Public consultation on re-written guidance on SUSAR (suspected unexpected serious adverse reaction) reporting during Clinical Trials

September 2010

Cancer Research UK welcomes the opportunity to comment on the re-written guidance on SUSAR (suspected unexpected serious adverse reaction) reporting during Clinical Trials. In our response to the consultation the Clinical Trials Directive (CTD) in January 2010, we welcomed the aims of the Directive but felt that these aims had not been fully realised and called for improved guidance (and other changes) in a number of areas, including SUSAR reporting. In particular, we raised the issues we have faced with SUSAR reporting in detail, particularly the administrative burden with little improvement to patient safety, and how we thought reporting could be improved.

We therefore welcome that this revised guidance has been published and we have the opportunity to provide comments. We have focused our response on the new guidance but we hope that this is an interim measure, and look forward to working with the Commission, the Medicines and Healthcare products Regulatory Authority (MHRA) and others to develop further improvements in the medium term.

About Cancer Research UK

Cancer Research UK (CR-UK)[1] is the world's leading charity dedicated to cancer research and the largest independent funder of cancer research in Europe. Over half of all cancer research in the UK is carried out by our doctors and scientists. Cancer Research UK's work is entirely funded by the public and in 2008/09 we spent £355 million on research, supporting the work of more than 4,500 scientists, doctors and nurses.

CR-UK funds research into all aspects of cancer from exploratory biology to clinical trials of novel and existing drugs as well as population-based studies and prevention research. Our scientists and doctors have made significant contributions to the development of half of the top 30 drugs used to treat cancer patients worldwide today. At CR-UK, we are involved with all stages of clinical trials, and we have a perspective both as a funder of academics conducting trials and as a sponsor of early phase trials.

Since CR-UK began funding trials in 1988, we have funded almost 300 therapeutic trials and more than 100,000 patients have taken part in these trials. In the same time period, the Drug Development Office (DDO) has sponsored and conducted over 100 early phase exploratory studies, with more than 2,000 patients entered on these trials. These exploratory studies were on new clinical agents, of which five have been taken to market by subsequent business partners.

[1] Cancer Research UK is a registered charity in England and Wales (1089464) and in Scotland (SC041666)

Acknowledgements

Our response has been collated following internal staff discussion and with contributions from the follow additional groups/individuals:

- Jabeen Ahmad, Head of Quality, Regulatory and Pharmacovigilance, and Catarina Macedo, Pharmacovigilance Manager, Drug Development Office (DDO)
- Julie Hearn, Head of Clinical Trials, and Silvia Grisendi, Clinical Trials Manager, and the Clinical Trials Units (CTU) Governance Leads

This response does not represent the views of any one individual or organisation listed above, but is the product of collaboration between all listed parties.

Comments

Our response to the consultation on the Clinical Trials Directive (in January 2010) included a call for SUSAR reporting to be changed, stating SUSAR reporting is an administrative burden that does not necessarily enhance patient safety. In particular, very large numbers of SUSAR reports are sent to all investigators in large trials for little purpose: their sheer volume makes it impossible to do anything other than scan and file them, and the chance of significant patterns being detected is not increased by simply sending them to every site. We called for the reporting system to be urgently changed to central scrutiny and risk assessment by the sponsor of the trial, which should be able to determine whether to alert investigators or not.

We also argued that SUSAR reporting is an administrative burden that does not necessarily enhance patient safety, especially where the drugs being tested already have an established safety profile, and that more recognition needs to be given to the role of the IDMC for monitoring patient safety within an individual trial.

We welcome the attempts to revise the existing EC guidance, but are concerned that additional clarification could introduce further administrative burden. We are also concerned that the guidance still does not go far enough in terms of distinguishing between the different types of sponsors (pharmaceutical company/drug manufacturer or university/hospital), or the different level of safety risk (i.e. a phase I/II testing a novel compound, rather than a phase III trial testing a licensed drug with an established safety profile but being tested in a new indication or treatment schedule) and would welcome a more thorough revision of the guidance.

We had a number of detailed comments on specific points of the draft revised guidance, which we have attached in a table in reference to the relevant section of the guidance. This includes comments, our rationale and where we thought it appropriate and helpful, suggestions on the guidance. In general, we found it extremely helpful that the guidance references International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines, in order to encourage international harmonisation.

We believe that in the longer term, resulting from the ongoing review of the Directive, more significant changes can be introduced that places a greater emphasis on risk assessment and reduces the burden on sponsors with safety. For example, we believe the reporting system should be urgently changed to central scrutiny and risk assessment by the sponsor of the trial, which should be able to determine whether to alert investigators or not.

We thank you again for the opportunity to provide comments and look forward to working with the Commission to develop further improvements to the Clinical Trials Directive. We have also provided comments on the draft guidance on harmonised requirements for non-investigational medicinal products (NIMPs) in CTA submissions and shared copies of both responses with the MHRA. If you would like to discuss these comments further, or have any queries, please do not hesitate to contact us (publicaffairs@cancer.org.uk).

Annex 1 - Cancer Research UK 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 (CT3)

The table below outlines Cancer Research UK comments on particular aspects of the guidance and where we thought it appropriate and helpful, suggested amendments.

No.	Section and Original Text	Comment, Suggested Amendments and Rationale
1	4. The scope of this detailed guidance is the scope of Directive 2001/20/EC, i.e. clinical trials as defined in Directive 2001/20/EC and performed in at least one Member State of the Union.	4. The scope of this detailed guidance is the scope of Directive 2001/20/EC, i.e. clinical trials as defined in Directive 2001/20/EC and performed in at least one Member State of the ***European*** Union. Rationale: For consistency within the document.
2	11. The purpose of this obligation is to ensure that the sponsor has the necessary information to continuously assess the risk-benefit balance of the clinical trial, in accordance with Article 3(2)(a) of Directive 2001/20/EC.	11. The purpose of this obligation is to ensure that the sponsor has the necessary information to continuously assess the ***benefit-risk*** balance of the clinical trial, in accordance with Article 3(2)(a) of Directive 2001/20/EC. Rationale: As per ICH E6, 'a trial should be initiated and continued only if the anticipated benefits justify the risks'. Therefore, philosophically the basis for the authorisation and continuation of a clinical trial is set, whereby benefits must always outweigh risks. Assuming that in a benefit-risk assessment, the benefit is the numerator and the risk is the denominator, it makes statements such as the 'benefit-risk is positive' logical. Consequently, the numerator should be bigger than the denominator and this balance should be positive. Furthermore, all CIOMS working group publications talk of benefit-risk. Given that these publications are made by highly regarded experts in their fields we would find it more appropriate to talk about benefit-risk, rather than risk-benefit. Volume 9A, for example, can be very confusing as it uses throughout risk-benefit. In an excerpt Volume 9A states: 'A medicinal product is authorised on the basis that in the specified indication(s), at the time of authorisation, the risk-benefit is judged positive for the target population.' Assuming that the mathematical convention is followed where the numerator precedes the

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		denominator, this statement from Volume 9A is confusing as it is stating the opposite of what it intends.
3	17. Medical and scientific judgement should be exercised in deciding whether an event is 'serious' in accordance with these criteria. Examples are provided in the note for guidance ICH E2A.	Comment: Very helpful clarification by referring to ICH E2 and the use of 'medical and scientific judgment' is also helpful.
4	19. The immediate reporting should allow the sponsor to take the appropriate measures to address potential new risks in a clinical trial. Therefore, the immediate report should be made within a very short period of time and under no circumstances exceed 48 hours following knowledge of the adverse event.	19. The immediate reporting should allow the sponsor to take the appropriate measures to address potential new risks in a clinical trial. Therefore, the immediate report should be made within a very short period of time and under no circumstances exceed ***24*** hours following knowledge of the adverse event. Rationale: We appreciate that the extension of the definition of immediate from 24 hours to 48 hours may seem like a helpful gesture. However, we consider that the changing the understanding of the concept of 'immediate' has many pitfalls. Globally, 'immediate' has been interpreted as 'within 24 hours'. This could result in confusion amongst ICH regions where the EU will be interpreting 'immediate' as 'within 48 hours'. In addition, 'immediate' in the post-authorisation setting will still be 'within 24 hours' and therefore it will unnecessarily open up a further gap between interventional clinical trial reporting requirements and post-authorisation reporting requirements. Given that there is a greater drive for integration of overall risk management and consequently reporting requirements, we would find it helpful if long standing conventions such as the interpretation of 'immediate' remain the same.
5	20. The follow-up report should allow the sponsor to assess in detail whether the adverse event requires a reassessment of the risk-benefit balance of the clinical trial, if those details were not already available and provided in the initial report.	20. The follow-up report should allow the sponsor to assess in detail whether the adverse event requires a reassessment of the ***benefit-risk*** balance of the clinical trial, if those details were not already available and provided in the initial report. Rationale: Same as for comment 2.
6	2.3.2 Non-immediate reporting In cases where reporting is not required immediately (see	2.3.2 Non-immediate reporting In cases where reporting is not required immediately (see section 2.3) the

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	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 IB.	investigator shall report within the appropriate timeframe taking account of the specificities of the trial and of the adverse event, as well as possible guidance in the ***protocol and/or*** IB. Rationale: We consider that the protocol rather than the IB should determine what is exempt from being reported as an SAE. In addition, we would find it more appropriate that these events are NOT called serious adverse events. Usually, if an event is exempt from being reported as serious (as per trial protocol and/or IB), these events are NOT marked as serious in the relevant databases. Otherwise, there would be no difference between these and the 'other' legitimate SAEs.
7	24. Article 17(1),(3) of Directive 2001/20/EC establishes the rules for reporting of suspected unexpected serious adverse reactions ('SUSARs') by the sponsor. 25. The purpose of these reporting obligations is to make regulators aware of SUSARs (cf. chapter 2C of the note for guidance E2A). This, in turn, is intended to give the relevant national competent authority and the Ethics Committee the possibility to • take measures to protect the safety of clinical trial participants; and • assess, in view of the various reported SUSARs, whether an IMP poses an unknown risk to the clinical trial participant.	• assess, in view of the various reported SUSARs, whether an IMP poses ***a potential*** risk to the clinical trial participant. Rationale: We consider that it is more correct to talk about potential risks, rather than unknown risks.
8	27. Thus, the definition of 'adverse reaction' includes causality between the event and the IMP.	27. Thus, the definition of 'adverse reaction' ***suggests some degree of causal relationship*** between the event and the IMP.

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		Rationale: We consider this more accurately describes the definition of adverse reaction.
9	28. An untoward and unintended response to a non-IMP (e.g. concomitant medications, background treatments, rescue medications or challenge agents) which does not result from an interaction with an IMP is, by definition, not a SUSAR.	Comment: Very helpful clarification, which should be kept.
10	4.2.3 Unexpectedness	4.2.3. ***Expectedness*** Rationale: Section 4.3.3 is entitled 'Expectedness'. Therefore, whole document should use same terminology for consistency. In addition, CIOMS VI also refers to this topic as expectedness.
11	34. The unexpectedness of an adverse reaction is determined by the sponsor according to the reference safety information. In this respect, reference is made to the detailed guidance CT-1.	34. The ***expectedness*** of an adverse reaction is determined by the sponsor according to the reference safety information. In this respect, reference is made to the detailed guidance CT-1. Rationale: Same as in comment 10 (above).
12	35. The definition of SUSAR is independent of whether the clinical trial has ended ('post-study SUSAR') or is still ongoing. The obligations related to SUSAR reporting do not finish with the end of the trial.	Comment: This is a helpful clarification. There is guidance in ICH E2B that relates to post-study events, which could be referenced here (Section III.E.3).
13	37. The sponsor is responsible for ensuring that only adverse reactions, i.e. causal events, are reported.	Comment: We would prefer to see this statement removed from the document. Rationale: We consider that the danger of under reporting is far greater than that of over-reporting. Also, when in doubt sponsors should report. We consider statements discouraging reporting confusing and unhelpful.
14	38. On the other hand, it is acknowledged that in some cases it is difficult to establish with absolute certainty that an event is causal.	Comment: We would prefer to see this statement removed from the document. Rationale: Causality is not about certainty, causality is about suspicion.

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		Therefore, this statement is incorrect and unhelpful in that it somehow creates the false concept that causality implies certainty. It does not.
15	39. To avoid over-reporting while, at the same time, ensuring that relevant events are reported, a 'reasonable causal relationship' should suffice. Chapter 3A1 of the note for guidance ICH E2A provides further information on the terms and scales used in this respect.	39. Chapter 3A1 of the note for guidance ICH E2A provides further information on the terms and scales used regarding ***causality assessment***. Comment: We would prefer to see this statement removed from the document. A straight reference to ICH E2A without side comments seems more appropriate and helpful. Rationale: We consider that the danger of under reporting is far greater than that of over-reporting. Also, when in doubt sponsors should report. We consider statements discouraging reporting confusing and unhelpful.
16	40. 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. 41. In the absence of information on the causality by the reporting investigator, the sponsor should consult the reporting investigator and encourage him to express an opinion on this aspect. The causality assessment given by the investigator should not be downgraded by the sponsor. If the sponsor disagrees with the investigator's causality assessment, both, the opinion of the investigator and the sponsor should be provided with the report.	Comment: Helpful clarification, which should be kept.
17	44. If information on the expectedness has been made available by the reporting investigator, this should be taken into consideration by the sponsor. 45. In the absence of information on the expectedness by the reporting investigator, the sponsor should consult the reporting investigator and encourage him to express an	Comment: Whilst the sponsor can encourage the Investigator to express his opinion on expecteness, our experience is that investigators tend to take a very non-conservative approach towards expectedness. For example, in oncology clinical trials, we saw many instances of investigators assessing events with a fatal outcome as expected. We consider that assessment of expectedness should be the responsibility of

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	opinion on this aspect. 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.	the sponsor, as this is a very regulatory concept. Investigators, and rightly so, are primarily selected based on their clinical expertise, rather than regulatory expertise. Expectedness is a very regulatory concept, as it is an assessment made against a regulatory document (IB or SPC). Therefore, we consider that such an additional assessment for Investigators to carry out is an added burden to the Investigators (who already find SAE reporting unpleasant) without any added benefit. While a sponsor may choose to consult the Investigator, we do not agree that local PIs should be asked to give an opinion or that we should 'encourage' an opinion from someone who may have said they don't know and then possibly contradict them on the report.
18	46. The sponsor of a clinical trial performed in at least one Member State has to report the following SUSARs of which he obtains knowledge: • all SUSARs occurring in that clinical trial. This is independent of whether the SUSAR has occurred in a trial site in a Member State or in a third country concerned; and • all SUSARs related to the same active substance (independent of pharmaceutical form and strength) in a clinical trial performed exclusively in a third country, if that clinical trial is – sponsored by the same sponsor; or – sponsored by another sponsor who is either part of the same mother company or who holds a development agreement with the sponsor.	• all SUSARs related to the same active substance (independent of pharmaceutical form and strength) in a clinical trial performed exclusively in a third country, if that clinical trial is – sponsored by the same sponsor; or – sponsored by another sponsor who is part of the same mother company. Comment: The proposed detailed guidance does NOT define what as development agreement is. In the Clinical Trial Authorisation Application there is scope to define if there is co-sponsorship or if there is delegation of sponsor responsibilities to another party. As a non-commercial organisation, we fear that if an Investigator conducted an 'Investigator led trial', where there is some sort of contract for the provision of the IMP by a Pharma company and there is also some provision for the Investigator to inform the Pharma company of safety matters arising from the Investigator led trial, that this constitutes 'a development agreement'. This would be catastrophic for Investigator led trials or non- commercial sponsor trying to conduct trials in areas where Industry has no economic interest, as it would burden these non-commercial entities with potential reporting from trials from third countries where the IMP may be undergoing trials in a completely different therapeutic area. These non-commercial organisations could end up having reporting obligations

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		for trials in a therapeutic area/area of expertise completely outside their own, with no control over those trial protocols, informed consent documents, GCP issues, etc. These aspects coupled with the mandatory requirement for electronic reporting into EVCTM could potentially seriously compromise the valuable work of non-commercial organisations in very important areas of research (e.g. glioma, pancreatic cancer, oncology paediatric trials).
19	48. It follows from section 4.4 that there is no need for the sponsor to report: • Adverse reactions not related to the IMP but to a non-IMP received by the subject and without interaction with the IMP: This is addressed through the reporting and follow-up measures outside SUSAR reporting (see section 4.2.1); or • SUSARs occurring in a clinical trial performed (partly or exclusively) in the EU for which he is not the sponsor. These SUSARs may come to the knowledge of the sponsor through spontaneous reports, publications (such as academic literature), or regulatory authorities.	• SUSARs occurring in a clinical trial performed (partly or exclusively) in the EU for which he is not the sponsor. Comment: Would prefer this section of text removed. Rationale: Same as for comment 18 above.
20	58. Non-relevant information does not require reporting.	Comment: Would prefer this section of text removed. Rationale: Sponsors should set out what their policy is in this respect. When in doubt the Sponsor should report. This kind of comment is unhelpful.
21	59. Medical judgement should be applied as regards the identification of non-relevant and relevant information.	Medical ***and scientific*** judgement should be applied as regards the identification of non-relevant and relevant information. Rationale: For some matters scientific judgment is also likely to be relevant. For example, a GMP quality issue with an impact on safety may require non-medical expertise for a fuller assessment of the safety issue; or, for example, results from an animal toxicology study may also benefit from the expertise of non-medical staff. In addition, for consistency throughout the document, as paragraph 17 of the consultation paper talks of 'medical and scientific judgment'.

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22	4.7.2.1 Timelines 65. There may be cases where the sponsor does not obtain knowledge of relevant new information about a SUSAR until after the 15 days referred to in section 4.7.2 have elapsed. 66. In these cases, the clock starts again at day zero, i.e. at the date of the receipt of new information. This information should be reported as a follow-up report within 15 days.	66. In these cases, the clock starts again at day zero, i.e. at the date of the receipt of new information. This information should be reported as a follow-up report within **7** days. Rationale: We appreciate that the extension of these reporting timelines from 7 days to 15 days (as proposed in the consultation paper for fatal and life-threatening SUSARs) may seem like a helpful gesture. However, we consider that the changing these timelines has many pitfalls. Globally, this may be raise issues in other countries and create even further confusion amongst ICH regions where the EU has now decided to extend the timelines for follow-up only to fatal and life-threatening SUSARs. Measuring compliance might take on a very complex nature and we would prefer if these timelines for SUSAR reporting remained unchanged.
23	70. Examples of non-relevant information are minor changes of dates (e.g. the day of the birth date) or corrections of typographical errors in the previous case version. Medical judgment should be applied, as a change to the birth date may constitute a relevant change (e.g. it may have implications for the age information of the patient).	70. Examples of non-relevant information are minor changes of dates (e.g. the day of the birth date) or corrections of typographical errors in the previous case version. Comment: Would prefer for this text to be removed. Rationale: Sponsors should have a policy on how to deal with case report versioning within their systems. Medical ***and scientific*** judgment should be applied, as a change to the birth date may constitute a relevant change (e.g. it may have implications for the age information of the patient). Rationale: For some matters, scientific judgment is also likely to be relevant. For example, a GMP quality issue with an impact on safety may require non-medical expertise for a fuller assessment of the safety issue; or, for example, results from an animal toxicology study may also benefit from the expertise of non-medical

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		staff. In addition, for consistency throughout the document, as paragraph 17 of the consultation paper talks of 'medical and scientific judgment'.
24	76. Sponsors may not have the resources and experience for direct reporting. In order to address this matter, the sponsor may: • where this possibility is provided for by the Member State concerned, use the possibility of indirect reporting; • where a commercial partner is involved (e.g. the marketing authorization holder of the IMP), delegate the direct submission to the partner; or • delegate direct reporting to another person (outsourcing).	Comment: Reference should be made to these details having to be captured in the Clinical Trial Authorisation application, where sponsors must identify any sponsor responsibilities that they intend to delegate.
25	78. In addition to the SUSARs to be reported in accordance with section 4.4, sponsors should report SUSARs related to the same active substance of the IMP (independent of pharmaceutical form and strength) in a clinical trial performed exclusively in another Member State, if that clinical trial is – Sponsored by the same sponsor; or – Sponsored by another sponsor who is either part of the same mother company or who holds a development agreement with the sponsor.	78. In addition to the SUSARs to be reported in accordance with section 4.4, sponsors should report SUSARs related to the same active substance of the IMP (independent of pharmaceutical form and strength) in a clinical trial performed exclusively in another Member State, if that clinical trial is – Sponsored by the same sponsor; or – ***Sponsored by another sponsor who is part of the same mother company.*** Comment: The proposed detailed guidance does NOT define what as development agreement is. In the Clinical Trial Authorisation Application there is scope to define if there is co-sponsorship or if there is delegation of sponsor responsibilities to another party. As a non-commercial organisation, we fear that if an Investigator is conducted an 'Investigator led trial', where there is some sort of contract for the provision of the IMP by a Pharma company and there is also some provision for the Investigator to inform the Pharma company of safety matters arising from the Investigator led trial, that this constitutes 'a development agreement'. This would be catastrophic for Investigator led trials or non- commercial sponsor trying to conduct trials in areas where Industry has no economic interest, as it would burden these non-commercial entities with potential reporting from trials from

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		third countries where the IMP may be undergoing trials in a completely different therapeutic area. These non-commercial organisations could end up having reporting obligations for trials in a therapeutic area/area of expertise completely outside their own, with no control over those trial protocols, informed consent documents, GCP issues, etc… These aspects coupled with the mandatory requirement for electronic reporting into EVCTM could potentially seriously compromise the valuable work of non-commercial organisations in very important areas of research (e.g. glioma, pancreatic cancer, oncology paediatric trials).
26	80. If the SUSAR occurred in a third country, and that clinical trial is performed also in the EU, the sponsor should directly report to ECVTM or chose any one Member State concerned which ensures indirect reporting.	Comment: Do not understand this provision. It is our understanding of the current legal framework, that if the trial has at least one site in a EU MS, then the EU MS CA where that site is situated, will receive the SUSAR via whatever electronic provisions are available in that EU MS. Surely, if electronic reporting into EVCTM is mandatory for all sponsors it follows that it is mandatory for the EU MS CAs to report electronically into EVCTM.
27	82. Regarding the details of reporting ICSRs to EVCTM, reference is made to the following documents: • The current version of *ICH Topic E2B - Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports*; and • The current version of the *note for guidance Eudravigilance human – processing of safety messages and individual case safety reports (ICSRs)*.	Comment: Helpful for reference being made to ICH guidelines, which should be kept.
28	4.7.4.2. In case of indirect reporting 84. The information should follow the structure as provided for direct submission, in order for the national competent authority to enter the data into EVCTM. 85. This should also apply during the transitional period referred to in section 4.7.3.3.	Comment: Helpful clarification, which should be kept.

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29	89. Regarding all aspects of SUSAR reporting (reporting procedures, timelines) reference is made to sections 4.7.1, 4.7.2, 4.7.4.2 and 4.8. Regarding the addressee, this should be only the Ethics Committee issuing the 'single opinion' in accordance with Article 7 of Directive 2001/20/EC of the Member State where the event occurred.	Comment: Helpful clarification, which should be kept. However, Ethics Committees in different Member States have differing requirements. For example, French Ethics Committees require domestic SUSARs as an expedited report and all others in a quarterly line listing. We would therefore appreciate clarification on how this will fit with this guidance.
30	108. The basic functionalities of EVCTM allow for: • Direct reporting based on the internationally agreed formats (i.e. the current version of ICH E2B, ICH M1 MedDRA and ICH M2); • Generating specific reports integrating traditional and quantitative statistical methods of signal detection with option of primary filtering on source country, type of report, drug characterisation, EudraCT number, sending organisations (national competent authorities, sponsors), date of reporting; • Querying for – Number of adverse reactions reported for one or more selected medicinal products or active substances; – Number of adverse reactions reported by age group or indication for one or more selected medicinal products or active substances; – Number of adverse reactions reported for a selected clinical trial based on the EudraCT number; – Individual case line listings for reactions grouped at any level of the MedDRA hierarchy for one or more selected medicinal products or active substances; • Static reaction monitoring reports for one or more selected medicinal products or active substances.	• Querying for – Number of SUSARs reported for one or more selected medicinal products or active substances; – Number of SUSARs reported by age group or indication for one or more selected medicinal products or active substances; – Number of SUSARs reported for a selected clinical trial based on the EudraCT number; Comment: Based on the available information, EVCTM only contains SUSARs; therefore, for correctness and clarity the querying functions can only output numbers of SUSARs (and not non-serious adverse reactions).

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31	General comment	In general, it is extremely helpful wherever possible to refer to ICH guidelines, since this encourages consistency, as the document often does. However, the guidance was difficult to read and could not be understood without referral to CT-1 and ICH E2A and this could be improved.