INFORMATION REQUIRED FOR ETHICS COMMITTEES	AT	BE	DK	FI	FR	DE	EL	IT	IE	LU	NL	PT	ES	SE	UK
If IMP not manufactured in E.U.:															
– Declaration of the QP that the manufacturing site works in compliance with GMP at least equivalent to EU GMP		No		No	No	No		Yes	No	No	Yes	No	No	No	No
– Copy of the importer authorization as referred to in Art. 13.1. of the Directive		No		No	No	No		Yes	No	No	Yes	No	No	No	No
Certificate of analysis for test product in exceptional cases:															
– where impurities are not justified by the specification or when unexpected impurities (not covered by specification) are detected		No	Yes	No	No	No		No	No	No	Yes	No	No	No	No
–															
Viral safety studies	Yes	A	Yes	No	No	No		No	No	No	Yes	No	No	No	No
Examples of the label in the national language	No	No	Yes	No	No	Yes		Yes	No	No	Yes	No	No	No	No
Applicable authorizations to cover trials or products with special characteristics (if available) e.g. GMOs, radiopharmaceuticals	No	No	Yes	No	No	No		Yes	No	No	Yes	No	No	No	No
TSE Certificate when applicable		No		No	No	No		Yes	No	No	Yes	No	No	No	No
Declaration of GMP status of active biological substance		No		No	No	No		No	No	No	Yes	No	No	No	No
Facilities & staff related															
Facilities for the trial	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
CV of the coordinating investigator in the MS concerned (for multicentre trials)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
CV of each investigator responsible for the conduct of the trial in a site in the MS concerned (principal investigator)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes A	Yes	Yes	Yes	Yes	Yes	Yes
Information on supporting staff in each site					Yes										
Finance related															
Provision for indemnity or compensation in the event of injury or death attributable to the clinical trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Any insurance or indemnity to cover the liability of the investigator and sponsor	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Compensation to subjects				Yes	Yes			Yes	Yes		Yes			Yes	

INFORMATION REQUIRED FOR ETHICS COMMITTEES	AT	BE	DK	FI	FR	DE	EL	IT	IE	LU	NL	PT	ES	SE	UK
Compensation to investigators	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Agreement between the sponsor and the trial site	Yes	Yes	No		Yes	Yes	Yes	Yes	Yes	Yes	A	Yes	Yes	Yes	Yes
Agreement between the investigators and the trial sites		Yes			No	Yes		Yes	Yes		A		No	No	
Certificate of agreement between sponsor and investigator when not in the protocol	No	Yes	No	No	No	No	Yes	Yes	Yes		A		Yes	No	No

MEMBER STATES' ADDITIONAL EXPLANATION

The symbol # means that the issue is being discussed in the MS.

The letter A preceding information below refer to letter under the MS column in the table above and provide additional explanation about the information to be provided.

Belgium:

A. Yes, but the protocol or the investigator's brochure can include this information. There is no need for a separate document.

Netherlands

A. Available on request

7.2 Information to be forwarded to the Ethics Committee in different new Member States

INFORMATION FOR ETHICS COMMITTEES

INFORMATION REQUIRED FOR ETHICS COMMITTEES	CY	CZ	EE	HU	LV	LT	MT	PL	SK	SI		NO	IS
MS SPECIFIC INFORMATION													
Receipt of confirmation of the EUDRACT number TBD ! This is not necessary !!		Yes			No	Yes						Yes	
Covering letter	Yes	Yes	Yes	Yes	Yes	Yes				Yes		Yes	
Application form	Yes	Yes	Yes	Yes	Yes	Yes						Yes	
Clinical trial protocol	Yes	Yes	Yes	Yes	Yes	Yes				Yes		Yes	
Investigator's brochure	Yes	Yes	Yes	Yes	Yes	Yes				Yes		Yes	
List of Competent Authorities to which the application has been submitted and details of decisions, if available	No	Yes	Yes	No	No	Yes				Yes			
Subject related													
Informed consent form	Yes	Yes	Yes	Yes	Yes	Yes				Yes		Yes	
Subject information leaflet	Yes	Yes	Yes	Yes	Yes	Yes				Yes		Yes	
Arrangements for recruitment of subjects	Yes	Yes	Yes	Yes	Yes	Yes				Yes		Yes	
Protocol related													
Summary of the protocol in the national language	Yes	Yes	Yes	No	No	Yes				Yes		No	
Outline of all active trials with the same IMP	No	No	No	Yes	No	No						Yes	
Peer review of the scientific value of the trial, when available, not compulsory	No	No	No	Yes	No	Yes				Yes		Yes	
Ethical assessment made by the principal/coordinating investigator, if not given in the application form	Yes	No	Yes	No	No	Yes				Yes		Yes	
IMP related													
Investigational Medicinal Product Dossier (IMPD)	No	No	No		No	No							
Simplified IMPD for known products. See table 1 in application to competent authorities	No	No	No	No	No	No				Yes		No	
Summary of Product Characteristics (SmPC) (for products with marketing authorisation in the Community)	No	No	Yes	No	No	Yes				Yes			
If IMP manufactured in E.U.:													
– copy of the manufacturer authorization referred to in Art. 13.1. of the Directive stating the scope of this authorization	No	No	No	No	No	Yes				No		No	

INFORMATION REQUIRED FOR ETHICS COMMITTEES	CY	CZ	EE	HU	LV	LT	MT	PL	SK	SI		NO	IS
If IMP not manufactured in E.U.:													
– Declaration of the QP that the manufacturing site works in compliance with GMP at least equivalent to EU GMP	Yes	No	No	No	No	No				No		No	
– Copy of the importer authorization as referred to in Art. 13.1. of the Directive	Yes	No	No	No	No	No				No		No	
Certificate of analysis for test product in exceptional cases:													
– where impurities are not justified by the specification or when unexpected impurities (not covered by specification) are detected	No	No	No	No	No	No				No		No	
–													
Viral safety studies	No	No	No	No	No	No				No		No	
Examples of the label in the national language	No	No	No	No	No	Yes*				No		No	
Applicable authorizations to cover trials or products with special characteristics (if available) e.g. GMOs, radiopharmaceuticals	No	No	No	No	No	Yes				No		No	
TSE Certificate when applicable	No	No	No	No	No	No				No		No	
Declaration of GMP status of active biological substance	No	No	No	No	No	No				No		No	
Facilities & staff related													
Facilities for the trial	Yes	Yes	Yes	Yes	Yes	Yes				Yes		No	
CV of the coordinating investigator in the MS concerned (for multicentre trials)	Yes	Yes	Yes	Yes	No	Yes				Yes		Yes	
CV of each investigator responsible for the conduct of the trial in a site in the MS concerned (principal investigator)	Yes	Yes	Yes	Yes	Yes	Yes				Yes		Yes	
Finance related													
Provision for indemnity or compensation in the event of injury or death attributable to the clinical trial	Yes	Yes	Yes	Yes	Yes	Yes				Yes		Yes	
Any insurance or indemnity to cover the liability of the investigator and sponsor	Yes	Yes	Yes	Yes	Yes	Yes				Yes		Yes	
Compensation to subjects	Yes	Yes	Yes	Yes	Yes	Yes				Yes		Yes	

INFORMATION REQUIRED FOR ETHICS COMMITTEES	CY	CZ	EE	HU	LV	LT	MT	PL	SK	SI		NO	IS
Compensation to investigators	Yes	Yes	Yes	Yes	No	Yes				No		Yes	
Agreement between the sponsor and the trial site	Yes	Yes	No	Yes	No	Yes				Yes		Yes	
Agreement between the investigators and the trial sites	Yes	Yes	No	Yes	No	Yes				No		Yes	
Certificate of agreement between sponsor and investigator when not in the protocol	Yes	Yes	No	No	No	Yes				No		Yes	

MEMBER STATES' ADDITIONAL EXPLANATION

Lithuania: *For authorized products in Lithuania, for other –acoording to Directive 2001/20/EC

7.3. Request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities and for opinion of the Ethics Committees in the European Union.

Module 1

This first module of the application form to be used to the Ethics Committee is the same as the form used in the submission to the competent authority.

To be found in 'Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial' Annex 1.

Module 2

The second module presented below, is intended to provide detailed information on the planned trial and also on aspect that might be specific for the Member State in case of multi-centre trials. The headings provided below is intended to give guidance on aspects that might be addressed when relevant. It is not intended to be a complete listing of all elements necessary for the Ethics Committee to consider during its work, but to indicate some and give examples that might have to be considered by the Ethics Committee in some Member States.

1. EudraCT trial number Ethics Committee trial ID
2.Title of the project (This should be understandable for laypersons)
3. Summary of the project. (justification and relevance)
4. Results of pre-clinical tests or reasons for not doing pre-clinical tests
5. Primary hypothesis in this trial (if relevant, also secondary hypotheses)
Research ethical considerations (Identify and state any possible problems that might occur. Present possible gain in knowledge to be obtained in the trial and its importance, possible risks for injuries or distress for the participants. Present your own evaluation of the risk-benefit ratio).
Reason for including persons from vulnerable groups, i.e. minors, temporaily or permanently incapacitated subjects.

8. Description of the recruitment procedure (all material to be used should be appended)
Procedure at the site to provide information and obtain consent from the subjects, or parents or legal representatives if applicable (who will give the information and when, need for legal representatives, witness etc).
10. Investigational procedures and any deviations necessary from the routine treatment
Risk assessment, foreseeable risks of treatment and procedures to be used (incl. pain, discomfort, violation of integrity and means to avoid and/or take care of unforeseen / unwanted events)
12. Previous experience of the conduct of similar research procedures at this site.
13. Any foreseeable benefit for included subjects
14. Relation between subject and investigator (patient-physician, student – teacher etc)
15. Procedures of the site to check if the subject participates simultaneously in other research or if a required period has elapsed since previous participation in research (of special importance when healthy subjects are included in pharmacology trials).
16. Requirements and methods for recording health control for healthy subjects (i.e. hospital files or other national requirements)
17. Methods for searching, recording and reporting adverse effects (describe when, by whom and how, i.e. open questions and/or according to lists)
18. Procedures used to protect the privacy of recorded data, source documents and samples (if applicable).
19. Plan for treatment or care after the subject has ended the participation in the trial (who will be responsible and where)
20. Statistical consideration and reasons for the number of subjects to be included in the trial.

21. Amount and procedure for remuneration or compensation of subjects (description of amount paid, during the participation in the trial and for what, i.e. travel cost, loss of earning, pain and discomfort etc) .
22. Rules for stopping or prematurely ending the trial at the site(s) in this Member State or as a whole
23. Agreement on investigator's access to data, publication policy etc. (if not available in the protocol)
24. Sources of funding (if not available in the protocol) and information on financial or other interests of the investigator(s).

NAME AND SIGNATURE OF APPLICANT - CO-ORDINATING INVESTIGATOR/PRINCIPAL INVESTIGATOR (and/or sponsor, if applicable)	
I hereby confirm that the information given in this application is correct and that I am of the opinion that it will be possible to conduct the trial in accordance with the protocol, national regulations and principles of Good Clinical Practice.	
Name : Surname : Address : Position: :	
Date :	Signature:

7.4 Advertising for trial subjects

This appendix is intended to provide guidance on items that might be relevant to consider when advertising for subjects who will be asked to participate in a clinical trial. The items listed do not comprise a complete list and should be modified according to the type of trial and national recommendations.

All advertisements for trial subjects should be included in the submission for approval by the Ethics Committee. The review by the Ethics Committee might also include the procedures to take care of subjects responding to the advertisement.

The advertisement might contain information on the following points:

1. The research nature of the project
2. The scope of the trial
3. Which type/group of subjects might be included
4. The investigator clinically/scientifically responsible for the trial, if possible or if required by local regulations.
5. The person, name, address, organisation, to contact for information
6. That the subject responding will be registered
7. The procedure to contact the interested subjects
8. Any compensation for expenses
9- That a response on the part of a potential subject only signifies interest to obtain further information

Information concerning the procedures to handle the answers to the advertisement might contain information on the qualifications of the person who will be responsible for the first contact with the subjects, i.e. might be a nurse. This is especially important when patients are replying to an advertisement. In addition, resources/procedures should be in place to provide information to and take care of patients not suitable for inclusion in the planned trial. Lack of suitability might be obvious at the first contact or after screening of the subjects who responded. There might be a description of how the patient will be given advice or help to contact a relevant institution/clinic not related to the planned trial.

All information to be provided to the respondent should be submitted to the Ethics Committee for approval. If there is a screening procedure to evaluate the suitability of the respondent two sets of information sheets might be used. One set could provide information on the procedure and the reasons for screening. It should be explained what the consequences might be in case of a certain outcome of the screening. For example if a biopsy shows pathological changed the patient will be asked if he/she is willing to participate in a trial and a brief overview of the trial be given. The second more extensive information could provide the detailed information on the trial and should follow the usual requirements.

Potential subjects should be informed that personal information might be recorded and will be protected according to national requirements. The procedure for giving the participating subject compensation or rewards and the amount(s) should be outlined. The applicant should

also describe the procedure for informing the subject on how he/she may be eliminated from the register.

7.5. Content of subject information

This appendix is intended to provide further guidance on items that might be of relevance for the subject information leaflet. It is not intended to provide a complete list of items which should be included, but to give some examples of items that might have to be considered if relevant to the particular trial.

7.5.1. Subject information, general aspects.

The information sheet should state clearly the justification for the trial, its relevance and objective and should contain at least all the items listed in the relevant section of the Community guideline on Good Clinical Practice (CPMP/ICH/135/95).

In addition written information should be provided on:

1.1 the contact point from which further information may be obtained relating to the trial and in case of injury, according to national requirements.

1.2 the names and addresses of the investigator, study nurse etc who are responsible for taking care of the included subjects.

1.3 any planned procedures for follow up after the end of the trial (for example for trials involving gene transfer medicinal products) and/or plans for additional care that might be needed due to findings during follow up.

1.4 any financial or other ties to the sponsor as well as institutional affiliations of the investigator as well as the name and address of sponsor /sources of funding

1.5 the Ethics Committee positive opinion.

1.6 the subject's rights to privacy and the means have taken to ensure protection of personal data.
This might include information on:

- procedures for coding,
- the arrangement with code-keys: the name of the person responsible for keeping the key and who will have access
- in the case of retention of subject samples and information,
    - to whom the data and samples are accessible
    - the location and duration of retention
    - name of the person who will be responsible for keeping the samples and the results
    - procedure for handling any retained identifiable samples
    - plans to anonymise or destroy samples after analysis

1.7 the subject's right to obtain updated information about what data is recorded as well as the right to require corrections of errors

1.8 the right of the subject (or parent or legal representative) to withdraw consent to participate in the trial

1.9 the fact that in the event of the withdrawal of consent to participate in the trial, no new data will be added to the database and that, according to national provisions, the subject (or parent, guardian or legal representative) may require all previously retained identifiable samples to be destroyed to prevent further analysis.

1. 10 the right of the subject (parent or legal representative) to be informed of any plans for new analyses on retained identifiable material that were not foreseen when the subject consented to participate in the study. The investigator might have to ask for new consent and the subject has the right to refuse further analyses, according to national rules.

7.5.2. Information in Pharmacogenetic trials

In clinical trials where genetic testing is included, this should be clearly explained to the subject. The information should give the background and purpose of the genetic tests, the planned analyses and whether the samples will be kept to make future analyses possible in conjunction with the planned project. When applicable, the information on the genetic part of the trial might be separate from the information on the other part. Information should be provided on the possibility for the subject to abstain from the genetic testing but still be able to participate in the non-genetic part of the trial, according to national recommendations. Further information on pharmacogenetic trials can be obtained from the position paper from the Committee for proprietary medicinal Products[10].

7.5.3. Trial specific and general explanatory information to subjects.

It might sometimes be useful to divide the information to be provided in two parts. One part should contain the information necessary for the subject to decide whether or not to participate in the planned trial. It could focus on the information specific for the planned trial and only contain information related to general issues and systems such as protection of privacy, insurance etc. as is relevant to the trial in question.
The second part should contain general information common to trials in the Member State. It might address and explain in more detail the national systems for the protection of the rights, welfare and safety of the subjects. The reasons for quality control and quality assurance and the need for Source Data Verification (SDV) as well as measures to protect the confidentiality of personal information, systems for labelling, analysing and publishing data and availability of insurance/indemnity systems could be explained. This general second part, once approved by the Ethics Committee, could be used where appropriate in similar trials in that Member State.

10 Position paper on terminology in pharmacogenetics, EMEA/CPMP/3070/01

EUROPEAN COMMISSION
ENTERPRISE DIRECTORATE-GENERAL

Single market : management & legislation for consumer goods
Pharmaceuticals : regulatory framework and market authorisations

Brussels,
ENTR/CT 3

Revision 1

Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use

April 2004

Table of contents

1. Introduction

This document sets out guidance on the collection, verification and presentation and decoding procedures of adverse event/reaction reports arising from clinical trials on medicinal products for human use.

2. Legal Basis

Article 18 of Directive 2001/20/EC requires the Commission to publish detailed guidance on the collection, verification and presentation of adverse event/reaction reports, together with decoding procedures for unexpected serious adverse reactions. The present guidance fulfils the obligations laid down in this Article.

3. Scope

This guidance applies to all clinical trials on medicinal products for human use conducted within the European Community. It applies to all investigational medicinal products (IMP*s*) for human use, independently from their marketing authorisation status in any Member State whether or not IMPs are used under the conditions of the marketing authorisation.

It provides detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from such trials. In addition, it sets out the responsibilities of the concerned parties.

4. Definitions

The definitions of Directive 2001/20/EC, Article 2, are applicable. These are further supplemented by terms from the following Community Guidelines where they are related to collection, verification decoding and presentation of adverse reaction reports arising from clinical trials:

Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95),

Note for Guidance on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports (CPMP/ICH/287/95 modification)

5. Investigator's Responsibilities

The responsibilities of the investigator in relation to the notification of Adverse Events (AEs) are set out in Directive 2001/20/EC: " The investigator shall report all Serious Adverse Events (SAEs) immediately to the sponsor except for those that the protocol or investigator's brochure identifies as not requiring immediate reporting. The initial report shall be promptly followed by detailed, written reports. The initial and follow-up reports shall identify the trial subjects by unique code numbers assigned to the latter".

Adverse events and/or laboratory abnormalities identified in the protocol as critical to the evaluation of safety must be reported to the sponsor by the investigator according to the reporting requirements within the time periods specified in the protocol.

The investigator shall supply the sponsor and the Ethics Committee with any additional requested information, notably for reported deaths of a subject.

6. Sponsor's Responsibilities

6.1 General Remarks

The sponsor is responsible for the ongoing safety evaluation of the investigational medicinal product(s).

The sponsor is responsible for the prompt notification to all concerned investigator(s), the Ethics Committee and competent authority of each concerned Member State of findings that could adversely affect the health of subjects, impact on the conduct of the trial or alter the competent authority's authorisation to continue the trial in accordance with Directive 2001/20/EC.

The sponsor is responsible for arranging structures and written standard operating procedures to ensure that the necessary quality standards are observed in every step of the case documentation, data collection, validation, evaluation, archiving and reporting.

6.2 Recording and Evaluation of Adverse Events (AEs)

Individual adverse events should be evaluated by the investigator and where indicated by the guidance in section 5, they should be reported to the sponsor for evaluation.This includes the evaluation of its seriousness and the causality between the investigational medicinal product(s) and/or concomitant therapy and the adverse event.

The sponsor has to keep detailed records of all AEs reported to him by the investigator(s') and to perform an evaluation with respect to seriousness, causality and expectedness.

On request of a competent authority in whose territory the clinical trial is being conducted, the sponsor should submit detailed records of all adverse events which are reported to him by the relevant investigator(s').

Case report processing concerns evaluation of data in individual cases, identification of individual cases requiring specific handling, recognition and processing of alerts, and any other data processing of aggregated cases.

6.2.1 Assessment of seriousness

Seriousness shall be determined according to the definition in Article 2 of the Directive 2001/20/EC taking into account the comments presented in Annex 1.

6.2.2 Assessment of causality

Causality shall be determined according to the definition of an adverse reaction as given in Article 2 of the Directive 2001/20/EC taking into account the comments presented in Annex 1.

All adverse events judged by either the investigator or the sponsor as having a reasonable suspected causal relationship to an investigational medicinal product qualify as adverse reactions. 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.

6.2.3 Sponsor's assessment of expectedness

The definition of the term "unexpected adverse reaction" is given in the Directive 2001/20/EC taking into account comments in Annex 1. Reports have to be considered as unexpected if they add significant information on the specificity or severity of an expected adverse reaction. The expectedness of an adverse reaction shall be determined by the sponsor according to the reference document as defined in the study protocol (e.g. investigator's brochure for an unapproved investigational medicinal product or summary of product characteristics (SmPC) for an authorised medicinal product in the European Community, which is being used according to the terms and conditions of the marketing authorisation). When the IMP has a MA in several MS with different SmPCs, the sponsor should select one of them as a reference document for assessing expectedness and must mention it in the protocol.

6.2.4 Data protection of trial subjects

The Community standards of confidentiality must always be maintained and any relevant national legislation on data protection must be followed.

6.3 Reporting of Serious Adverse Reactions (SARs)

6.3.1 Standards for expedited reporting

6.3.1.1 What must be reported ?

6.3.1.1.1 Suspected Unexpected Serious Adverse Reactions (SUSARs)

All suspected adverse reactions related to an IMP (the tested IMP and comparators) which occur in the concerned trial, and that are both unexpected and serious (SUSARs) are subject to expedited reporting. Additionally for IMPs that have not a marketing authorisation in any MS of the European Community, any other SUSAR associated with the IMP and as soon as the sponsor becomes aware of them are subject to expedited reporting. This includes:

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

6.3.1.1.2 Other safety issues requiring expedited reporting

Other safety issues also qualify for expedited reporting where they might materially alter the current benefit-risk assessment of an IMP or that would be sufficient to consider changes in the IMP administration or in the overall conduct of the trial, for instance:

- single case reports of an expected serious adverse reactions with an unexpected outcome (e.g. : a fatal outcome),
- an increase in the rate of occurrence of an expected serious adverse reaction, which is judged to be clinically important,
- post-study SUSARs that occur after the patient has completed a clinical trial and are reported by the investigator to the sponsor,

- new event relating to the conduct of the trial or the development of the IMP likely to affect the safety of the subjects, such as :
  - a serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial,
  - a significant hazard to the subject population such as lack of efficacy of an IMP used for the treatment of a life-threatening disease,
  - a major safety finding from a newly completed animal study (such as carcinogenicity).
  Where the IMP is authorised in a MS and the sponsor is the marketing authorisation holder, the reporting of SUSARs should take into account national requirements intended to manage duplication of reports in the context of the Directive 2001/83/EC, Regulation 2309/93/EC and the: 'Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (Eudravigilance – Clinical Trial Module)'.

6.3.1.2 What should not be reported ?

Expedited reporting is not usually required:
- for reactions which are serious but expected,
- for non-serious adverse reactions whether expected or not.

It is usually also inappropriate to report events that are considered unrelated to the investigational medicinal product.

6.3.1.3 Who should report and whom to report to?

The sponsor should report all the relevant safety information previously described to the concerned competent authorities and to the Ethics Committee concerned (see section 6.3.1.6.5).

The sponsor shall inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of subjects (see section 6.4).

6.3.1.4 Managing SUSARs associated with active comparator or placebo

The sponsor must report to the competent authority and the Ethics Committee of the concerned Member States all SUSARs associated with a comparator product in the concerned clinical trial even if this product is authorised. In addition, it is recommended that the sponsor report them to the marketing authorisation holder and inform it of the previous notification to the competent authority. But in all cases reporting SUSARs from a clinical trial to the competent authority should only take place through the sponsor.

Events associated with placebo will usually not satisfy the criteria for a serious adverse drug reaction and therefore for expedited reporting. However, where SUSARs are associated with placebo (e.g. reaction due to an excipient), it is the sponsor's responsibility to report such cases.

6.3.1.5 When to report ?

6.3.1.5.1 Fatal or life-threatening SUSARs

The competent authority and the Ethics Committee in the concerned Member States should be notified as soon as possible but no later than 7 calendar days after the sponsor has first knowledge of the minimum criteria for expedited reporting.

In each case relevant follow-up information should be sought and a report completed as soon as possible. It should be communicated to the competent authority and the Ethics Committee in the concerned Member States within an additional eight calendar days.

6.3.1. 5.2 Non fatal and non life-threatening SUSARs

All other SUSARs and safety issues, described in section 6.3.1.1.2, must be reported to the competent authority and the Ethics Committee in the concerned Member States as soon as possible but no later than 15 calendar days after the sponsor has first knowledge of the minimum criteria for expedited reporting. Further relevant follow-up information should be given as soon as possible.

6.3.1.6 How to report ?

6.3.1.6.1 Minimum criteria for initial expedited reporting of SUSARs

Information on the final description and evaluation of an adverse reaction report may not be available within the required time frames for reporting. For regulatory purposes, initial expedited reports should be submitted within the time limits as soon as the minimum following criteria are met:

a) a suspected investigational medicinal product,
b) an identifiable subject (e.g. study subject code number),
c) an adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship,
d) an identifiable reporting source,

and, when available and applicable:

- an unique clinical trial identification (EudraCT number or in case of non-European Community trials the sponsor's trial protocol code number)
- an unique case identification (i.e. sponsor's case identification number).

6.3.1.6.2 Follow-up reports of SUSARs

In case of incomplete information at the time of initial reporting, all the appropriate information for an adequate analysis of causality should be actively sought from the reporter or other available sources. The sponsor should report further relevant information after receipt as follow-up reports.

In certain cases, it may be appropriate to conduct follow-up of the long-term outcome of a particular reaction.

6.3.1.6.3 Format of the SUSARs reports

Electronic reporting should be the expected method for expedited reporting of SUSARs to the competent authority. In that case, the format and content as defined by the Guidance[1] should be adhered to.

The CIOMS-I form is a widely accepted standard for expedited adverse reactions reporting. However, no matter what the form or format used, it is important that the basic information/data elements described in annex 3, when available, be included in any expedited report (some items may not be relevant, depending on the circumstances; for initial expedited reporting see also section 6.3.1.6.1).

The latest version of MedDRA should be applied, using version 4.1 or later versions. Lower level terms (LLT) should be used.

6.3.1.6.4 Form and format of the reports about other important safety issues also qualifying for expedited reporting

Other important safety issues also qualifying for expedited reporting (see section 6.3.1.1.2), should be notified by a letter under the heading of safety report. The fist page of the report

[1] *Detailed Guidance on the European database of Suspected Unexpected Serious Adverse Reactions (Eudravigilance-Clinical Trial Module)*