BfArM
Federal Institute for Drugs
and Medical Devices

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**Consolidated comments of
the Federal Institute for Drugs and Medical Devices (BfArM),
the Paul-Ehrlich-Institute (PEI) and
the Federal Ministry of Health (BMG)**

To

**The Commission's Public Consultation Document
"Draft detailed guidance on the collection, verification and
presentation of adverse reaction reports arising from clinical trials on
medicinal products for human use ('CT-3')"**

2.3. (18) "…..that are identified as not required immediate reporting in the protocol or the investigator's brochure ('IB')."
Instead of making reference to the investigators brochure it might be better to refer to the approved reference safety document such as investigator's brochure ('IB') or summary of product characteristics ('SmPC').

2.3.2. "…serious adverse event, as well as possible guidance in the IB."
The possible guidance should preferably in the clinical trial protocol rather than in the IB.

4.3.3. (43) Please replace 'product information' by 'reference safety information' (RSI), which should be specified as suggested by AFSSAPS:
"RSI is:

- The investigator's brochure in effect at the start of the reporting period (see section 5), for a medicinal product not authorised in any member state.
- The summary of product characteristics for an authorised IMP in any MS which is being used in the clinical trial according to the terms and conditions of the marketing authorisation ('MA').
  If the IMP has a MA in several MSs with different SmPCs the sponsor should select the most appropriate SmPC, with reference to the patient safety, as the reference document for assessing expectedness.

The RSI is the same for the whole clinical trial in all the MS concerned. It is clearly identified in the protocol and in the cover letter and attached to the CTA."

4.3.3. (44 and 45) Interpretation of both paragraphs might be inconsistent. We suggest merging both paragraphs into one resulting in:

“if both sponsor and investigator disagree in the opinion of expectedness, both opinions should be reported.”

4.4. (46) There are no provisions how to handle SUSARs that occur in a trial with the same active substance exclusively in other EU/EEA-countries under the responsibility of the same sponsor. Such SUSARs should also be subject of expedited reporting to the Member State where the trial is run in parallel.
Following wording for second bullet point is proposed:

- all SUSARs related to the same active substance (independent of pharmaceutical form and strength) in a clinical trial performed exclusively in other EU or third countries, if …

4.5. (48) [also paragraphs 4.2.1 (28), 4.6. (51), 4.11.3. (99)]
NIMP without interaction to IMP are not subject of reporting.
Unexpected serious adverse events related to *non approved (in the EU)* NIMPs should be subject of expedited reporting to the concerned MS/NCA, since they may jeopardise the safety of the clinical trial participants.
Since the term adverse reaction is only linked to IMPs, we suggest to use the term ‘unexpected serious adverse events related to NIMP’.

Further, the reporting of adverse events of NIMPs is in alignment with the Guidance on the Investigational Medicinal Products (IMPs) and other medicinal products used in Clinical Trials (EudraLex Vol 10, Ch III: section 3.4. Adverse drug reaction related to NIMPs). This is also supported by the fact that there is no obligation to compile a DSUR for a NIMP since it is not a drug under development.

Proposed wording (first bullet point)

- Adverse **events** not related to the IMP received by the subject….

Adding proposed new bullet points:

- Adverse reactions related to a non-IMP received by the subject shall be reported by the sponsor of that trial if the non-IMP is not an approved drug in the EU.
- If the non-IMP is an approved drug in the EU the sponsor shall forward a fully documented ICSR to the MAH of the non-IMP that shall report the ADR in accordance with the provisions laid down in Directive 2001/83 as amended.
- Adverse reactions related to interactions between IMP and non-IMP shall only be reported by the sponsor. The sponsor shall send a fully documented ICSR to the MAH of the non-IMP.

4.7.1.2. (60) In case studies which are exclusively performed in third countries a valid EudraCT number is not available, therefore the input into EVCTM should be possible with sponsor study number only. The minimum criteria should also include the active substances for the suspect or interacting IMPs .

4.7.2.1. (64) The wording is misleading and needs to be clarified. There is no additional day 0 for the additional 8 days.

4.7.3.2. (74, 75) If a Member State establishes direct reporting obligations it has to be ensured that all SUSARs (not only SUSARs occurring in that Member State), i.e. initial and follow-ups according to section 4.4., 4.7.1 and 4.7.2, are submitted directly to the Member States where the trial is conducted.

2nd bullet point of 75 might be extended to "… enters this information into EVCTM (hereinafter referred to as 'indirect reporting'). The national competent authorities of the Member States concerned are then informed through EVCTM."

A mix-up of direct and indirect-reporting depending on the occurrence of an ADR needs to be avoided. In any case there should be clear rules for responsibilities.

In addition, it should be clarified how the reporting through EVCTM to all concerned Member States (NCAs) will be processed. There also should be more details with regard to lag-times (e.g. technical due to processing of new input or interface with EudraCT, and so on), format, reporting, and so on of this subsequent forwarding; See chapter 6.

It should be defined in detail what is meant by "reporting through EVCTM". We understand or expect an immediate forwarding to all concerned MS. In any case it should be ensured by the Agency that all SUSARs are forwarded without delay. This might also be applied to the transitional phase.

4.7.3.2. (76) With regard to the sponsor, we would like to suggest that a differentiation is needed between commercial and non-commercial sponsors as well as small enterprises. Only for the later two the paragraph 76 should be applicable.

Proposed wording for the 1st bullet point:
"where this possibility is provided by the Member State concerned and when the clinical trial is only conducted in that Member State or the SUSAR occurred in that MS, use the possibility of indirect reporting;"

4.7.3.3.
All parties involved might be well advised to perform the transitional reporting procedures – see paragraph 77 and 78 - as long as necessary to ensure sufficient reporting to MS concerned and to build up confidence - meaning the transition phase might even be longer than up to the time when the EVCTM might has reached the specified functionalities.

(77) It should be pointed out here that the reporting to MS concerned should always be performed independent of the type of EudraVigilance reporting chosen.

(79) In analogy to paragraph 75 the MS may determine the type of reporting (direct versus indirect).

4.7.3.3. (80, especially 81)
With regard to studies exclusively performed in third countries the way of reporting should be direct. Only in cases where the sponsor is not able to report directly, an indirect reporting should be possible. In this case a MS concerned by another CT with this IMP, which offers indirect reporting for third country SUSARs might be chosen.

Proposed wording (replace no 80 and 81): “If the SUSAR occurred in a third country the sponsor ensures that the SUSAR is reported to EVCTM through direct reporting in addition to reporting to the Member States according to the provisions laid down in section 4.4., 4.7.1 and 4.7.2.”

4.8. Reporting of non fatal and non life-threatening SUSARs should be identical to 4.7., especially the content of initial and follow-up reporting. One exception is the timeframe of initial reporting of 15 days only.

4.9. (89) It should be pointed out that according Article 17(3)(a) of Directive 2001/20/EC Ethics Committees (EC) do not have access to EVCTM, since this database is only accessible for the Commission, the Agency, and the NCAs.

4.10. (91) Adding a time frame for providing the line listings would be appreciated. We would like to suggest quarterly reports.

4.11.1. It should be emphasised that blinded reports are under no circumstances acceptable.

4.11.1 (95) It should be clarified that also in these types of clinical trials any fatal or life-threatening event must be assessed whether it is IMP related or not, in order to detect potential SUSARs early. Classifying these types of events as endpoints does not dispense the sponsor from his obligation to report according Article 17 of Directive 2001/21/EC.

4.11.1 (96) For such trials we suggest to replace the term ‘strongly encouraged to appoint’ by ‘shall appoint’.
The paragraph should be amended that composition and operation of the DMSC should be either provided within or appended to the protocol or as an additional charter document attached to the CTA.

5. (105) As the ICH E2F mainly addresses commercial sponsors as well as MA holders it should be emphasised that these reporting obligations are also

applicable for non commercial sponsors. Reference to the DSUR templates for non commercial sponsors should be made.
It should further be noted, that for clinical trials of short duration (less than 1 year) the safety report may be included in the summary of the clinical trial report.

6. (see also 4.7.3. (73)) We fully endorse the need to improve EVCTM. The 'basic and enhanced' functionalities should cover the NCA's description of needs for SUSAR assessment delivered by CTFG.

We would like to propose – in analogy to the pharmacovigilance of authorized medicinal products (as in review of the Regulation 726/2004)– the following wording:
'The Agency, in collaboration with the National Competent Authorities of the Member States, represented by the CTFG and the Commission, should draw up the functional specifications for the EVCTM database, together with a timeframe for their implementation.
The Agency should prepare an annual report on the EVCTM database and send it to the European Parliament, the Council and the Commission. The first annual report shall be prepared by [date to be inserted, xy year/s after entry into force of this Guideline].
The Management Board of the Agency shall on the basis of an independent audit report that takes into account the agreement of the CTFG and (the majority) of the NCAs/MSs, confirm and announce when full functionality of the EVCTM database is achieved and the system meets the defined functional specifications mentioned in the first subparagraph.
Any substantial change to the EVCTM database and the functional specifications should always take into account the recommendation of the CTFG.'

Nevertheless, we would like to suggest removing section 6 from this guidance document – only adding the above proposed paragraph - , since the guidance focuses on the sponsor's obligations and section 6 provides only functionalities of EVCTM for the NCAs.