adverse event, …" More explanation would be helpful.	"… taking into account of the specificities of the trial and of the **previously specified type of serious adverse event qualifying for non-immediate reporting**, …"
4. *WG-CTL*	**4**	**4.2.1** **29**	**6**	Proposal to delete sentence as it confuses instead of clarifies. It is explained in section in 4.3.2	
6. *WG-CTL*	**4**	**4.3**	**6**	"Assessment of seriousness, causality and unexpectedness"	"Assessment of seriousness, causality and **expectedness**"
7. *WG-CTL*	**4**	**4.3.2.** **38.**	**6**	Facing the difficulties in establishing a causality assessment it should be considered whether for the purpose of clarity for all involved parties the clear definition of a binary system (causality excluded / causality possible) could be proposed in	

				this guidance. In practice, it turns out to be difficult for the investigators to differentiate between four or more scaling levels for causality. Furthermore, defining a binary system would eliminate the gray area for "unlikely" related events, which – depending on the sponsor's rationale - are partially already considered as related (and thus, as an adverse reaction) and partially are considered as not related (and thus, as an adverse event only). The guideline ICH E2A / 3.A.1., which is referenced here, does not provide useful guidance for this issue. The report of CIOMS working group VI recommends that the investigator be asked to use a binary decision for the drug causality (related/not related) for serious adverse events (chapter IV).	
8. *WG-CTL*	**4**	**4.3.3.** **44. &45.**	**7**	There appears to be no rationale for seeking the investigator's assessment of expectedness of an SAE and it remains unclear why this task should be accomplished by the investigator. The sponsor is to be considered to be the central point where all information on the safety of an IMP is continuously bundled and thus should be considered to be the only party to perform the expectedness assessment. The administrative burden for the investigator to review in detail the IB and/or SmPC in order to accomplish this task cannot be justified by any improvement in patients' safety as the required assessment of expectedness will be performed by the sponsor anyway and in a much more profound manner.	
9. *WG-CTL*	**4**	**4.6** **51.**	**8**	"…or under the provisions on pharmacovigilance as set out in Directive 2001/83/EC." We think Regulation 726/2004 should be included in this sentence as well	"…or under the provisions on pharmacovigilance as set out in Directive 2001/83/EC **and Regulation 726/2004, respectively**."
10. *WG-CTL*	**4**	**4.7.1.2.** **60, 61.**	**9-10**	The foot notes should refer to the ICH E2B (R3).	

11. *WG-CTL*	**4**	**4.7.3.1.** **73 line 3**	**11**	"…accordance with section 6.2 of this detailed guidance towards 'enhanced functionalities…." The "enhanced functionalities" are described in 6.3	"…accordance with section **6.3** of this detailed guidance towards 'enhanced functionalities…."
12. *WG-CTL*	**4**	**4.7.3.2.** **74. to 76.**	**11-12**	It is appreciated that two options for reporting to EVCTM are offered, since the establishment of a connection to EVCTM involves a high workload. This represents, in particular for small companies/institutions, a much higher workload than the SUSAR reporting by fax. However, we think that there should be clearer rules as to when member states should allow indirect reporting to EVCTM, i.e.: - Non commercial trials - Studies sponsored by small or medium sized companies.	
13. *WG-CTL*	**4**	**4.7.3.2.** **76** **Last bullet**	**12**	Delegate direct reporting to another person (outsourcing)	Delegate direct reporting to another person **or company** (outsourcing)
14. *WG-CTL*	**4**	**4.7.3.3.** **80.**	**12**		In the second line it should read "**EVCTM**" instead of "ECVTM".
15. *WG-CTL*	**4**	**4.7.3.3.** **81.**	**13**		In the third line it should read "**EVCTM**" instead of "ECVTM".
16 *WG-CTL*	**4**	**4.9.** **89.**	**14**	This rule is appreciated. However, it should be clarified that besides NCAs (and investigators) the ECs are the only addressees of SUSAR reports and that other institutions (e.g. in Spain: Comunidades Autonomas) should not need to be included in the SUSAR notification by the sponsor.	Add a new line: **Beside reporting to NCAs, ECs and investigators, the EU member states should not require reporting to any other**

					institution.
17. *WG-CTL*	**4**	**4.10.** **90, 91**	**14**	A clear statement as to the investigators should receive aggregated line listings of SUSARs and that the blind should be maintained would be much appreciated (actually like it used to be in the "old" guidance)	Paragraph 91 should read like this: **Reporting of SUSARs to investigators should take the form of aggregated line listing of blinded SUSARs.**
18. *WG-CTL*	**4**	**4.11.1.** **94.** **Line 7**	**14**	Investigators should not have access to unblinded information unless this is required for an individual investigator in the case of an emergency, for a specific subject. This should become clear from this guidance.	Paragraph 94 should be read like this: "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."
20. *WG-CTL*	**5**	**104.**	**16**		It should read "… and the Ethics Committee **issuing the 'single opinion' in accordance with Article 7 of Directive 2001/20/EC of the Member State concerned**."
21. *WG-CTL*	**6**	**Section 6**	**16 - 17**	In this section it should be pointed out that the rules for validation of ICSRs should be uniform throughout the EU NCAs. No specific national rules from NCAs should apply for the technical validation of ICSRs.	

2. General comments

None