afssaps
Agence française de sécurité sanitaire des produits de santé

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Afssaps response to the Commission's consultation detailed guidance on the collection, verification and presentation of adverse reactions reports arising from clinical trials on medicinal products for human use (CT3)

Afssaps fully supports the project of short-term improvements and clarification of the European clinical trials safety monitoring system and is pleased to submit comments on the draft corresponding guidance.

1. General comments

1.1. The new guidance is certainly shorter than the previous one as it gives reference to other available and applicable guidelines rather than detailing all practical issues in only one document. This option has been chosen by the Commission in order not to duplicate documents; however it may be difficult for some sponsors such as academic sponsors or SMEs to find easily all the information referred to in the guidance (i.e. ICH documents). Furthermore, the previous guidance detailed roles and responsibilities of sponsors and we think that it is a valuable information to be maintained in the document.

1.2. The guidance should have clarified the role of the national competent authorities (NCAs) and of Ethics Committees (EC) in clinical trials safety monitoring.
Their roles can be derived from the directive but should be clearly identified in the document.
As it is the responsibility of NCAs to ensure public health, as only NCAs have access to Eudravigilance database, as only NCAs can inspect Clinical Trials (CT) and only NCAs can suspend or stop a CT, then the responsibility to assess CT safety data is for the NCAs. EC is responsible for assessing ethical aspects of CTs. There is a need for the 2 bodies to communicate.

1.3. What SUSARs ECs are supposed to receive is not clear in the guidance. Although we understand that the Commission guidance is supposed to stick to the directive, no detail is given: should ECs receive on an expedited basis only the SUSARs occurred in the trial for which they gave the opinion? Only those occurring in their territory? All the SUSARs that NCAs will also receive?
Furthermore, the ECs' objectives on the issue of SUSARs is not clear and should be discussed. In France, ECs are supposed to decide whether or not a change of the informed consent is necessary, implying communication between EC and the NCA who assesses data.

1.4. The guidance should more clearly distinguish the expedited reporting procedures (sections 2 to 4) and the periodic safety reporting (section 5).

1.5. The guidance introduces the Development Safety Update Report (DSUR) that should replace the Annual Safety Report when the ICH E2F guideline is published and implemented.
On that point, we would suggest the Commission:
- to publish also the templates of DSUR for non commercial sponsors, as an attachment of the guidance.
- to organise a centralised declaration of the DIBD (development international birthdate), and to give further details on when (at the time of the CTA application), by whom (sponsor) and how (in EudraCT or EV-CTM) the DIBD has to be notified.
- to organise a single European electronic repository of DSUR in order to simplify the process.

Our opinion is that all these proposals can be set up within the guidance, without changing the directive.

1.6. We fully endorse the need to improve EV-CTM functionalities in order to make it the single CT safety database in Europe.
We strongly support that the description of the national competent authorities should be provided by the CTFG.
However, further provisions should be given in the guidance regarding
- how and when sponsors should populate EV medicinal product dictionary;
- how and when EudraCT and EV-CTM will be linked.

1.7. Some other safety issues not falling within the definition of SUSARs may require rapid communication to regulatory authorities (this is the wording of chapter 3A2 of ICHE2A guideline) because they might influence the benefit risk assessment of the IMP or of the CT, such as lack of efficacy, major safety issue from non clinical studies, overdose…
Those events are not SUSARs and they may not require a urgent safety measure by the sponsor nor a substantial amendment nor an early termination of the CT as stated in Section 4.11.3.

These are the reasons why we would like to stress again the need that these information are reported to NCAs, as it is currently performed in accordance the guidance and the ICHE2A guideline.

2. Detailed comments

2.1. Indirect reporting: we understand that 3 options should be offered to Member State (MS) to organise SUSARs reporting in EV-CTM. Regarding SUSARs from 3rd countries, we do not agree with the option that lets the sponsors choose the MS who will enter those SUSARs in EVCTM, since some MS (for instance France) will not be able to offer such an option. The wording should be modified and replaced by “or chose any on MS concerned which offers ensuring indirect reporting” (paragraphs 80 and 81).

2.2. What SUSARs to be reported?

- As over - reporting is one of the most important issue, it should be said clearly that SUSARs to be reported are only those related to IMP.
- The choice of the reference safety information (RSI) needs further clarification:
  - Replace “product information” by “reference safety information” (section 43)
  - Clarify that the RSI is:
    - The investigator’s brochure in effect at the start of the reporting period (see section 5), for a MP not authorised in any member state (MS).
    - The summary of product characteristics for an authorised IMP in any MS which is being used in the CT according to the terms and conditions of the MA.
      When the IMP has a MA in several MS with different SMPc, the sponsor should select the most appropriate SMPc, with reference to 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 in an acceptable language.
  - Paragraph 60: it is not clear whether the “relevant information” detailed in this paragraph corresponds to the “minimum reporting criteria” mentioned in paragraph 56 (we guess yes so harmonisation of wordings in necessary). Furthermore, it should be précised that all the criteria are needed. The valid EudraCT number is required “if appropriate”, since not all CTs have an Eudract number.

- Section 4.7.1.2. “content of initial reporting” and section 4.7.2.2. “content of follow up information” concern not only life - threatening SUSARs (section 4.7) but all SUSARs (section 4.8): so, they should cover the 2 types of SUSARs and not be limited only to one of them.

- Section 4.11 should clearly states that only unblinded SUSARs are to be reported by the sponsor to NCAs and to EV-CTM, as a general rule. Furthermore, for trials in high morbidity or high mortality disease we should have further information on how to get a common agreement by all NCAs concerned in the case of multinational CTs (section 95)

We hope these comments are useful for the Commission to bring further harmonisation in the implementation and understanding of the CT directive.