EORTC comments to the public consultation document CT-3

Page	Article	Comment
Page 4	Article 2.2.2, 14	The seriousness criterion is still "it requires hospitalization or prolongation of existing hospitalization". The "Inpatient" is not mentioned as it is in: - In "ICH Topic E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting", it's "requires inpatient hospitalization or prolongation of existing hospitalization". It can look minor but it has an impact on the collection, the querying and thus the procedures. Please specify which definition of hospitalization should be used? - In Directive 2001/20/EC, it's "requires hospitalization or prolongation of existing hospitalization" - In "Detailed guidance on the collection, verification, and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use", it's "requires hospitalization or prolongation of existing inpatients' hospitalization Or the one of ICH E2A?
Page 4	Article 2.3, 18	IB is not the only reference document: Ref CT- point 58: 58. The IB as last amended and approved by the national competent authority or equivalent document (e.g. SmPC for marketed products) serves as the reference safety information for the assessment of the expectedness of any adverse reaction that might occur during the clinical trial. Please adapt this section e.g.: The investigator has to immediately report all serious adverse events with the exception of those that are identified as not requiring immediate reporting in the protocol or the reference document (e.g. the investigator's brochure ('IB'), summary of product characteristics ('SmPC') or guidance document for therapies other than medical products). It would be greatly appreciated if an example would be given here, is it e.g. "A hospitalisation which was planned before the patient consented for study participation and where admission did not take longer than anticipated"?
Page 5	Article 2.3.2	This is the first time we see a dichotomy between immediate and non immediate reporting. Is this a new feature? Does non

		immediate reporting represent the standard AE reporting or is it something intermediate between SAE and AE? If so this adds to the confusion on how to define a 3rd category. Or does it refer to the "other safety issues requiring expedited reporting"? This section is very unclear and confusing. What is considered as the "appropriate timeframe"? What kind of guidelines should be specified in the reference document? In cases where reporting is not required immediately (see section 2.3) the investigator shall report within the appropriate timeframe taking account of the specificities of the trial and of the serious adverse event, as well as possible guidance in the reference document ~~IB~~
Page 6	4.2.3, 33	"If not only nature but also intensity (severity) should be taken into account while deciding if SAE is an SUSAR". Please be aware that the info on severity is usually not mentioned in IB or SmPC.
Page 6	4.2.3, 34	The rules for use of IB or SmPC as reference docs in point 32 are incomplete and confusing: In point 34 reference is made to the detailed guidance CT1. There (CT1, point 56) it is stated that "The approved SmPC maybe be used in place of IB if the IMP ……. is used according to terms of marketing authorization. This is for me missing in CT 3 article 4.2.3. More explanation could be given e.g. on what should be currently used as reference in trials w/ drugs used in new indication or at higher dosages and/or different schedules? Could non-commercial sponsor in these types of trials have the possibility to choose between IB or SmPC depending if it is performed with one brand product (i.e. use IB if provided by the involved company/MAH), or if it is performed with different brand products containing the same active substance use single SmPC? Would this flexibility be Ok as long as CAs of countries participating to the trial uniformly approved the protocol and reference documents that are listed in this protocol?
Page 6	4.3.2, 37	Sponsor should ensure that only AR are reported: What about the SAEs which could be associated with the trial procedure?
Page 7	Article 4.3.2, 40	Causality assessment should always be made by the investigator: The assessment of causality is ~~often~~ made by the investigator. On the role of the investigator's assessment of the causality, reference is made to chapter 3A1 of the note for guidance ICH E2A.

Page 7	Article 4.3.3, 43	The 'expectedness' of a serious adverse reaction is assessed in the light of the applicable product information (e.g. IB or SmPC or guidance document for therapies other than medical products).
Page 7	Article 4.3.3, 45	This part seems to be a copy of point 41. It is the sponsors' responsibility to assign an expectedness and not the investigator. Changing this responsibility could lead to a lot of problems
Page 7	Article 4.3.3, 45	Please also give advice on how expectedness should be performed in trials with multidrug regimens when multiple drugs are administered at the same time (or is there a separate guideline on that)?
Page 8	Article 4.6, 50	Volume 9A instead of Volume 9
Page 11	Article 4.7.3.1, 71 and 74	In 4.7.3.1 it says that the addressee of the SUSAR is the concerned MS but in 4.7.3.2 , it indicates that it goes to all MS concerned, though through the EVCTM. This can be confusing. There should be one rule, once EVCTM is able to forward the cases to the MS, not to all MS, but only to the MS where the event occurred. The other MS can view the info via the data warehouse tool. If direct and indirect reporting is still possible at the same time, this will lead again to double reporting and confusion.