EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

London, 01 February 2010
Doc. Ref. EMA/764025/2009

EUDRAVIGILANCE EXPERT WORKING GROUP COMMENTS ON THE EUROPEAN COMMISSION PUBLIC CONSULTATION PAPER –

"ASSESSMENT OF THE FUNCTIONING OF THE "CLINICAL TRIALS DIRECTIVE" 2001/20/EC (ENTR/F/2/SF D(2009) 32674)"

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8668
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

TABLE OF CONTENT

1 Executive Summary

The EudraVigilance Expert Working Group (EV-EWG) welcomes the Public Consultation Paper on the Assessment of the Functioning of the Clinical Trials Directive 2001/20/EC as published by the European Commission on 9 October 2009.

In response to this public consultation, the EV-EWG has prepared this document, which focuses mainly on safety reporting and the implementation of a fully functioning EudraVigilance Clinical Trial Module that can support the protection of the health and safety of clinical trial participants.

The document is based on elements addressed in the frame of the EudraVigilance Action Plan (Doc. Ref. EMEA/82645/2007) which was adopted by the Heads of Medicines Agencies (HMA-Human) in April 2007 and further endorsed by the European Medicines Agency Management Board in London, UK in June 2007. This Action Plan addresses several areas requiring further improvement, including safety reporting in clinical trials and EudraVigilance.

Although the EV-EWG elaborated jointly proposals and options with the Clinical Trials Facilitation Group (CTFG) on how the identified issues could be improved, it has become evident that within the current legal framework, especially as regards the differing regulatory approaches in Member States, no substantial improvements can be achieved.

The EV-EWG would therefore like to take the opportunity to highlight the present implementation challenges in the context of clinical trials and would like to put forward proposals on how they could be addressed.

2 The current legal framework in relation to SUSAR reporting and EudraVigilance

The current legal framework in relation to SUSAR reporting and EudraVigilance as laid down in Directive 2001/20/EC and Volume 10 can be summarised as follows:

- The provisions regarding the recording and the notification of SUSARs, related to interventional clinical trials for which at least one site is located within the European Economic Area (EEA), are defined in Article 17 of the Clinical Trials Directive 2001/20/EC. It requires the sponsors to record and report on an expedited basis to the National Competent Authorities (NCAs) of the concerned Member States (MSs) all relevant information about SUSARs.

- According to paragraph 3 of Article 17, each MS "shall see to it" that all SUSARs to an Investigational Medicinal Product[1] (IMP) which are brought to its attention are immediately entered in the European database, i.e., the EudraVigilance Clinical Trial Module (EVCTM).

[1] An Investigational Medicinal Product (IMP) is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form; Directive 2001/20/EC.

[2] 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).

[3] Detailed Guidance on the European database of Suspected Unexpected Serious Adverse Reactions (Eudravigilance – Clinical Trial Module) (ENTR/CT 4).

[4] Clinical Safety Data Management: Definitions and Standards for Expedited Reporting

[5] 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)

[6] Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (EudraVigilance – Clinical Trial Module) (ENTR/CT 4)

- In accordance with Article 2 (c) of Directive 2001/20/EC, the provisions laid down in Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data apply.

- In accordance with paragraph 3 of Article 11, the European database is operated "with the assistance of the Agency".

- As required in line with Article 18 of Directive 2001/20/EC, detailed guidance on the collection, verification and presentation of adverse event/reaction reports, together with decoding procedures for unexpected serious adverse reactions have been drawn up (Doc. Ref.: ENTR/CT 3[2]and ENTR/CT 4[3]).
- The different scenarios of SUSARs reporting applicable to sponsors of interventional clinical trials (phase I-IV) with at least one investigator site in the EEA have been laid down in the Detailed Guidance ENTR/CT 3. The scenarios are defined according to:

    a) The origin of SUSARs:
        - Within the concerned interventional clinical trial,
        - Within another interventional clinical trial with the same tested IMP,
        - Within any other source: spontaneous reporting, non-interventional trials or organised data collection systems other than interventional clinical trials involving the same active substance(s) of the tested IMP.

    b) The marketing status of the IMP in the Community:
        - IMP with a marketing authorisation within the EEA,
        - IMP without a marketing authorisation within the EEA.

    c) The role of the sponsor:
        - Sponsor is also Marketing Authorisation Holder (MAH) of the IMP within the EEA,
        - Sponsor is not MAH of the IMP within the EEA.
- Depending on the scenario applicable, the requirements concerning the expedited reporting of SUSARs may vary and the various possible options have been presented in the Detailed Guidance ENTR/CT 3 (See Annex 1).
- The roles and responsibilities of the stakeholders regarding the electronic reporting to EVCTM of SUSARs occurring in interventional clinical trials have been defined in the Detailed Guidance ENTR/CT 4. According to this guidance,
    - The Community sponsor reports SUSARs electronically to EVCTM, including third country SUSARs,
    - All SUSARs occurring in the Community shall be sent electronically by the sponsor to the MS in whose territory the reaction occurred and to the other concerned MSs and the Agency (EVCTM),
    - Third country reports shall be sent electronically by the sponsor to the concerned MSs and to Agency (EVCTM).
- Electronic reporting requirements of Individual Case Safety Reports (ICSRs) to EudraVigilance have been summarised in the Detailed Guidance ENTR/CT 4 (See Annex 2), depending on
    - The marketing authorisation status of the IMP in the Community (with or without marketing authorisation in the EEA),
    - The role of the sponsor (sponsor is or is not MAH of the IMP within EEA),
    - The origin of the SUSARs (within or outside EEA),
    - The source of the SUSARs (interventional clinical trials, spontaneous reports, non-interventional trials).

3 Comments on the Consultation Items

3.1 Key Issue N°2 & N°3: Inconsistent Implementation of the Clinical Trials Directive & Regulatory Framework Not Always Adapted to the Practical Requirements

3.1.1 Current issues related to SUSAR reporting

3.1.1.1 Issues related to differences in reporting requirements

In the frame of the implementation within the EEA of Directive 2001/20/EC and of the related Detailed Guidance (ENTR/CT 3 and ENTR/CT 4), the EV-EWG, in collaboration with the Clinical Trial Facilitation Group (CTFG), conducted a survey in 2007. The objective was to obtain a better overview of SUSARs reporting requirements of the MSs in the EEA and to assess the impact on the reporting to EVCTM. The outcome of this survey is presented in Annex 3.

The survey has highlighted several areas of disharmony in the SUSARs reporting process, which impact:

- On the sponsors, who have to comply with divergent requirements and different legislations across the EEA (Directive 2001/20/EC, Directive 2001/83/EC as amended and Regulation (EC) No 726/2004),
- On the establishment of a fully functioning EudraVigilance Clinical Trial Module that is meant to support the monitoring of the safety of patients enrolled in clinical trials and the initiation of rapid actions in case the safety and health of patients might be at risk.

Differences in national reporting requirements according to the origin and/or the source of SUSARs were identified in the survey as follows:

a) Based on the origin of SUSARs, sponsors may be requested to:
   - Report only SUSARs that occur in the territory of the concerned MS,
   - Report SUSARs that occur in the territory of the concerned MS as well as SUSARs that occur in the territory of other MSs in the EEA (in case of multi-centre interventional clinical trials),
   - Report all SUSARs independent of the country of occurrence (EEA- and non-EEA) to the concerned MS,
   - Report SUSARs with various combinations of the above;

b) Based on the source of SUSARs, sponsors may be requested to:
   - Report only SUSARs that are related to an IMP and which occur in the concerned interventional clinical trial (reporting rules following Directive 2001/20/EC),
   - Report SUSARs related to an IMP and which occur in other interventional clinical trials than the concerned one (reporting rules following Directive 2001/20/EC),
   - Report SUSARs related to the active substance(s) of an IMP and which occur in any other sources than an approved interventional clinical trial (reporting rules following Directive 2001/83/EC/ as amended and Regulation (EC) No726/2004),
   - Report SUSARs based on various combinations of the above.

3.1.1.2 Lack of clear reporting rules to EVCTM and of enforcement of electronic reporting

Divergent national approaches in relation to reporting of SUSARs to EVCTM have been identified as follows:

- Sponsors report to EVCTM all SUSARs originating in the territories of MSs and in third countries,
- Sponsors report to EVCTM only third countries SUSARs while the concerned MSs report to EVCTM SUSARs which originate in their territory.

The 2009 statistics on the reporting to EVCTM are presented in Annex 4. These data show that:

- Some NCAs report SUSARs to EVCTM, according to the transposition of the Clinical Trials Directive 2001/20/EC into their national legislation,
- The number of non-commercial/"academic" sponsors reporting to EVCTM is actually very low compared to commercial sponsors.

The different reporting situations have a major negative impact on the data quality in EVCTM by either creating duplicated reports or by reports not being submitted at all, thus reducing the ability of the European database to support the monitoring of safety data from interventional clinical trials and of taking rapid measures to minimise potential risks to trial participants.

The report of the 'European Commission-European Medicines Agency Conference on the Operation of the Clinical Trials Directive (Directive 2001/20/EC) and Perspectives for the Future' (Doc. Ref.: EMEA/565466/2007, 30-November-2007) acknowledged that the lack of harmonised implementation across the MSs of the safety reporting rules in interventional clinical trials remained a major problem. It highlighted that national procedures addressing the safety and monitoring of interventional clinical trials have led to create unnecessary burden by having to submit multiple reports to various parties. The necessity to streamline the reporting system of safety information and to use available resources and tools in better analysing this interventional clinical trials information was strongly emphasised.

Furthermore, no legally binding requirements exist to report electronically to EVCTM, according to national law in Member States, which leads to the fact that SUSARs are often not entered in the European database.

3.1.1.3 Divergence in implementing the Data Protection Directive (Directive 95/46/EC)

The EV-EWG conducted a survey on the personal data protection requirements of Member States based on the principles laid down in Directive 95/46/EC. This survey identified different approaches of national laws in meeting the data protection requirements in the context of safety reporting.

The lack of harmonised rules in the EU is unconstructive for sponsors especially in the context of multi-centre clinical trials, where they need to report in line with national rules. It also has a negative impact on EVCTM and the efforts to protect public health.

3.1.1.4 Need to establish clear 'responsibilities' for EVCTM

Article 11, paragraph (3) refers to the operation of the 'European database with the assistance of the European Medicines Agency (the Agency)'. Since the roles and responsibilities for the database are not clearly defined as regards the maintenance of the system from a technical point of view and from an operational perspective, especially as regards data collection, management and the provision of high quality of data, this leaves the Agency and National Competent Authorities in a difficult position.

3.1.1.5 Need to improve tools for evaluating suspected serious adverse reactions

According to Article 17 (2) of Directive 2001/20/EC, the sponsors of clinical trials should provide once a year to the MSs in whose territory the clinical trial is being conducted and to the Ethics Committees with a listing of all suspected Serious Adverse Reactions (SARs), which have occurred over this period.

To facilitate the scientific evaluation of the safety data of IMPs, it is necessary to collect this information in one common repository and one common format.

Annual Safety Reports (ASR)/Development Safety Update Reports (DSURs) should focus on the analysis of the risk-benefit balance of a medicinal product and the monitoring of the safety of patients enrolled in clinical trials rather than a detailed presentation of ICSRs, which is burdensome from a data management perspective and does not add to the evaluation of the data presented.

3.2 Consultation item N°6 & N°7 – Reporting of Suspected Unexpected Serious Adverse Drug Reactions (SUSARs)

3.2.1 Proposal for simplification of SUSAR Reporting

As regards the harmonisation and simplification of SUSAR reporting the following options are proposed:

I) Interim Simplification of SUSARs Reporting: Sponsors submit all SUSARs to EudraVigilance and local SUSARs to the concerned Member State

Based on this interim proposal, the sponsor reports all SUSARs electronically to EudraVigilance. They are made immediately accessible to all MSs by means of the EudraVigilance Data Warehouse and Analysis System (EVDAS). In addition, SUSARs originating in the country of a MS are also sent electronically by the sponsor to the concerned MS.

Under these conditions, the sponsor of an interventional clinical trial authorised in the EEA reports:

1. To the concerned MS, SUSARs of the concerned interventional clinical trial originating in the country of the MS and involving
   - The Medicinal Product (MP) tested in the concerned interventional clinical trial,
   - The comparator tested in the concerned interventional clinical trial,
   - The placebo tested in the concerned interventional clinical trial (i.e. reaction due to one or more excipients).

   The MS does not submit SUSARs to EudraVigilance.
2. To the EudraVigilance Clinical Trial Module (EVCTM):
   a) SUSARs of the concerned interventional clinical trial, originating within or outside the EEA and involving
      - The MP tested in the concerned interventional clinical trial,
      - The comparator tested in the concerned interventional clinical trial,
      - The placebo tested in the concerned interventional clinical trial (i.e. reaction due to one or more excipients);
   b) SUSARs originating outside the EEA, occurring in interventional clinical trials other than the concerned interventional clinical trial and involving:
      - The active substance(s) of the MP tested in the concerned interventional clinical trial.

3. To the EudraVigilance Post-Authorisation Modules (EVPM):

   a) SUSARs originating outside the EEA, occurring in any sources other than interventional clinical trials (non-interventional trials, spontaneous reports) and involving:

   - The active substance(s) of the MP tested in the concerned interventional clinical trial.

The reporting obligations of SUSARs for medicinal products authorised in the EEA are fulfilled by the MAH when reporting to EVPM according to Directive 2001/83/EC as amended and Regulation (EC) No 726/2004. Therefore the sponsors should ensure that SUSARs originating in third countries and falling under the scope of Directive 2001/83/EC as amended and Regulation (EC) No 726/2004 are submitted only once to EVPM.

A detailed flowchart is presented in Figure 1 of Annex 5.

The EV-EWG considers option 1 as an effective interim approach of harmonisation of SUSARs reporting in the EEA. This option can be put in place rapidly without major system adaptations.

II) Long-term simplification of SUSARs Reporting – Option 2: Sponsors submit SUSARs to EudraVigilance only

With this long-term proposal all the SUSARs involving the IMP(s) of the concerned interventional clinical trial authorised in the EEA are only submitted electronically to EudraVigilance. Subsequently, SUSARs originating in the country of a MS are automatically transmitted electronically by EudraVigilance to the concerned MS.

The sponsor of an interventional clinical trial authorised in the EEA reports:

1. To EVCTM SUSARs of the concerned interventional clinical trial, originating within or outside the EEA and involving:
   - The MP tested in the concerned interventional clinical trial,
   - The comparator tested in the concerned interventional clinical trial,
   - The placebo tested in the concerned interventional clinical trial (i.e. reaction due to one or more excipients).
2. To EVCTM SUSARs originating outside the EEA, occurring in interventional clinical trials other than the concerned interventional clinical trial and involving:
   - The active substance(s) of the MP tested in the concerned interventional clinical trial.
3. To EVPM SUSARs originating outside the EEA, occurring in any sources other than interventional clinical trials (non-interventional trials, spontaneous reports) and involving:
   - The active substance(s) of the MP tested in the concerned interventional clinical trial.

The reporting obligations of SUSARs for medicinal products authorised in the EEA are fulfilled by the MAH when reporting to EVPM according to Directive 2001/83/EC as amended and Regulation (EC) No 726/2004. Therefore the sponsors should ensure that SUSARs originating in third countries and falling under the scope of Directive 2001/83/EC as amended and Regulation (EC) No 726/2004 are submitted only once to EVPM.

SUSARs from interventional clinical trials, originating in the country of a MS are automatically and instantaneously forwarded by EudraVigilance to the concerned MS. Alternatively, all the SUSARs of interventional clinical trials originating within and outside the EEA, sent to EVCTM by sponsors, and related to the active substance(s) of MPs

tested in interventional clinical trials authorised in the EEA are automatically and instantaneously forwarded by EudraVigilance to MSs wishing to populate their database. The filtering by clinical trial authorised in the country of a MS will have to be performed at the level of the NCAs.

A detailed flowchart is presented in Figure 2 of Annex 5.

The EV-EWG considers this long-term solution as the most efficient one as it would allow for the automatic rerouting of SUSARs from EVCTM to the concerned MSs and a single reporting point for Sponsors.

The mandatory provision of a valid EudraCT number in each report is a pre-requisite to allow for the adequate assessment of reports by Member States.

3.2.2 Proposal for further strengthening compliance with European Data Protection Legislation

In June 2008, the Agency notified the European Data Protection Supervisor (EDPS) regarding the data processing operations carried out in the context of EudraVigilance. In the response to this notification, the EDPS issued an Opinion on 7 September 2009, which was generally positive and confirmed conformance of the Agency with the provisions of Regulation 45/2001.

Focusing on the current safety data exchange process in the EU, the EDPS made several recommendations in his Opinion.

Whilst EudraVigilance is governed by Regulation (EC) 45/2001, the biggest challenge is to promote a uniform application of the general principles of Directive 95/46/EC by all Member States.

As a major step forward to address the recommendations of the EDPS, the Agency proposes to engage actively with the article 29 Data Protection Working Party with the aim of developing harmonised data protection rules in the EU specific to pharmacovigilance and reporting of adverse reactions in clinical trials.

3.2.3 Proposal to improve tools for evaluating *suspected serious adverse reactions*

It is proposed that sponsors should report electronically all suspected SARs to EVCTM based on the international ICSR standard format. This should therefore be applicable to the suspected expected SARs related to all investigational medicinal products being studied in interventional clinical trials authorised in the EEA. Sponsors should report suspected expected SARs electronically:

- At the same time of the submission of the ASRs/DSURs in accordance with the requirements described in the Detailed Guidance ENTR/CT 3 or
- On ongoing basis.

3.2.4 Proposal to establish clear ‘responsibilities’ for EVCTM

It is proposed that the roles and responsibilities of the Agency, National Competent Authorities and Sponsors as regards the maintenance of the system from a technical point of view and from an operational perspective, especially as regards data collection, management and the provision of high quality of data are clearly defined in legislation.

3.3 Consultation item N°8 & N°12 – Report of SUSARs to the Community Database (EudraVigilance) requiring amendment of the Clinical Trial Directive

3.3.1 Proposal to improve reporting of SUSARs to EudraVigilance

In addition to the proposals related to the simplification of SUSAR reporting in the EU (chapter 3.2.1), the following should be provided:

- A legal basis that mandates electronic reporting of SUSARs and suspected expected SARs to EVCTM, which should be a common, central directory/repository for all suspected SARs and an efficient tool for Member States in rapidly identification safety issues during clinical trials.
- A legal basis for the mandatory population and maintenance of the EudraVigilance Medicinal Product Dictionary (EVMPD) with IMPs. The EVMPD is needed to assist the safety monitoring activities in the EEA by coding medicinal products and active substances in ICSRs, which are reported to EudraVigilance. IMPs should be entered at the same time sponsors are registering interventional clinical trials in the EudraCT database. The data should be provided based on the international standard currently being developed by ICH in collaboration with Standards Developments Organisations as outlined below.
- A clear reference in legislation as regards the use of international standards; as regards EudraVigilance, this refers in particular to the ISO Individual Case Safety Report (ICSR) and ISO Identification of Medicinal Products (IDMP) projects.
- A full alignment of the EudraCT database with the international IDMP standards to allow for the collection of structured, well organised data that can be shared with the EVMPD; this is to avoid double entries of the information by the sponsors in the future.

3.4 Consultation item N°8 & N°12 – Proposal of harmonisation of safety definition related to SUSARs

While the definition of SUSARs should be understood the same way by all stakeholders, different interpretations of the seriousness criteria, the expectedness and the adverse reaction definition have been used in the Community, resulting in heterogeneity of SUSARs reported to EudraVigilance. The harmonisation of safety definitions is therefore an important prerequisite to develop a reliable system of monitoring of interventional clinical trials.

3.4.1 Proposal for harmonisation of seriousness criteria

The seriousness of an adverse reaction is defined according to the five criteria listed in Article 2, paragraph (o) of Directive 2001/20/EC (i.e. Results in death, Is life threatening, Requires hospitalisation or prolongation of existing hospitalisation, Results in persistent or significant disability or incapacity, Is a congenital anomaly or birth defect). However the sixth criterion known as 'Important medical events', defined in ICH E2A[4] Guideline and addressed in Annex 1 of the Detailed Guidance ENTR/CT 3, is not included in Directive 2001/20/EC. In this case, medical and scientific judgement has to be exercised in deciding whether expedited reporting is appropriate in situations that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in Article 2, paragraph (o) of Directive 2001/20/EC.

Practice has shown that sponsors have different interpretations as regards the seriousness assessment of adverse reactions in interventional clinical trials. This 'Important medical events' criterion is therefore left to the medical judgment of the investigator or the sponsor, resulting in differing decisions, depending on the sponsor and, within the sponsor organisation, depending on the assessor.

It is therefore important for the sponsors to develop a list of 'Important medical events' terms which should be used to assist the seriousness assessment of the reactions which fall outside the five seriousness criteria defined in Article 2, paragraph (o) of Directive 2001/20/EC. This will ensure a consistent interpretation of medically important events and will guarantee a reliable approach in the reporting of serious adverse reactions by the sponsors. This list should be included in the study protocol and investigator brochure and any amendment during the study should be clearly documented in the study report.

A list of 'Important Medical events based on MedDRA Preferred Terms has recently been developed by the EV-EWG to assist the seriousness assessment based on the 6th criterion and to support the reliable reporting of serious adverse events by all stakeholders. The EV-EWG recommends the use of this list, which is publicly available on the EudraVigilance website. In case of special circumstances related to the indications or the populations involved in the interventional clinical trials, terms can be added or deleted from this list.

3.4.2 Proposal for harmonisation of the definition of the term 'Unexpected'

The expectedness of adverse reactions in interventional clinical trials relates to the list of adverse reactions included in the investigator brochure taken as the reference safety information or any equivalent reference document such as a Summary of Product Characteristic (SPC). The definition of the term 'Unexpected' is provided in Article 2, paragraph (p) of Directive 2001/20/EC and is completed in Annex 1 of the Detailed Guidance ENTR/CT 3.

Currently this definition leaves room for interpretation as to how suspected adverse reactions are included in the reference safety information and when during the course of the interventional clinical trial they are included as suspected expected adverse reactions. Depending on the sponsor procedures, a suspected adverse reaction can be considered expected and included in the investigator brochure after it has been reported only once or after a thorough assessment of several reports has been made by the sponsor.

The EV-EWG recommends that suspected adverse reactions remain "unexpected" until a thorough assessment of the concerned SUSARs has been made by the sponsor leading to their inclusion (or not) as suspected adverse reactions into the safety section of the investigator brochure or the reference safety information (e.g. SPC for authorised MP). This has been discussed and summarised in the Reports of CIOMS Working Group VI and VII and the ICH E2F guideline 'Development Safety Update Report'.

3.4.3 Proposal for harmonisation of the definition of the term 'Adverse Reaction'

The term 'Adverse reaction' defined in Article 2, paragraph (n) of Directive 2001/20/EC as 'All untoward and unintended responses to an investigational medicinal product related to any dose administered' leaves room for interpretation in the determination of a causality assessment between an event and an IMP. It is a recognised rule that the investigator should provide a causality assessment and be encouraged to express its opinion on what the cause of the adverse event might be. When a causality assessment is not provided by the investigator, it is the sponsor's responsibility to assess the causal role of the suspected IMP. However there is no clearly defined rule as to which causality assessment should be taken into account when there is a disagreement between the investigator and the sponsor.

The EV-EWG strongly suggests that a possible causal relationship between an adverse event and an IMP should always be assumed when there is a disagreement between the sponsor and the investigator on the causal role of the suspected IMP.

The EV-EWG also recommend making mandatory the reporting of the causality assessment of the investigator and of sponsor in all ICSRs transmitted electronically to EVCTM and thus for all events/reactions reported in the ICSRs. This would allow to easily distinguishing in EVDAS suspected reactions from events.

3.4.4 Proposal for a harmonisation of un-blinding rules

Depending on the un-blinding procedures put in place by the sponsor in the interventional clinical trial, SUSARs are reported blinded or un-blinded to the NCAs and a sizeable number of blinded reports exist in EudraVigilance. To avoid blinded SUSARs to be reported, it should be strongly recommended that sponsors follow the Detailed Guidance ENTR/CT 3, Paragraph 5.1.8, reiterating ICH E2A Guideline recommendations to un-blind all SUSARs before reporting them to EVCTM. Whether or not the result of breaking the treatment code is known only by the persons in charge of drug safety monitoring in the concerned interventional clinical trial, should be left to the judgement of each sponsor. As a consequence, the expectedness and causality assessment should be made carefully and in line with the recommendations presented above. While blinded SUSAR reports do not help signal detection, properly assessed un-blinded SUSARs involving similar reactions could lead to an evaluation of the risk in the context of the overall drug development or the interventional clinical trial itself and to their inclusion in the safety section of the investigator brochure or of the reference safety information as possible expected reactions.

This recommendation is based on the fact that SUSARs generally affect a very small proportion of the patients in the study. However, when the un-blinding interferes with the integrity of the interventional clinical trial (e.g. when an event reported in the SUSAR is also an efficacy endpoint in interventional clinical trials conducted in high morbidity and high mortality diseases), it is strongly recommended to set up an Independent Data Monitoring Committee to review safety data, as described in the Detailed Guidance ENTR/CT 3, Paragraph 5.1.9. Whether or not the result of the un-blinding is known only by the people in charge of monitoring drug safety in the concerned interventional clinical trial, should be left to each sponsor to organise.

3.4.5 Proposal for harmonisation of the reporting of placebo

The Detailed Guidance ENTR/CT 3 recommends reporting SUSARs involving placebo only when they are suspected to be associated to one of the excipients usually well tolerated of the placebo. In this situation it is not possible to evaluate SUSARs imbalance between the group treated with the tested MP or comparator and the other one treated with placebo.

With the implementation of the electronic reporting, the burden of manipulating and tracking paper ICSRs is no longer an issue. On the contrary the reporting of adverse reactions not included in the safety section of the investigator brochure or of the reference safety information of the tested MP or comparator, and involving a placebo treatment, would help to assess signals based on SUSARs by providing the background incidence of these events.

It would therefore be useful to report all SUSARs involving placebo or comparators and occurring in interventional clinical trials authorised in the EEA, for which detailed information on the number of patients included in the clinical trials is available in the EudraCT database.

3.5 Consultation item N°13 – Reporting of SUSARs by Non-Commercial/ "Academic" Sponsors

3.5.1 Proposal for adverse drug reaction reporting by Non-Commercial/ "Academic" Sponsors

The EV-EWG does not recommend the exclusion of non-commercial/"academic" sponsors from the rules of the Clinical Trials Directive. This would otherwise require the implementation of new legal reporting rules applicable to adverse drug reactions occurring in clinical trials conducted by non-commercial/"academic" sponsors. This is particularly important in order to maintain the ability of EudraVigilance to monitor the safety of all medicinal products being studied and authorised within the Community and to alert NCAs of potential risks to patients.

The simplification of SUSAR reporting as outlined in chapter 3.2.1 should therefore be applied to non-commercial sponsors who are able to report SUSARs electronically.

The requirements for sponsors of interventional clinical trials authorised in the EEA to report all SUSARs originating in third countries, outside the concerned interventional clinical trial and involving the active substance(s) of the MP(s) tested in the concerned interventional clinical trial, would not be applicable to non-commercial sponsors as this information is only available to commercial sponsors.

However, should they become informed of such cases, non-commercial sponsors should only report them to EudraVigilance when they are aware that the cases have not already been submitted electronically to EudraVigilance by the commercial organisation (MAH or sponsor) responsible for the MP.

For non-commercial sponsors not able to submit electronically SUSARs to the concerned MSs and /or to EVCTM, the following options are proposed based on clear, written agreements:

1. Option 1- If a commercial partner is involved in the concerned interventional clinical trial, this partner is responsible for submitting all SUSARs of the concerned trial electronically to EVCTM.
2. Option 2- For national interventional clinical trials authorised and conducted in one MS only, the non-commercial sponsor, not able to submit ICSRs electronically, reports on paper all SUSARs of the concerned trial to the MS of the country where the interventional clinical trial is authorised. The MS is then responsible to submit these reports electronically to EVCTM.
3. Option 3- For international multi-centre interventional clinical trials authorised and conducted in more than one MS (including also multi-centre clinical trials conducted within and outside the EEA), the following options are proposed:
    a. The non-commercial sponsor identifies an alternative organisation to which the electronic submission to EVCTM is delegated,
    b. The non-commercial sponsor develops the means to submit electronic reports to EVCTM,
    c. Following agreement with the concerned MS, the non-commercial sponsor reports on paper SUSARs to the MS where the interventional clinical trial is first authorised. This MS is then responsible to submit these reports electronically to EVCTM.

When submitting an application to conduct a clinical trial, non-commercial sponsors should be requested to indicate the proposed means used for the electronic reporting of SUSARs to EVCTM i.e., through commercial partner, through NCA with paper reports,

via an alternative organisation or directly by electronic reporting. This should be conditional to the granting of the authorisation to conduct the clinical trial.

3.5.2 Proposal for populating the EudraVigilance Medicinal Product Dictionary with IMPs by Non-Commercial/ "Academic" Sponsors

Currently non-commercial sponsors do not have the possibility to populate the EVMPD with IMPs. This restricted access will be removed in the next update of the EVMPD, which is part of the EVDAS Phase IIb development plan. Once the EVMPD has been updated the following options are proposed for non-commercial sponsors not able technically to populate the EVMPD:

1. Option 1- Electronic reporting to EVMPD can be outsourced to for example the commercial partner involved in the concerned interventional clinical trial or another external Clinical Research Organisation (CRO). This 'partner' is responsible for entering and maintaining the IMP(s) information in the EVMPD despite not being the main sponsor of the interventional clinical trial.
2. Option 2- For national interventional clinical trials authorised and conducted in one MS only, the non-commercial sponsor, reports in the EudraCT Clinical Trial Application (CTA) form all the information necessary for the population of the EVMPD with the IMP(s). The MS authorising the interventional clinical trial is then responsible to populate the EVMPD with the corresponding IMP(s) (if not already available in the EVMPD).
3. Option 3- For international multi-centre interventional clinical trials authorised and conducted in more than one MS (including also multi-centre clinical trials conducted within and outside the EEA):
    a. The non-commercial sponsor identifies an alternative organisation to which the population of the EVMPD with the IMP(s) of the concerned interventional clinical trial (if not already available in the EVMPD) is delegated/outsourced,
    b. The non commercial sponsor develops the means to populate the EVMPD with the IMP(s) of the concerned interventional clinical trial (if not already available in the EVMPD),
    c. Following agreement with the concerned MS(s) the non-commercial sponsor reports in the EudraCT CTA form all the information necessary for the population of the EVMPD with the IMP(s). The first MS authorising the clinical trial is then responsible to populate the EVMPD with the corresponding IMP(s) (if not already available in the EVMPD).

When submitting an application to conduct a clinical trial, non-commercial sponsors should be requested to indicate the proposed means used for the population of the EVMPD with the corresponding IMP(s) i.e., through commercial partner, through NCAs with the EudraCT application, via an alternative organisation or directly by electronic reporting. This should be conditional to the granting of the authorisation to conduct the clinical trial.

As a long-term solution, the full adaptation of EudraCT and the EVMPD with the ISO IDMP standards and the sharing of the IMP information by both systems should be envisaged to avoid duplication of efforts (see chapter 3.3.1).

Annex 1: Standard for expedited reporting of SUSARs presented in Paragraph 5.1.1.1 of the Detailed Guidance ENTR/CT 3 [5]

The sponsor of a clinical trial (Phase I-IV) with at least one investigator site in the Community should report SUSARs according to the following scenarios:

a) SUSARs which occur within the concerned trial

All suspected adverse reactions related to an investigational medicinal product (the tested investigational medicinal products and comparators) which occur in the concerned trial, and that are both unexpected and serious (SUSARs) are subject to expedited reporting.

b) SUSARs which occur outside the concerned clinical trial

(1) For investigational medicinal products that have a marketing authorisation in a Member State and the sponsor is the marketing authorisation holder:

Where the investigational medicinal product has a marketing authorisation in a Member State, and the sponsor is the marketing authorisation holder, the reporting of SUSARs which occur

(i) outside the concerned clinical trial and outside any other clinical trial (including SUSARs arising from any organised data collection system other than interventional clinical trials) should be in accordance with the Regulation (EC) No. 726/2004, Directive 2001/83/EC as amended and

(ii) if it occurs in a clinical trial according the 'Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (Eudravigilance – Clinical Trial Module)'.

(2) For investigational medicinal products that have a marketing authorisation in a Member State and the sponsor is not the marketing authorisation holder:

Where the investigational medicinal product has a marketing authorisation in any Member State, and the sponsor is not the marketing authorisation holder, any SUSARs associated with the investigational medicinal products that occur in another trial conducted by the same sponsor in a third country should be reported.

(3) For investigational medicinal products that do not have a marketing authorisation in any Member State of the Community:

Where the investigational medicinal product does not have a marketing authorization in any Member State of the Community, any SUSARs associated with the investigational medicinal products are subject to expedited reporting, as soon as the sponsor becomes aware of them. This includes:

- SUSARs which occur in another trial conducted by the same sponsor either in the Community or in a third country (i.e. in EEA countries),
- SUSARs which are identified by spontaneous reports or a publication,
- SUSARs which are transmitted to the sponsor by another regulatory authority.

Annex 2: Electronic reporting to EudraVigilance presented in Paragraph 6 of the Detailed Guidance ENTR/CT 4[6]

Table 1
SUSARs arising directly from clinical trials

Case Type	Community Marketing Authorisation Status	Origin	Destination	Timeline	Format	Reporter [1]	Reference
Case originates from a Clinical Trial with at least one investigator site in the EEA and the sponsor or an associated sponsor runs the trial:							
Clinical Trial	Pre[2]	EEA[4]	EV CT[6]	7/15 days	E2B(M)[8]	EEA Sponsor	Dir 2001/20/EC
Clinical Trial	Post[3]	EEA	EV CT	7/15 days	E2B(M)	EEA Sponsor	Dir 2001/20/EC
Clinical Trial	Pre	exEEA[5]	EV CT	7/15 days	E2B(M)	EEA Sponsor	Dir. 2001/20/EC
Clinical Trial	Post	exEEA	EV CT	7/15 days	E2B(M)	EEA Sponsor	Dir. 2001/20/EC
Case originates from a Clinical Trial without an investigator site in the EEA, but the IMP is being studied in another clinical trial with at least one investigator site in the EEA and the sponsor or an associated sponsor runs the EEA trial:							
Clinical Trial	Pre	exEEA	EV CT	7/15 days	E2B(M)	EEA Sponsor	Dir. 2001/20/EC
Clinical Trial	Post	exEEA	EV CT	7/15 days	E2B(M)	EEA Sponsor	Dir. 2001/20/EC and EudraLex Volume 9[10]
Case originates from a Clinical trial without an investigator site in the EEA and the IMP is not being studied in the EEA by the sponsor or an associated sponsor *(this information is included in this guidance for information and completeness – refer to Volume 9 of the 'Rules Governing Medicinal Products in the European Union')*:							
Clinical Trial	Pre	exEEA[4]	None	None	None	None	Not reportable in the EEA
Clinical Trial	Post	exEEA	EV CT	15 days	E2B(M)	EEA MAH	EudraLex Volume 9 and Dir. 2001/83/EC

[1] Reporter – the party responsible for ensuring that reports are made to Eudravigilance and to the concerned Member States
[2] Pre – means there is NO marketing authorisation in any EEA Member State
[3] Post – means there is a marketing authorisation in at least one Member State of the EEA
[4] EEA = Report of a reaction meeting the definition of a SUSAR occurring in the community

[5] exEEA = Report of a reaction meeting the definition of a SUSAR occurring outside the community
[6] EV CT: EudraVigilance Clinical Trial Module (EVCT)

Table 2
Case meeting the definition of a SUSAR obtained from Spontaneous Reports* (i.e. not arising from clinical trials)

Case Type	Community Marketing Authorisation Status	Origin	Destination	Timeline	Format	Reporter [1]	Reference
Case is a Spontaneous Report involving an IMP that is studied in at least one investigator site in the EEA and the sponsor or an associated sponsor runs the EEA trial:							
Spontaneous report	Pre	EEA	EV PM	7/15 days	E2B(M)	EEA Sponsor	Dir. 2001/20/EC, only if the EEA Sponsor becomes aware of the report
Spontaneous report	Post	EEA	EV PM[7]	15 days	E2B(M)	EEA MAH	Dir 2001/83/EC, Reg2309/93/EC, Eudralex Vol 9[10]
Spontaneous report	Pre	exEEA	EV PM	7/15 days	E2B(M)	EEA Sponsor	Dir. 2001/20/EC, only if the EEA Sponsor becomes aware of the report
Spontaneous report	Post	ex EEA	EV PM	15 days	E2B(M)	EEA MAH	Dir 2001/83/EC, Reg2309/93/EC, Eudralex Vol 9

*** The definition of spontaneous report is given in EudraLex volume 9. Spontaneous reports are unsolicited reports that arise outside clinical trials or organised data collection systems other than interventional clinical trials.**

[1] Reporter – the party responsible for ensuring that reports are made to Eudravigilance and to the concerned Member States
[2] Pre – means there is NO marketing authorisation in any EEA Member State
[3] Post – means there is a marketing authorisation in at least one Member State of the EEA
[4] EEA = Report of a reaction meeting the definition of a SUSAR occurring in the community
[5] exEEA = Report of a reaction meeting the definition of a SUSARoccurring outside the community
[6] EV CT: EudraVigilance Clinical Trial Module (EVCT)
[7] EVPM EudraVigilance Human Post-Authorisation Module (EVPM)
[8] ICH E2B(M) DATA ELEMENTS FOR TRANSMISSION OF INDIVIDUAL CASE SAFETY REPORTS Amended Guideline : November 2000, CPMP/ICH/287/95 correction - ICH E2B(M)
[10] VOLUME 9 – PHARMACOVIGILANCE: Medicinal Products for Human and Veterinary Use
For reports from post-authorisation studies, which qualify as clinical trials, Directive 2001/20/EC should be applied from the date of its implementation. In the meantime relevant national legislation should be followed in addition to the requirements stated above.

Table 3
Case meeting the definition of a SUSAR arising from organised data collection system other than interventional clinical trials*

Case Type	Community Marketing Authorisation Status	Origin	Destination	Timeline	Format	Reporter [1]	Reference
Case originates from a from any organised data collection system other than interventional clinical trials *(this information is included in this guidance for information and completeness – refer to Volume 9 of the 'Rules Governing Medicinal Products in the European Union')*:							
Solicited	Pre	EEA	EV PM	15 d	E2B(M)	EEA Sponsor	As defined in ICH E2D[9], reporting should follow Volume 9. Only applies if IMP is studied in EEA., and if the EEA Sponsor has knowledge of the reports
Solicited	Pre	exEEA	EV PM	15 d	E2B(M)	EEA Sponsor	As defined in ICH E2D, reporting should follow Volume 9. Only applies if IMP is studied in EEA., and if the EEA Sponsor has knowledge of the reports
Solicited	Post	EEA	EV PM	15 d	E2B(M)	EEA MAH	As defined in ICH E2D reporting should follow Volume 9.
Solicited	Post	exEEA	EV PM	15 d	E2B(M)	EEA MAH	As defined in ICH E2D, reporting should follow Volume 9.

***Solicited reports are reports that arise from organized data collection systems other than invterventional clinical trials. They are defined in ICH E2D.**

As both clinical trial SUSARs and post-marketing ICSRs will be held in Eudravigilance it is logical that where a report is made concerning a case to Eudravigilance, it should only be made once and in accordance with the applicable legislation.

---

[1] Reporter – the party responsible for ensuring that reports are made to Eudravigilance and to the concerned Member States
[2] Pre – means there is NO marketing authorisation in any EEA Member State
[3] Post – means there is a marketing authorisation in at least one Member State of the EEA
[4] EEA = Report of a reaction meeting the definition of a SUSAR occurring in the community
[5] exEEA = Report of a reaction meeting the definition of a SUSARoccurring outside the community
[6] EV CT: EudraVigilance Clinical Trial Module (EVCT)
[9] ICH E2D: Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting; Adopted by CPMP, 20 November 2003, issued as CPMP/ICH/3945/03
[10] VOLUME 9 – PHARMACOVIGILANCE: Medicinal Products for Human and Veterinary Use
For reports from post-authorisation studies, which qualify as clinical trials, Directive 2001/20/EC should be applied from the date of its implementation. In the meantime relevant national legislation should be followed in addition to the requirements stated above.

Annex 3: SUSARs Expedited Reporting Requirements in Member States

A total of 28 National Competent Authorities (NCAs) out of 31 have responded to the survey which was conducted in 2007. To keep confidentiality of the results, letters from A to Z plus ZA and ZB are used to identify each NCA.

Table 1
Expedited (7/15-days) reporting requirements of SUSARs originating in <u>the territory of a Member State</u> and related to an IMP or the active Substance(s) of an IMP for which an interventional clinical trial has been approved in <u>this Member State</u>

Type of SUSAR	Concerned Member States 7/15 days expedited reporting by sponsor to the Competent Authority	Concerned Member States 7/15 days expedited reporting by sponsor to EudraVigilance**
SUSARs related to an IMP and occurring in the approved interventional clinical trial	A[1], B, C, D, E, F, G, H, I, J, K, L, M, N, O, P, Q, R, S, T, U, V, W, X, Y, Z, ZA, ZB	C, D, H, J*, K, L, M, O, S, T, U, V*, W, X*, Z, ZA, ZB*
SUSARs related to the active substance(s) of an IMP and occurring in any other sources than an approved interventional clinical trial (e.g., compassionate use)	B, E, F, I[1], K, Z	K, Z ♦

*: Reporting requirement to EudraVigilance not legally binding according to concerned Member State national law.

♦: Reports following Directive 2001/83/EC as amended or Regulation (EC) No 726/2004 are made available to EudraVigilance by the concerned Member State and should not be submitted to EudraVigilance by the sponsor.

**: For electronic reporting to EudraVigilance, SUSARs originating from non-interventional trials, compassionate use or spontaneous reporting, should be submitted to the EudraVigilance Post-authorisation Module (EVPM). SUSARs originating from interventional clinical trials should be submitted to the EudraVigilance Clinical Trial Module (EVCTM).

A[1]: Only SUSARs related to a clinical trial authorised in country A should be reported. SUSARs occurring within or outside EEA and related to a clinical trial approved in country A (same EUDRACT Number) should therefore be also reported.

I[1]: When IMP is not authorised in any EEA country.

Table 2
Expedited (7/15-days) reporting requirements of SUSARs originating in the territory of <u>another Member State</u> and related to an IMP or the active substance(s) of an IMP for which an interventional clinical trial has been approved in the <u>concerned Member State</u>

Type of SUSAR	Concerned Member States 7/15 days expedited reporting by sponsor to the Competent Authority	Concerned Member States 7/15 days expedited reporting by sponsor to EudraVigilance**
SUSARs related to an IMP and occurring in the approved interventional clinical trial	A[1], E, F, G, I, J, K, M, N, O, P, Q, S, T, U, V, Z, ZA	B[1], D, J*, K, L, M, O, S, T, U, X*, Y, Z, ZA, ZB*
SUSARs related to an IMP and occurring in another/other interventional clinical trial(s)	E, F, I[1], K, Z	B[1], K, Z
SUSARs related to the active substance(s) of an IMP and occurring in any other sources than an approved interventional clinical trial (e.g., compassionate use, spontaneous reporting, non-interventional trials)	E, F, I[1], K, Z	B[1], K, Z ♦

*: Reporting requirement to EudraVigilance not legally binding according to concerned Member State national law.

♦: Reports following Directive 2001/83/EC as amended or Regulation (EC) No 726/2004 are made available to EudraVigilance by the Member State in whose territory the incident occurred and should not be submitted to EudraVigilance.

**: For electronic reporting to EudraVigilance, SUSARs originating from non-interventional trials, compassionate use or spontaneous reporting, should be submitted to the EudraVigilance Post-authorisation Module (EVPM). SUSARs originating from interventional clinical trials should be submitted to the EudraVigilance Clinical Trial Module (EVCTM).

A[1]: Only SUSARs related to a clinical trial authorised in country A should be reported. SUSARs occurring within or outside EEA and related to a clinical trial approved in country A (same EUDRACT Number) should therefore be also reported.

B[1]: Waiver must be applied not to report to this NCA.

I[1]: When IMP is not authorised in any EEA country.

Table 3
Expedited (7/15-days) reporting requirements of SUSARs originating outside the EEA and related to an IMP or the active substance(s) of an IMP for which an interventional clinical trial has been approved in the concerned Member State

Type of SUSAR	Concerned Member States 7/15 days expedited reporting by sponsor to the Competent Authority	Concerned Member States 7/15 days expedited reporting by sponsor to EudraVigilance**
SUSARs related to an IMP and occurring in the approved interventional clinical trial	A[1], E, F, I, J, K, M, N, O, P, Q, T, U, V, Z, ZA	B[1], D, J*, K, L, M, O, T, U, X*, Y, Z, ZA, ZB*
SUSARs related to an IMP and occurring in another/other interventional clinical trial(s)	E, F, I[1], K, Z	B[1], K, Z
SUSARs related to the active substance(s) of an IMP and occurring in any other sources than an approved interventional clinical trial (e.g., compassionate use, spontaneous reporting, non-interventional trials)	E, F, I[1], K, Z	B[1], K, Z ♠

*: Reporting requirement to EudraVigilance not legally binding according to concerned Member State national law.

**: For electronic reporting to EudraVigilance, SUSARs originating from non-interventional trials, compassionate use or spontaneous reporting, should be submitted to the EudraVigilance Post-authorisation Module (EVPM). SUSARs originating from interventional clinical trials should be submitted to the EudraVigilance Clinical Trial Module (EVCTM).

♠: The reporting obligations of SUSARs for medicinal products authorised in the EEA are fulfilled by the MAH when reporting to EVPM according to Directive 2001/83/EC as amended and Regulation (EC) No 726/2004. Therefore the sponsors should ensure that the SUSARs originating in third countries and falling under the scope of Directive 2001/83/EC as amended and Regulation (EC) No 726/2004 are submitted only once to EVPM.

A[1]: Only SUSARs related to a clinical trial authorised in country A should be reported. SUSARs occurring within or outside EEA and related to a clinical trial approved in country A (same EUDRACT Number) should therefore be also reported.

B[1]: Waiver must be applied not to report to this NCA.

I[1]: When IMP is not authorised in any EEA country.

Annex 4: Reporting status in EVCTM in 2009

Table 1
Number of serious ICSRs, including backlog, reported on monthly basis to EVCTM in 2009, distributed by type of sending organisation

2009	Commercial Sponsors	Non-Commercial/ "Academic" Sponsors	NCAs	Total
January	4,392	58	1,441	5,891
February	5,926	70	1,719	7,715
March	6,304	67	1,883	8,254
April	6,166	42	2,031	8,239
May	5,437	42	1,902	7,381
June	5,703	48	1,964	7,715
July	6,704	64	1,785	8,553
August	5,104	28	1,909	7,041
September	5,662	63	2,307	8,032
October	6,014	52	2,012	8,078
November	6,654	88	2,146	8,888
December	6,660	117	2,036	8,813

Table 2
Average number of organisations reporting on monthly basis to EVCTM in 2009

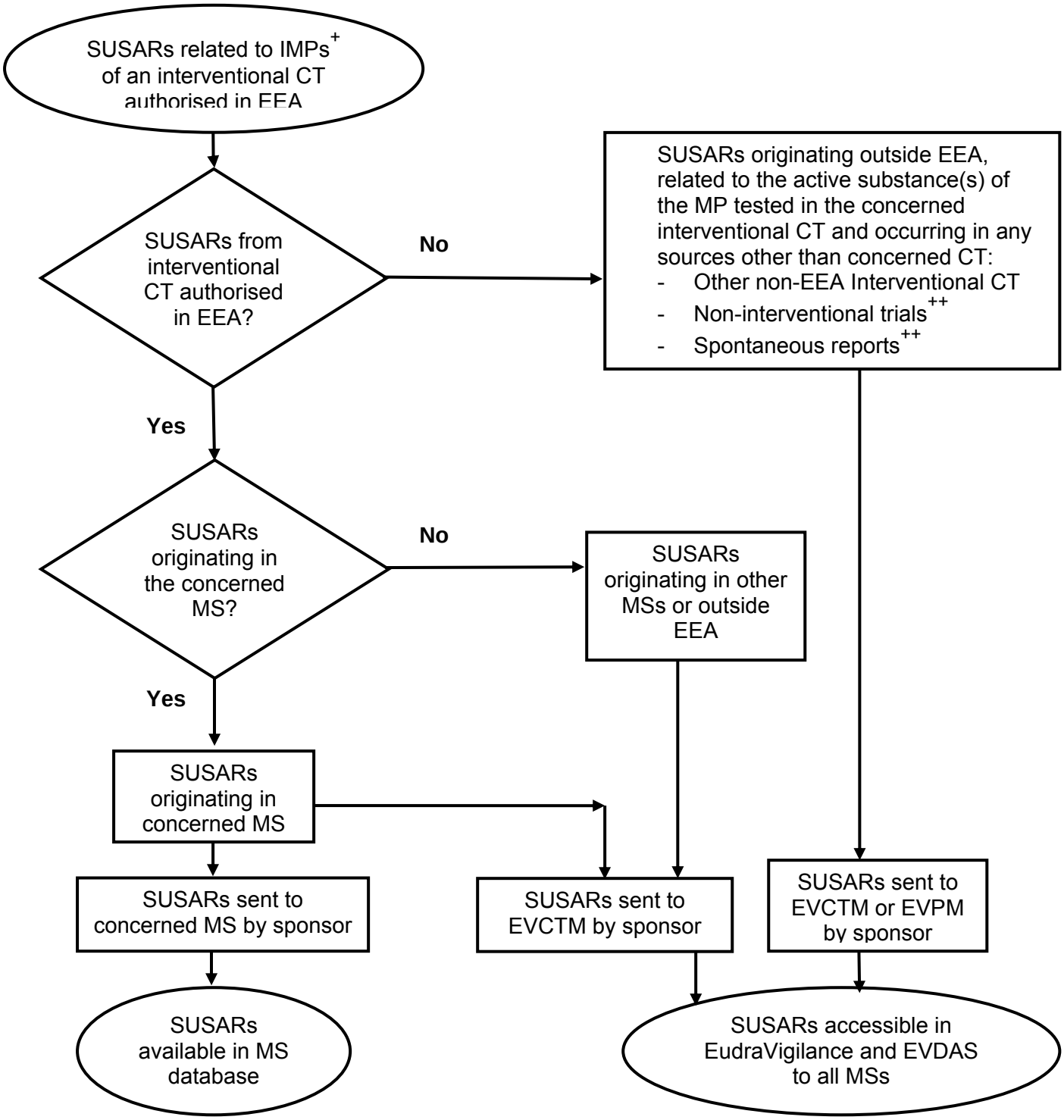
Commercial Sponsors	Non-Commercial/ "Academic" Sponsors	NCAs
138	14	9

Table 3
Total cumulative number of serious ICSRs and cases, including backlog, reported to EVCTM up to 31-Dec-2009

	Number of ICSRs	Number of Cases	Origin of Cases EEA / Non-EEA (%)	Origin of Cases Sponsors / NCAs (%)
EVCTM	339,467	140,148	51 / 49	81 / 19

Annex 5: Detailed flowcharts of reporting requirements options presented in Chapter *3.2.1*

Figure 1, SUSARs flowchart as proposed as interim option



+ An Investigational Medicinal Product is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form; Directive 2001/20/EC.

++ The reporting obligations of SUSARs originating outside EEA for MPs authorised in the EEA are fulfilled by the MAH when reporting to EVPM according to Directive 2001/83/EC as amended and Regulation (EC) No 726/2004. Suspected serious adverse drug reactions related to MPs authorised in EEA and originating in the country of a MS are sent by the MS to EVPM.

The interim solution has several advantages:

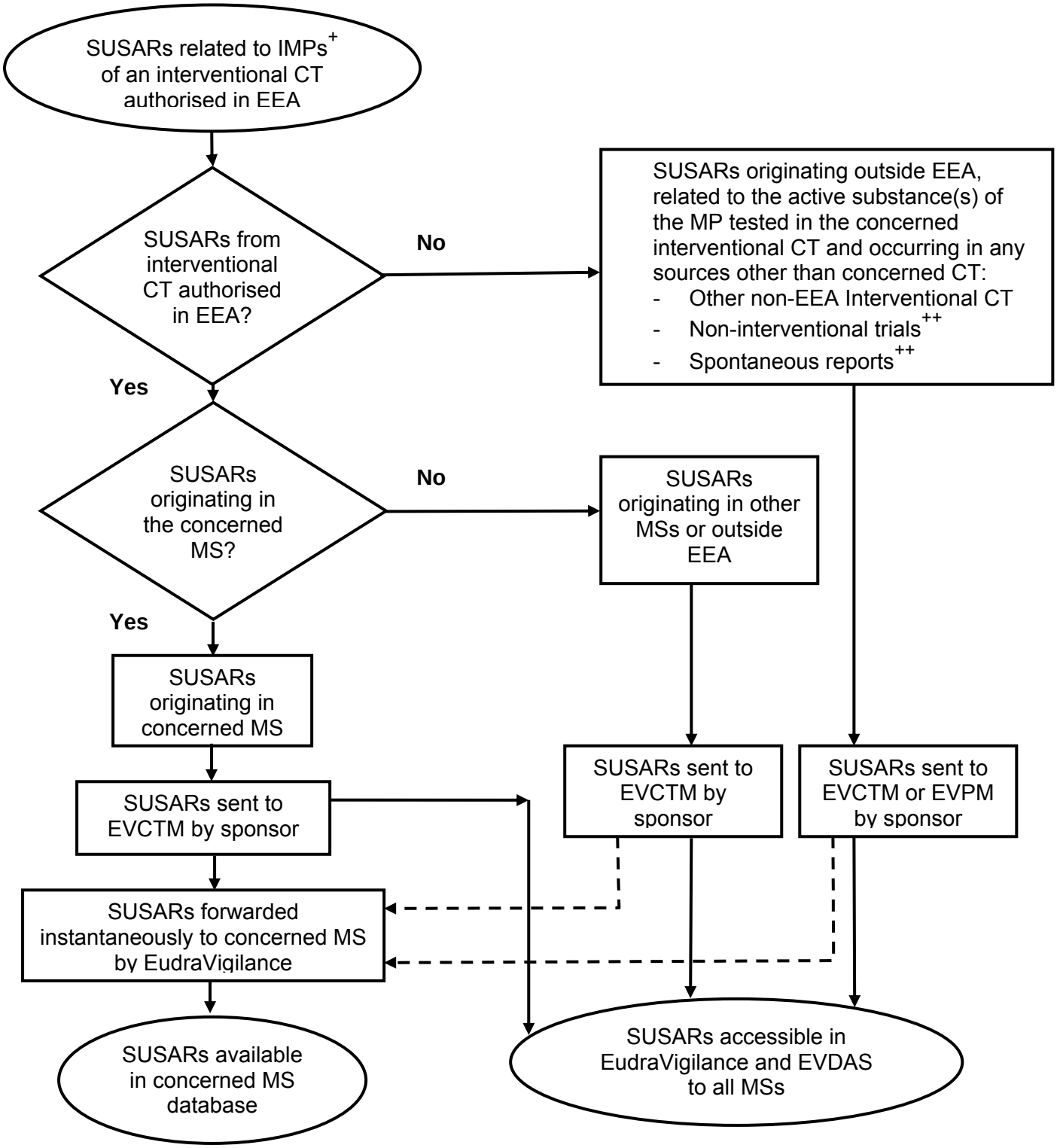
- The MSs with a system able to receive electronic reports have the possibility to populate their own database with SUSARs of the concerned interventional clinical trial and originating in their own territory without manual data entry;
- The MSs are able to carry out quality control of the reports of SUSARs originating in their territory;
- It also provides reassurance to MSs that they have received all SUSARs originating in their territory;
- The MSs do not need to submit SUSARs originating in their territory to EVCTM as they are sent by the sponsors;
- This reduces the timelines for SUSARs to be available in EudraVigilance since they do not need to be processed and submitted by the concerned MS to EVCTM;
- The MSs are able to retrieve all SUSARs related to the concerned interventional clinical trial by querying EVDAS with the corresponding EudraCT number;
- The MSs are able to retrieve in EVDAS other SUSARs related to the same MP and occurring in another/other interventional clinical trial(s) authorised in the EEA,
- The MSs are able to retrieve in EVDAS all SUSARs related to the active substance(s) of the tested MP and occurring in any other sources than the approved interventional clinical trial;
- The risk of duplicates in EudraVigilance is substantially reduced since the sponsors are the only source of reporting.

However this option presents several constraints:

- The sponsors have to adapt their system to submit third countries SUSARs to EudraVigilance and EEA and SUSARs of the concerned interventional clinical trial both to the MS in whose territory the reactions originated and to EVCTM;
- The MSs need to have a system capable of receiving reports electronically.

Although, as part of the interim option, sponsors have to submit SUSARs to at most two repositories (i.e. the concerned MS database for SUSARs originating in the country of a MS and EudraVigilance (EVCTM or EVPM) for all SUSARs), this is a step forward solution to a common repository for all SUSARs involving the active substance(s) of MPs tested in interventional clinical trials authorised in the EEA. This proposal reduces the risk of SUSAR duplicates in EudraVigilance and it allows the establishment of a database fully populated with SUSARs thus enhancing the ability of EVDAS to monitor the safety of interventional clinical trials and to alert NCAs of potential risks to trial patients.

Figure 2, SUSARs flowchart as proposed as long-term solution



+ An Investigational Medicinal Product is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form; Directive 2001/20/EC.

++ The reporting obligations of SUSARs originating outside EEA for MPs authorised in the EEA are fulfilled by the MAH when reporting to EVPM according to Directive 2001/83/EC as amended and Regulation (EC) No 726/2004. Suspected serious adverse drug reactions related to MPs authorised in EEA and originating in the country of a MS are sent by the MS to EVPM.

The long-term solution brings several benefits for the sponsors and the MSs in term of cost and simplification of electronic reporting:

- Depending of the specifications set up, the MSs with a system able to receive electronically ICSRs, have the possibility to populate their own database
  - With SUSARs of the concerned interventional clinical trial and originating in their own territory or
  - With SUSARs of interventional clinical trials originating within and outside the EEA and related to the active substance(s) of MPs tested in interventional clinical trials authorised in the EEA;
- The sponsors interact with only one common repository i.e., EudraVigilance (EVCTM or EVPM);
- This option reduces for the sponsors the costs and the complexity of reporting to each individual concerned MS.
- It decreases the costs of some MSs in establishing and/or updating their own system to receive and to submit SUSARs electronically to EVCTM;

The disadvantages of this option are limited and concern particularly technical aspects:

- Technical adaptations of the EudraVigilance System is required in order to be able to forward automatically and instantaneously to the concerned MSs, depending on their requirements, all SUSARs of interventional clinical trials sent to EVCTM by sponsors, related to the active substance(s) of the MPs tested in interventional clinical trials authorised in the EEA and originating:
  - Within the territory of the concerned MS or
  - Within and outside the EEA.

Once the legal obligations have been adopted for sponsors to report SUSARs to EVCTM only and the technical solution is available to automatically and instantaneously forward SUSARs to MSs, the long-term solution could be implemented allowing the sponsors to interact with only one system.