Gilead Sciences International Limited comments on the 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"

Page and section number	Gilead Comment	Proposal
General Comments	The document is poorly presented and references many associated guidances, therefore it is no longer a stand alone guide for users.	The original document layout was logical and consistent – revision to that would have been easier rather than complete rewrite. Relevant definitions and text should be included in this document and not just cross-referenced; for example, the definition of adverse event – why not include rather than refer to ICH E2A when other definitions are included?
Page 2:1.2 line 4	The scope is defined as clinical trials as defined in 2001/20 and performed in at least one member state.	Please state within scope that it covers all *interventional clinical trials* and reinstate the language from the original guidance that clarified that it covered all IMPs, independent from their market authorisation status and whether or not used under the conditions of their market authorisation.
Page 3: 1.3 line 6	There are no definitions under the heading definitions and they follow in the section relating to the investigator below.	Move definitions or text referring to definitions to this section and retain the Annex 1 from the original CT-3.
Page 3: 1.3 line 7	Reference to implementing guidelines is out of context under a heading of definitions.	Delete as at best is a reference and should be added as such.
Page 3: 2 Lines 10 & 11	The heading is misleading.	The heading should clarify that this relates to investigator responsibilities with regard to

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	The document is inconsistent in when it includes or cross references text from associated regulations, directives or guidances.	reporting to the sponsor. The proposed inclusion of text in line 10 is not required and line 11 relates to the sponsor not the investigator. Original text from CT-3 regarding recording and evaluation of AEs (4.2.2) and assessment of seriousness (4.2.3) and causality (4.2.4) should be included under this section regarding investigator responsibilities.
Page 3: 2.2 Line 12	This is duplicated in 2.2.2 line 14.	Remove duplication and retain definitions in annex 1 as in current guidance.
Page 4 line 15	It is not clear what the intent behind this sentence is – please clarify.	
Page 4 line 16 and 17	As above.	Place all clarifications associated with definitions in annex 1. Retain specificity and severity language with definition as later appears under sponsor responsibilities. Retain text about death in the context of if the event posed a risk of death as in the current guidance.
	Is there any plan to extend seriousness criteria to those events that arise from transmission of infectious agents in clinical trials?	
	Is there any plan to provide clinical trial guidance in the context of overdose,	

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	medication error, pregnancy regardless of SAEs being reported and product complaint reports with SAEs – even if not regulatory reported but reported to the sponsor.	
Page 4: 2.3 Heading	Heading of extent and timelines was unclear	Focus text on timelines only.
Page 4: lines 18, 19, 20 and 2.3.2	The differences in reporting by investigators to sponsor was confusing and contradictory.	Text should require investigator to report all SAEs to sponsor no later than 48 hours or as defined in the study protocol.
Page 4: line 18	Reference to not requiring immediate reporting was vague and unclear – what did this mean to refer to?	Retain guidance from current CT-3 regarding management of data in morbidity/mortality trials (5.1.9) and consider including under sponsor rather than investigator responsibilities.
Page 5: 2.4 line 21	In a later part of the guidance an identifiable subject includes initials and date of birth.	Clarify if the intent in line 21 is that initials should not be used? Remove from later section of the document if that is the intent in line with data privacy E2B conventions re PRIVACY & UNKNOWN.
Page 5: 3 line 22	Reporting should be clear that this relates to the sponsor.	Heading should be recording rather than reporting as clarify that non-serious AEs are usually recorded in a case report form associated with the study, reviewed in aggregate and generally do not result in expedited reports to Concerned Member States.
Page 5: 4	Order hard to follow	Needs to flow from receipt, assessment, evaluation and reporting.

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Page 6: line 27	Clarity required	An ADR includes causality between the event and the IMP *in the context of this guidance as it pertains to clinical trials.*
Page 6: line 28	This is very unclear. It suggests a SUSAR is an unexpected SADR and only if it pertains to the IMP.	The guidance needs to be clearer as to what sponsors need to do with reports from non IMP data that is reported in the context of the study. Guidance with regard to comparators and other MAHs is lost from current guidance – even if sponsors report for signal detection purposes to other MAHs this needs to be included.
Page 6: line 33	There is no reference to specificity in the context of a SADR.	Include current guidance language regarding specificity and severity of SADRs.
Page 6: Line 35	Guidance states that SUSAR obligations continue beyond the end of the trial but provide no guidance for reporting.	Language such that SADRs and those that meet the criteria for SUSAR – should be reported by investigator to sponsor and sponsor to CA, if appropriate, regardless of the completion of the trial if a causal association is suspected and all other criteria are met.
Page 6: line 36	Confusing – any report sent as serious by an Investigator would never be downgraded and in clinical studies non serious AEs are not typically received by safety departments.	Delete this text.
Page 6: line 37	Confusing – if the Sponsor is responsible for submitting SUSARs – these are causally associated.	Align with reporting requirements and do not duplicate as risk of contradiction.
Page 7: Lines 40 and 41	Duplicative.	Align with investigator responsibilities as

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		mixed responsibilities captured.
Page 7: line 42	As above re line 36.	Align with reporting requirements and do not duplicate as risk of contradiction.
Page 7: Lines 44 and 45	Contradicts line 42. Investigators are generally not required to assess expectedness.	Delete 44 and 45.
Page 7: 4.4	With the new EU framework all events will be reported – in clinical trials assume no plans to send all SAEs and not just SUSARs.	Clarification required.
Page 7: line 46	Mother company and development agreements.	Please state affiliate or local operating company and confirm what is intended by a development agreement – is that a co-development partnership?
Page 7: Line 47	Please define and explain transitional arrangements.	
Page 7: Line 48 1st bullet	ADRs not related to the IMP and not interacting with the IMP not to be reported.	Clarification is required – should the Sponsor at least advise the other MAH if it is an SADR with their product? What if the non IMP or non IMP interacting product is the Sponsor's product? Ho will such data be reviewed? This suggests it goes nowhere.
Page 7: Line 48 2nd bullet	SUSARs from trials exclusively in the EU for which you are not the sponsor.	Please add clarity that not expedited to authorities but databased for signal detection purposes as Sponsor sends. Provide guidance for such scenarios where it is ex EU.
Page 8: 4.6 Lines 49-52	Is this not scope and is it required?	

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Page 9: Line 53	References ethics committee notifications under a heading for Competent authorities.	Please have discreet heading for the reports that have to go to authorities, ethics and investigators and the type of reports.
Page 9: Line 54	Clarity is required as to who reports to EudraVigilance CTM – authorities or study sponsors.	Clarification required.
Page 9: Line 56	Day 0 = Di0 is unclear.	Clarification required.
Page 9: Line 57	Why is reporting split into initial and follow up and what is meant by "relevant" in this context.	Clarify that all information should be reported in initial or follow up reports unless an administrative change and that is what it seems is intended here. Original guidance text was clearer.
Page 10: Line 62	Line 21 only references a unique number – now several elements are listed – what is required.	Clarification is requested.
Page 11: Lines 63-70	Very hard to follow what is required – seems overly complicated and could be aligned more with line 57 etc to flow better.	Original guidance was clearer.
Page 11: Line 73	As for line 54.	Clarification required.
Page 12: line 77	Clarity on the meaning and intent of transitional reporting – hard to follow.	Clarification required.
Page 12: Line 78	Clarification required on the meaning of mother company and development agreement.	Confusing so best to keep simply that it is always the study sponsor.
Page 13 Lines 82 through 88	Hard to follow.	If there are two different expectations until EVCTM is effective and upgraded the guidance would be better to have two discreet sections only and enter expectations in clear sub headings to that effect.

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Page 14 Line 89	Makes no provision for use of line listings to ethics committees, only SUSARS and makes no reference to the annual report.	Clarify line listings can be deployed and ethics should still receive ASRs.
Page 14 Line 92	As above rather than reference the E2A guidance it would be helpful to have relevant text.	Put text from E2A here as do in part in line 94.
Page 14 Line 94	Text needs punctuation or rewriting as could be read to mean investigators or those involved in evaluation should have data as need access.	Rewrite/punctuate.
Page 14 Line 95 - 97	Warrants a stand alone header Line 97 references 4.2.4 that does not seem to link with the topic referenced.	As in current guidance.
Page 15 Line 98	Clarity required regarding not reporting non IMP reactions and also reporting to MAH of a comparator or other drug seems to have been lost.	Align with current guidance or explicitly state reporting to other MAH not required.
Page 15 Line 99 - 102	Align with current guidance on other safety issues that may warrant communicating and add examples and not just the way of communicating.	Align with current guidance.
Page 15 Line 103	Note is made to reference of the DSUR which is assumed ICH guidance will provide a template for – no guidance is provided on format of listings in this draft guidance.	Include a listing annex.
Page 16 line 106 -109	Unclear on why database functionality is included in the guidance.	

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Other comments	Lacking or unclear in new guidance compared to current guidance: • What should not be reported – too vague and does not mention non-serious ADRs. • Clear delineation of responsibilities to authorities, ethics and investigators. • Format of SUSARs – lost on database functionality. • Clarity that substantial amendment etc is a means for form and format of other safety reports reporting (5.1.6.4 in current guide). • Definitions and abbreviations. • Content of line listings.	