Dear European Commission

Thank you for the opportunity to provide our input to the new CT-3 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).* We look forward to reading the final draft.

We have a few comments and you may make our suggestions/comments public.

1. General

We are pleased to know that the EC is combining the three documents (CT-3, CT-4, and the Q&A), making the new document the central document for guidance on how to handle adverse reactions in clinical trials. In doing so, one must recognize the importance of ensuring that the information is accurate and complete.

2. 'Participant' compare to 'Subject' and 'Patient'

People who agree to take part in clinical research do so by signing an informed consent form. Informed consent may be sought from a person who is either a patient (phase II to IV) or a volunteer. It is a personal decision to play an active role in the clinical research project (Chalmer 1999). The term 'subject' suggests that this role is passive, unimportant, not self-governing and that the person is inferior. Furthermore, the term has connotations with subservience and non-consent. Clinical research participants may be patients; but people do not choose to be patients, whereas they can choose to take part in clinical research. Participants in clinical trials do not receive treatment but rather either an investigational or control intervention. So the use of the term 'patient' in a research setting blurs the distinction between treatment and healthcare with investigation. The European Clinical Research Infrastructures Network (www.ecrin.org) advocate the use of the term "participants" and not 'patients' or 'subjects'.

Reference: Chalmers, I. People are "participants" in research. *BMJ* 1999; 318:1141 (24 April). http://www.bmj.com/cgi/content/full/318/7191/1141/a?view=long&pmid=10213744

3. Determining of SUSAR

The information on who is ultimately responsible for determining if a SUSAR has occurred appears to be unclear.

On line #34 of the new CT-3, it states:

…*unexpectedness of an adverse reaction is determined by the sponsor according…*

But, on line #45 of the new CT-3, it states:

…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 be provided with the report…

4. Ensuring of SUSARs to CA

According to Article 17 (1) of the Directive 2001/20/EC, the sponsors are responsible for ensuring that all SUSARs are reported to the CA and Ethics Committee of their respective Member States. In line # 71-76, the sponsors are to report the SUSARs via EudraVigilance Clinical Trial Module (EVCTM) and EudraVigilance will forward the reported case to the respective CA (line #73). Our concerns are:

- It is unclear how EudraVigilance inform the sponsor that the reported SUSARs have been received by their respective CA

- It is unclear whether EudraVigilance will also forward the reported SUSAR to the respective Ethics Committee.

5. Transition period

In the new CT-3 line #77-81, during the transition period, the sponsors are to report the SUSARs directly to their CA and EC. Our concerns are:

- It is unclear to the sponsor how long 'transition period' is? What is the estimated timeline for the new guideline to be published?

- It is unclear how EudraVigilance avoid receiving duplicate reports of SUSARs.

6. Access to and analysis of SUSARs

Accurate and sufficient report of harm (as well as benefit) in clinical trials is very important for evidence-based medicine and it makes good clinical practice. Unfortunately, it is well researched that reporting of harm in clinical trials is insufficient (Ioannidis 2009, Pitrou, 2009). The new CT-3 document is contributing to the improvement of adverse events reporting by emphasizing the importance of collecting harm information and establishing a centralized location for reporting of SUSARs (hence the EVCTM). We encourage the EC to provide guidance on how harm data (e.g., SUSARs) can be made more transparent to the public. The new CT-3 does not seem to expand on this issue. For instance, it is unclear how the EudraVigilance, once the SUSARs are the received, make the reported SUSARs public for interested researchers to conduct analysis nor if there is a clear explanation on what the EudraVigilance does with the reported SUSAR beside forwarding them to the respective CA.

Reference:

Ioannidis, JP. Adverse events in randomized trials. Neglected, restricted, distorted, and silenced. *Arch Intern Med*. 2009;169 (19):1737.

Pitrou, I, Boutron I, Ahmad N, Ravaud P. Reorting of safety results in published reports of randomized controlled trial. *Arch Intern Med.* 2009;169 (19):1756-1761.

Regards,

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On behalf of

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