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QUESTIONS & ANSWERS SPECIFIC TO ADVERSE REACTION REPORTING IN CLINICAL TRIALS

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All updates to this questions and answers document are presented and discussed in the "*Ad hoc* group for the development of implementing guidelines for the 'Clinical Trials Directive' 2001/20/EC". This group is chaired by the Commission and is composed of representatives of all EU Member States and EEA contracting parties.

Reference Number	Question	Answer
ID 001	What are the minimum criteria as regards electronic reporting of Suspected Unexpected Suspected Adverse Reactions (SUSARs) in accordance with ICH E2B(R2)?	The relevant information for the electronic transmission of a valid Individual Case Safety Report (ICSR) should include - A valid EudraCT number where applicable in the ICH[1] E2B(R2) data element A.2.3.1 'study name' (see also Question ID 008), - One identifiable patient in the ICH E2B(R2) section B.1 (see also Question ID 007), - One identifiable reporter in the ICH E2B(R2) section A.2, - One reaction/event in the ICH E2B(R2) section B.2, - One suspect drug in the ICH E2B(R2) section B.4. It is often difficult to obtain all the information in each section. Therefore, any one of several data elements is considered sufficient to define an identifiable subject (e.g. CT code number, initials, age, sex) or an identifiable reporter (e.g. initials, address, qualification). In addition, to properly process the report, the following administrative information should be provided: - The sender's (case) safety report unique identifier (ICH E2B(R2) data element A.1.0.1), - The receive date of the initial information from the primary source (ICH E2B(R2) data element A.1.6), - The receipt date of the most recent information (ICH E2B(R2) data element A.1.7), - The worldwide unique case identification number (ICH E2B(R2) data element A.1.10), - The sender identifier (ICH E2B(R2) data element A.3.1.2).
ID 002	What is considered relevant follow-up information?	Relevant follow-up information relates to any new or updated information on a case that impacts on its medical interpretation. Medical judgement should be applied as regards the identification of relevant follow-up information requiring expedited reporting. Situations where the seriousness and/or expectedness criteria and/or the causality assessment related to an individual case are downgraded should also be considered as significant change and thus reported on an

[1] ICH Harmonised Tripartite Guideline – Maintenance of the ICH Guideline on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports – E2B(R2). International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; Step 4 version, 5 February 2001.

Reference Number	Question	Answer
		expedited basis (e.g. in case follow-up information leads to a change of the expectedness from serious unexpected to serious expected or causality assessment is changed from related to non-related). In addition, the sponsor should also report follow-up information on an expedited basis where new administrative information is available that could impact on the case management. This information may be specifically relevant for the receiver to manage potential duplicates (e.g. new case identifiers have become known to the sponsor, which may have been used in previous transmissions. This information should be provided in the ICH E2B(R2) data element A.1.11 'Other case identifiers in previous transmissions'). Another example refers to the ICH E2B(R2) data element A.1.8 'Additional available documents held by sender', whereby new documents that have become available to the sponsor may be relevant for the medical assessment of the case. In contrast, non-significant information, which does not impact on the medical evaluation of the case, does not require expedited reporting. This may refer for example to minor changes of dates (e.g. the day of the birth date) or corrections of typos in the previous case version. Naturally, medical judgment should be applied, as a change to the birth date may constitute a significant change (e.g. with implications on the age information of the patient).
ID 003	When does the clock for expedited reporting start for initial and follow-up report?	The clock for expedited reporting of initial report (day 0 = Di 0) starts as soon as the information, containing the minimum reporting criteria, has been brought to the attention of the sponsor or the person to whom the sponsor has delegated the task of safety reporting (cf. Q&A document in Chapter V of volume 10 of EudraLex). The same applies if significant new information on the case is received by the sponsor, i.e. the reporting time clock begins again (day 0 = Df 0) for the submission of the follow-up report from the day the sponsor receives relevant follow-up information.
ID 004	With reference to Article 17(1)(a) of Directive 2001/20/EC, what are the	For fatal and life threatening SUSARs the sponsor should report at least the minimum information[2] as soon as possible[3] and in any case no later than seven days after being made aware of the case.

[2] Minimum information (ICH E2BR(2) guideline): The minimum information for the transmission of a report should include at least the EudraCT number, one identifiable patient (section B.1), one identifiable reporter (section A.2), one reaction/event (section B.2), and one suspect drug (section B.4). Because it is often difficult to obtain all the information, any one of several data elements is considered sufficient to define an identifiable patient (e.g., initials, age, sex) or an identifiable reporter (e.g., initials, address, qualification). It is also recognized that the patient and the reporter can be the same individual and still fulfil the minimum reporting criteria. In addition, to properly process the report, the following administrative information should be provided: the sender's (case) safety report unique identifier (A.1.0.1), the date of receipt of the most recent information (A.1.7), the worldwide unique case identification number (A.1.10) and the sender identifier (A.3.1.2).

Reference Number	Question	Answer
	timelines for sponsors regarding the reporting of initial and follow-up information about suspected unexpected serious adverse reactions that are fatal or life threatening? How should this be handled from a practical point of view as regards electronic reporting in accordance with ICH E2B(R2)?	• If the initial report is incomplete, e.g., if the sponsor has not provided all the information/assessment within seven days, the sponsor should submit a completed report based on the initial information within an additional eight days. In this instance, the receipt date should not be changed with regard to the initial report. As regards the electronic reporting of Individual Case Safety Reports (ICSRs) this means that the date specified in the ICH E2B(R2) field A.1.6'Receive date' should equal the date specified in the ICH E2B(R2) field A.1.7'Receipt date'. If significant[4] new information on an already reported case is received by the sponsor, the clock starts again at day zero[5] i.e. at the date of receipt of new information (field A.1.7). This information should be reported as a follow-up report within 15 days. As regards the electronic reporting of Individual Case Safety Reports (ICSRs) this means that the date specified in the ICH E2B(R2) field A.1.6'Receive date' should be equal the date when the initial report was received and in the ICH E2B(R2) field A.1.7'Receipt date' the date should be indicated when significant new information on the case was received by the Sponsor.
ID 005	With reference to Article 17 paragraph 1b of Directive	For SUSARs which are not fatal or life-threatening, the sponsor shall ensure that all relevant information, containing the minimum reporting criteria, is reported as soon as possible but within a maximum of 15 days of

[3] Article 17(1)(a) Directive 2001/20/EC.

[4] Significant new information relates to any new or updated information on the case that impacts on the medical interpretation of the case e.g. change in the causality assessment. Therefore, the identification of significant new information requiring expedited reporting always requires medical judgement. Situations where the seriousness and/or expectedness criteria and/or the causality assessment related to an individual case are downgraded (e.g. follow up information leads to a change of the expectedness from serious unexpected to serious expected or causality assessment is changed from related to non-related) should also be considered as significant change and thus reported on an expedited basis. In addition, the sponsor should also report follow-up information on an expedited basis, where new administrative information is available, that could impact on the case management e.g. new case identifiers have become known to the sponsor, which may have been used in previous transmissions (ICH E2B(M) field A.1.11 'Other case identifiers in previous transmissions'); this information may be specifically relevant for the receiver to manage potential duplicates. Another example refers to ICH E2B(M) field A.1.8 'Additional available documents held by sender', whereby new documents that have become available to the sponsor may be relevant for the medical assessment of the case. In contrast, non-significant information, which does not impact on the medical evaluation of the case, does not require expedited reporting. This may refer for example to minor changes of dates (e.g. the day of the birth date) or corrections of typos in the previous case version. Naturally, medical judgment should be applied, as a change to the birth date may constitute a significant change (e.g. with implications on the age information of the patient).

[5] The clock for expedited reporting starts (day 0) as soon as the minimum information has been brought to the attention of the sponsor or an organisation having a contractual arrangement with the sponsor for this clinical trial. The same applies if significant new information on the case is received by the sponsor, i.e. the reporting time clock begins again for the submission of the follow-up report from the day the sponsor receives relevant follow-up information.

Reference Number	Question	Answer
	2001/20/EC, what are the timelines for sponsors regarding the reporting of initial and follow-up information about SUSARs that are not fatal or life-threatening? How should this be handled from a practical point of view as regards electronic reporting in accordance with ICH E2B(R2)?	first knowledge by the sponsor of such a valid case. - As regards the electronic reporting of the initial Individual Case Safety Report (ICSR), the date specified in the ICH E2BR(2) data element A.1.6 'Receive date' should be equal the date specified in the ICH E2BR(2) data element A.1.7 'Receipt date'. Relevant follow-up information should be subsequently communicated within an additional 15 days. - As regards the electronic reporting of follow-up ICSRs, the date specified in the ICH E2BR(2) data element A.1.6 'Receive date' should be equal to the date when the initial report was received. The date in the ICH E2BR(2) data element A.1.7 'Receipt date' should indicate the date when significant new information on the case was received by the Sponsor. The clock for expedited reporting for the initial report (day 0 = Di 0) starts as soon as the information, containing the minimum reporting criteria for a valid report, has been brought to the attention of the sponsor or an organisation having a contractual arrangement with the sponsor for this clinical trial. The same applies if relevant follow-up information on the case is received by the sponsor i.e. the clock for expedited reporting (day 0 = Df 0) begins again for the submission of the follow-up ICSR from the day the sponsor receives relevant follow-up information. See also questions ID 001, ID 002 and ID 003 for the definitions of minimum criteria for electronic reporting, relevant follow-up information and clock start for expedited reporting.
ID 006	What are the reporting timelines for follow-up reports which describe fatal or life-threatening outcome while the initial report was not fatal or life-threatening?	In this situation, 2 timelines for expedited reporting with 2 different clock starts should be considered. 1. The clock for expedited reporting of the initial non-fatal or non-life threatening report (day 0 = Di 0) starts as soon as the initial information, containing the minimum reporting criteria for a valid report, has been brought to the attention of the sponsor or an organisation having a contractual arrangement with the sponsor for this clinical trial. The initial non-fatal or non-life threatening report should be reported as soon as possible but within a maximum of 15 days (at Di 15) after first knowledge of such valid report by the sponsor or organisation having a contractual arrangement. 2. The clock for expedited reporting of the fatal or life threatening follow-up report (day 0 = Df 0) starts as soon as the follow-up information has been brought to the attention of the sponsor or an organisation having a contractual arrangement with the sponsor for this clinical trial. The fatal or life threatening follow-up report should be reported as soon as possible but within a maximum

Reference Number	Question	Answer
		of 7 days (at Df 7) after first knowledge of such report by the sponsor or organisation having a contractual arrangement. See also questions ID 001, ID 002 and ID 003 for the definitions of minimum criteria for electronic reporting, relevant follow-up information and clock start for expedited reporting.
ID 007	What are the reporting scenarios for follow-up reports which describe fatal or life-threatening outcome while the initial report was not fatal or life-threatening and the initial report has not yet been submitted to the Competent Authorities and EudraVigilance?	The reporting timelines corresponding to this situation are presented in Question ID 005. Three different scenarios may apply if the initial report has not yet been submitted to the Competent Authorities and to EudraVigilance: 1. If the fatal or life threatening follow-up information is received between 0 and 7 days after the receipt of the initial non-fatal or non-life threatening information (Di 0 ≤ Df 0 ≤ Di 7), one combined report should be created with the information of the initial and follow-up reports and submitted as soon as possible but within a maximum of 7 days (Df 7) after the receipt of the follow-up report. • The date entered in the ICH E2B(R2) data element A.1.6 'Received date' should be Di 0 and the date entered in the ICH E2B(R2) data element A.1.7 'Receipt date' should be Df 0. 2. If the fatal or life threatening follow-up information is received between 8 and 15 days after the receipt of the initial non-fatal or non-life threatening information (Di 7 < Df 0 ≤ Di 15): • 2a. If possible, one combined report should be created with the information of the initial and follow-up reports and submitted as soon as possible but within a maximum of 15 days (Di 15) after the receipt of the initial information. The date entered in the ICH E2B(R2) data element A.1.6 'Received date' should be Di 0 and the date entered in the ICH E2B(R2) data element A.1.7 'Receipt date' should be Df 0. • 2b. If it is not possible to submit one combined report within a maximum of 15 days (Di 15) after the receipt of the initial information, an initial and a follow-up report should be submitted: – The initial non-fatal or non-life threatening information should be reported as soon as possible but within a maximum of 15 days (Di 15) after first knowledge of such report. The date entered in the ICH E2B(R2) data elements A.1.6 'Received date' and A.1.7 'Receipt date' should be identical: Di 0. – The fatal or life threatening follow-up information should be reported after the initial report but within a maximum of 7 days (at Df 7) after first knowledge of the follow-up information. The date entered in the ICH E2B(R2) data element A.1.6 'Received date' should be Di 0 and the

Reference Number	Question	Answer
		date entered in the ICH E2B(R2) data element A.1.7 'Receipt date' should be Df 0. Initial and follow-up information should always be clearly distinguished in the ICH E2B(R2) data element B.5.1 'Case narrative including clinical course, therapeutic measures, outcome and additional relevant information' and the change of the seriousness criteria highlighted. Example 1: A fatal or life threatening follow-up information is received 4 days (Di 4 = Df 0) after the receipt of the initial non-fatal or non-life threatening information. One report is created and submitted as soon as possible but no later than 11days (Di 11) after the receipt of the initial non-fatal or non-life threatening information. Example 2: A fatal or life threatening follow-up report is received 10 days (Di 10 = Df 0) after the receipt of the initial non-fatal or non-life threatening report. a) If possible one combined report is created and submitted no later than 15 days (Di 15) after the receipt of the initial information. b) If the time frame is too short to submit one combined report: - One initial report containing the information received at Di 0 is created and submitted as soon as possible but no later than 15 days (Di 15) after the receipt of the initial non-fatal or non-life threatening information. - A follow-up report containing the information received at Df 0 is then created and submitted no later than 17 days (Df 0+7 = Di 17) after the receipt of the initial non-fatal or non-life threatening information.
ID 008	How does the ICH E2B format have to be filled when Data Privacy rules apply?	Regarding the ICH E2B(R2) data element B.1.1 'Patient (name or initials)': If the initials of the subject are known to the sender but cannot be transmitted due to data privacy requirements, this field should be populated with 'PRIVACY'. The same principles apply for ICH E2B(R2) section A.2 'Primary source(s) of information' and section E2B(R2) B.1.10 for a parent-child/fetus report for the information concerning the parent.
ID 009	How should sponsors report the EudraCT number as regards electronic reporting in accordance with ICH	For any transmission to the EudraVigilance Clinical Trial Module (EVCTM), a valid EudraCT number should be included in the ICH E2B(R2) data element A.2.3.1 'Study name' as follows: a) For SUSARs originating in the EEA:

Reference Number	Question	Answer
	E2B(R2)?	- 'Valid EudraCT Number#Study abbreviated name' b) For SUSARs originating outside the EEA: - 'Valid EudraCT Number#Study abbreviated name' for clinical trials authorised in the EEA and for clinical trials not authorised in the EEA which are part of an agreed Paediatric Investigation Plan; - '#Study abbreviated name' for clinical trials non-authorised in the EEA and which are not part of an agreed Paediatric Investigation Plan. The EudraCT Number should be the number identifying the clinical trial in the EudraCT database and should have the format YYYY-NNNNNN-CC, where - YYYY is the year in which the number has been issued, - NNNNNN is a six digit sequential number, - CC is a check digit. For clinical trials <u>in the EEA, which started before 01 May 2004 and thus do not have a EudraCT number</u>, the following generic EudraCT Number should be used in the data element 'Study name' (ICH E2B(R2) A.2.3.1 for these clinical trials only: - **EVCT-000000-16** It is important to maintain the structure of the concatenation with the '#' symbol ('YYYY-NNNNNN-CC#Study abbreviated name' or '#Study abbreviated name') in the data element 'Study name' (ICH E2B(R2) A.2.3.1) to obtain a successful outcome of the validation of this data element. Failure of the validation on the first part of the reported data ('YYYY-NNNNNN-CC#' or '#') will generate an error message. Any local clinical trial numbers (used to identify clinical trials at national levels) should be entered in the ICH E2B(R2) data elements B.5.4 'Sender's comments' . The ICH E2B(R2) data element A.2.3.1 'Study name' () is limited to 100 characters. If necessary the study name should be abbreviated in the concatenation. The entire study name can be included in the ICH E2B(R2) data element B.5.1 'Case narrative including clinical course, therapeutic measures, outcome and additional relevant information'.
ID 010	How to report placebo that	In exceptional circumstances when excipient(s) is considered as suspect or interacting, placebo can be

Reference Number	Question	Answer
	may be involved in SUSARs as regards electronic reporting in accordance with ICH E2B(R2)?	reported in the ICSRs electronically in the following data elements: - 'Proprietary medicinal product name' (ICH E2B(R2) data element B.4.k.2.1) - 'Relevant past drug history' (ICH E2B(R2) data element B.1.8) - 'Relevant past drug history of parent' (ICH E2B(R2) data element B.1.10.8) When a placebo is reported in the ICH E2B(R2) data element B.4.k.2.1 'Proprietary medicinal product name', the suspected ingredient(s) of the placebo should be specified in the ICH E2B(R2) data element B.4.k.2.2. 'Active substance name'.
ID 011	In order to maintain the integrity of a study, is it acceptable to report blinded SUSAR to the EudraVigilance Clinical Trial Module (EVCTM) or only submission of unblinded cases is accepted?	As a general rule, in line with the Detailed Guidance on the Collection, Verification and Presentation of Adverse Reaction Reports Arising from Clinical Trials on Medicinal Products for Human Use (ENTR/CT 3), treatment codes should be broken by the sponsor before reporting a SUSAR to the Competent Authorities and the Ethics Committees of the concerned Member States and to EudraVigilance. For clinical trials in high morbidity and/or high mortality disease, where efficacy end-points could also be adverse reactions reported as SUSARs or when mortality or another "serious" outcome (that may potentially be reported as a SUSAR) is the efficacy endpoint in a clinical trial, the integrity of the clinical trial may be compromised when the blind is systematically broken. Under these and similar circumstances, it may be appropriate to reach agreement with the Competent Authorities in advance concerning serious events that would be treated as disease related and not subject to systematic un-blinding and expedited reporting. For these cases, expedited reporting should not apply. Handling of these adverse events must be clearly defined in the study protocol. For such trials, sponsors are strongly encouraged to appoint an independent Data Monitoring Committee in order to review safety data of the ongoing trial on a regular basis and when necessary to recommend to the sponsor whether to continue, modify or terminate the clinical trial. The Guideline on Data Monitoring Committees (Doc. Ref. EMEA/CHMP/EWP/5872/03 Corr) should be followed. The composition and operation of a Data Monitoring Committee should be described in the study protocol. **Cases of SUSARs which are not listed in the study protocol as study end points should be reported un-blinded.** For blinded SUSARs reports which have already been submitted to the Competent Authorities and to EudraVigilance Clinical Trial Module, follow-up reports should be provided once the case has been un-

Reference Number	Question	Answer
		blinded to update the ICSR.
ID 012	How should sponsors report SUSARs described in the scientific literature and which originate in a clinical trial authorised in the EU?	Based on the current reporting requirements described in the Detailed Guidance ENTR/CT 3, SUSAR reports are submitted by the sponsors of clinical trials on an expedited basis as soon as they are made aware of them. These reports are therefore submitted to the relevant Competent Authorities and the Ethics Committees of the concerned Member States before the corresponding articles are published in the scientific literature. In order to avoid the submission of duplicate reports, when those SUSARs are reported in the scientific literature they should not be submitted to the Competent Authorities and the Ethics Committees of the concerned Member States nor to EudraVigilance on an expedited basis. If new information is included in an article describing an already reported case, the sponsor should update the case with this information and report it as follow-up information to the Competent Authorities and the Ethics Committees of the concerned Member States and to EudraVigilance within 15 days.
ID 013	There are cases where the MAH of an IMP is not sponsor, but is informed by a sponsor of a SUSAR related to an authorised medicinal product which is an IMP in a clinical trial performed in the EEA. How should the MAH process this information?	In this situation, the case should not be reported by the MAH to the Competent Authorities and the Ethics Committees of the concerned Member States nor to EudraVigilance. Only the sponsor should report the case. However if the MAH is made aware of any safety information which could impact on the benefit risk balance of the marketed medicinal product the MAH should analyse it in the corresponding PSUR.
ID 014	How should be reported a serious adverse reaction originating from a clinical trial authorised in the EEA, when the reaction is suspected to be related only to another authorised medicinal product taken concomitantly, which is not part of the clinical trial	1. If the serious adverse reaction is not related to the IMP (tested product or comparator) but is suspected to be related to a concomitant treatment, which does not follow the definition of Non-Investigational Medicinal Product (NIMP), then the case did not occur within the framework of the clinical trial protocol. It should be reported in accordance with the applicable pharmacovigilance rules. 2. If the serious adverse reaction is suspected to be an interaction between the concomitant treatment and the IMP, then the case occurred within the framework of the clinical trial protocol. In this situation, the rules on SUSAR reporting in accordance with Article 17 of Directive 2001/20/EC apply. 3. If the serious adverse reaction is suspected to be related to either the concomitant treatment or the IMP and cannot be attributed to only one of these, then the case occurred within the framework of the clinical trial protocol. In this situation, the sponsor should report the SUSAR in accordance with Article 17 of Directive 2001/20/EC.

Reference Number	Question	Answer
	protocol and which does not follow the definition of Non-Investigational Medicinal Product (NIMP)?	