Item / Section number	Comment
Item 41	There may be situations where the investigator does not provide a causality assessment for a serious adverse event despite (repeated) requests by the sponsor, e.g. he does not give any assessment, or in his opinion the causality is "unassessable". If in such a situation the sponsor's assessment of causality is "no reasonable causal relationship" and the event is unexpected, is the event reportable as a SUSAR?
Item 45	What was the rationale for including the investigator in the determination of expectedness? The concept of expectedness, while fundamental for pharmacovigilance in clinical trials, may be less familiar to the investigator with his mainly clinical perspective. There may be a risk that the investigator considers events as "expected" in the sense of "anticipated" for the individual patient or the disease under treatment, rather than "expected" in the regulatory sense for the IMP. It is unclear what information would be contributed to an individual case by adding the investigator's opinion on expectedness.
Items 48, 51, 52	It is clearly stated that adverse reactions not related to the IMP but to a non-IMP (NIMP) are not reportable as SUSARs from the concerned clinical trial. However, if the sponsor is the MAH for the NIMP, do serious adverse reactions to the NIMP occurring in the concerned clinical trial have to be reported according to Regulation 726/2004 or Directive 2001/83/EC? If the sponsor is not the MAH for the NIMP, does he have to notify the MAH of the serious adverse reaction to the NIMP to allow expedited reporting by the MAH?
Item 75	The options of direct and indirect reporting may lead to different reporting approaches among the member states (MS) in which the study is conducted. We propose the following approach for consideration: For all SUSARs regardless of origin from EU or Non-EU, we suggest direct reporting by the sponsor (or partner, or delegate) to EVCTM only, and distribution by EVCTM to all concerned MS including the MS where the SUSAR occurred.
Item 78	Does the "clinical trial performed exclusively in another Member State" refer to one single other MS, or does it include trials performed in several other MS? Does this section also refer to trials performed in another MS/ other MS plus a non-EU third country?

Item / Section number	Comment
Section 4.7.3.3, item 78	We understand that after the transition phase there will be no need to report SUSARs from another clinical trial conducted in another/ other Member State(s) to the Member States participating in the concerned trial due to availability of the enhanced functionalities. Is this understanding correct?
Item 89	According to this section, SUSARs are only reportable to the Ethics Committee issuing the "single opinion" (concerned EC) of the Member State where the event occurred. In the 2nd revision of the Detailed Guidance ENTR/CT3, a strong recommendation is made to inform the concerned ECs about other SUSARs at least every 6 months (with a copy to the competent authorities concerned). Will this approach now be abandoned? This would mean that concerned ECs will only be informed about domestic SUSARs.
Item 91	Is expedited reporting of individual SUSAR reports to investigators an alternative to periodic SUSAR reporting?
Item 94	It is not clear why investigators are mentioned twice in this section, at first to be maintained blinded, subsequently to receive unblinded information.
Item 97	In contrast to section 5.1.8 of the 2nd revision of the Detailed Guidance ENTR/CT3, there is no mention of reassessment of expectedness after unblinding if the product administered is a comparator. What is the rationale for this?
Section 4.11.3	In contrast to section 5.1.1.2 of the 2nd revision of the Detailed Guidance ENTR/CT3, there is no elaboration on other safety issues requiring expedited reporting. In particular, there is no mention of • SAEs related to study conduct or study procedures • Anticipated end or temporary halt for safety reasons of a trial conducted with the same IMP in any other country by the same sponsor • Safety relevant DMC recommendations Are all these aspects to be considered as covered by the term "events/other observations" that may require action to protect the safety of the subjects?