"Please do take into account that this is a translation of the original French version validated in the Quality Management System (QMS) of Cliniques universitaires Saint-Luc through the software Ennov GED. Therefore in case of doubt, differences, inconsistency or discrepancy in this English version, the French version shall prevail"

1 PROCEDURE'S OBJECT

The procedure describes the responsibilities and rules for the clinical trials' pharmacovigilance management and experiments with a medical device materiovigilance management.

2 PROCEDURE'S SCOPE

2. Consultations

3. Medico-technic

4. Ward and One-day clinic

3 RESPONSIBILITIES AND AUTHORITIES

INVESTIGATOR AND SPONSOR OBLIGATIONS RELATED TO THE PHARMACOVIGILANCE OF THE CLINICAL TRIALS.

	INVESTIGATOR		**SPONSOR**	
	role	***deadlines***	**role**	***deadlines***
AE	Collect, register, evaluate, follow until resolution	*Continuously*	Record	*Continuously*
SAE	Define if the SAE is a SUSAR or not. Notify the sponsor.	*Immediately (24h according to protocol)*	Report to the MAH	*Immediately*
DEATH	Notify the sponsor and the Leading (+ Non Leading) Ethics Committee	*Immediately (24h according to protocol)*	Report to the MAH	*Immediately*
SUSAR	Notify the sponsor	*Immediately (24h according to protocol)*	Report to the national competent authority, to Ethics Committee and to investigators	*7 days(death) /15 days (other)*
DSUR	-		Prepare and report to the national competent authority, to Ethics Committee and to investigators (each country	*1x/year in the 60 days following the anniversary date of the first authorisation of the CTA by a CA.*

			concerned by the trial)	

SPONSOR'S TASKS FOR THE SAE / SUSAR REPORTING

Registered medication (in the indication or not)	**Sponsor**
SAE	
Yes	MAH : report to the FAMHP vigilance department.
	Non MAH : report to the MAH
No	**Report to the FAMHP R&D department**
SUSAR	
Yes	report to the FAMHP vigilance department, the LEC , the investigators
No	**Report to the FAMHP R&D department**, the LEC , the investigators

SPONSOR'S TASKS FOR THE SAE REPORTING TO HEALTH AUTHORITIES IN EXPERIMENTS WITH MEDICAL DEVICES NON CE REGISTERED OR OFF-LABEL USED

All the SAE must be fully registered and immediately communicated to the Health Authorities of the member states where the clinical investigations take part.

4 PROCEDURE'S REVISION

5 PROCEDURE'S DESCRIPTION

5.1 PREAMBLE :PROTOCOL :

In terms of pharmacovigilance (and materiovigilance), different tasks are attributed to the sponsor and to the investigator.

The study protocol must clearly state:

- sponsor's name
- sponsor's related tasks in terms of pharmacovigilance (and materiovigilance)
- investigator's related tasks in terms of pharmacovigilance (and materiovigilance)
- tasks delegated to a third party : in non commercial trials, pharmaceutical companies who provide drugs (medical devices) for a trial may take on responsibility for adverse reaction reporting.
- the adverse events reporting procedures :

- which events should be notified to the sponsor and the timelines for notification.
- which type of events should not be notified?
- depending on the risks associated to the trial, the period of time during which investigators should notify the SAE after the end of the trial.

- the unblinding procedure in case of SUSAR.

5.2INVESTIGATOR'S RESPONSIBILITIES:

The investigator's responsibilities entail:

- reporting of serious adverse events to the sponsor.
- reporting of certain non-serious adverse events and/or laboratory abnormalities to the sponsor.
- reporting to participants any new element which could influence their safety during or after the end of the trial.

5.2.1 ADVERSE EVENTS :

- He identifies continuously, register and notify the adverse effects and events.
- He evaluates them regarding to :
    - seriousness
    - expectedness
    - causality
    - intensity
- He will follow them until their resolution.

The *expectedness and seriousness* of an adverse effect determine the type of reporting to the health authorities and the ethics committee. It is the investigator responsibility to determine the unexpected character of an adverse event.

5.2.2 SAE (SERIOUS ADVERSE EVENT):

- The investigator/sub investigator shall **notify** all serious adverse events immediately (within a very short period of time and under no circumstances should this exceed 24 hours following knowledge of the serious adverse event) to the sponsor except for those that the

protocol or investigator's brochure identifies as not requiring immediate reporting. The immediate report shall be followed by detailed, written reports. The immediate and follow-up reports shall identify subjects by unique code numbers assigned to the latter. The assessment of whether there is a reasonable possibility of a **causal relationship** is usually made by the investigator. The causality assessment given by the investigator may not be downgraded by the sponsor.

- Assessment of expectedness is usually done by the sponsor. If information on expectedness has been made available by the reporting investigator, this should be taken into consideration by the sponsor.
- For **double blind** trials, the investigator assesses seriousness, causality and expectedness as if the patient was receiving the study medication/medical device. As regards to the sponsor, when an event may be a SUSAR the blind will be broken only for that specific subject. Only those events occurring among patients on active drugs will be considered to be SUSARs requiring reporting to the regulatory authority and ethics committee. The investigator must notify the sponsor of each unblinding performed. The unblinding procedures must be described in the protocol and will be documented by the investigator.
- For reported death of a subject, whatever the cause could be, the investigator shall supply simultaneously the sponsor and the Ethics Committee (Leading and non-leading) with any additional information requested.
- The investigator uses the standard **CIOMS SAE FORM (105-AAHRPP-FORM-019)** for **the SAE (being SUSAR or not)** notification to the sponsor (within the timeframes defined in the protocol).
- The same SAE form should be used for the follow up of non finished events. The following information must be found :
    - complete description of the reactions
    - outcome
    - in case of death : cause and relationship with the IMP + necropsy report
    - other relevant etiologies
    - stop date and treatment details
    - additional tests or treatments and their results
- The investigator follows the SAE until its resolution or until progression has been stabilized (in case no resolution can be reached).
- The investigator is responsible for reporting to the sponsor all serious adverse events in relation to subjects treated by him in the clinical trial. The investigator does not need to actively monitor subjects for adverse events once the trial has ended, unless provided

otherwise in the protocol. Serious adverse events occurring to a subject after the treatment of that subject has ended should be reported to the sponsor if the investigator becomes aware of them.

5.2.3 SUSAR:

A SUSAR is a SAE but is also unexpected and possibly related to the IMP. **The reporting requirements are the same as for the SAE.**

- Events to be reported to the sponsor (assimilated to the SUSAR) :
    - individual report of expected events with an unexpected issue (unexpected **severity**)
    - a clinically significant increase in the **frequency** of expected adverse events.
    - SUSAR occurring after the end of the patient participation to the trial (new cancers, foetal malformation…)
    - new clinical or non clinical data that could negatively influence the patient's security (lack of efficacy).
    - SUSARs associated with a comparator product follow the same reporting requirements as for the test IMP.
    - where SUSARS are associated with placebo (e.g. reaction due to an excipient or impurity) , the sponsor should report such cases

5.2.4 REPORTS:

The investigator receives the SUSARS' reports (only blinded information unless unblinded information is judged necessary for safety reasons), and the Development Safety Update Reports related to the trial.

5.3 SPONSOR'S RESPONSIBILITIES:

The sponsor's responsibilities entail:
- recording of adverse events
- SUSARS reporting to the national competent authority and the Ethics Committee.
- information of the investigators concerning the procedures related to the adverse events notification. These should be specified in the protocol.

- providing enough blank SAE forms to the investigators.
- submitting a Development Safety Update Report (DSUR) (106-AAHRPP-FORM-018) to the national competent authority and the ethics committee.
- the sponsor should continuously weigh anticipated benefits and risks of the clinical trial

- arrange for systems and written standard operating procedures to ensure compliance with the necessary quality standards

- follow up the SAE collected
- inform the investigators concerning any new element which could influence the participants' safety during or after the end of the trial.

5.3.1 ADVERSE EVENTS:

- the sponsor is recording **all the adverse events** reported by the investigators.
- the sponsor continuously evaluates the drug safety profile and takes the responsibility of the unblinding (only in case of safety issues for the patient) if necessary.
- the sponsor notifies as soon as possible investigators, ethics committee and national competent authorities of any new information that could negatively influence the health of the subjects, impact the study or modify the authorization given by the competent authority to conduct the trial.
- the sponsor may delegate the tasks and functions as necessary to comply with the regulations. In certain circumstances the MAH or the patent holder can take on responsibility for adverse reaction reporting in place of a non commercial sponsor.

5.3.2 SAE :

- if the sponsor is the MAH in the country where the study takes place, he sends the SAE to the competent authority (in Belgium : FAMHP- vigilance department).
- **if he is not the MAH (in case of non commercial trial) he sends the SAE to the MAH..**
- if the IMP has not yet a marketing authorization, the sponsor sends the SAE to the competent authority (FAMHP- R&D department).
- SAE must be forwarded by the MAH to the vigilance department of the FAMHP within 15 calendar days after he is first aware of the reaction.

5.3.3 SUSAR:

- as a general rule only unblinded SUSARs should be reported to the FAMHP, as well as the Ethics Committee
- the non commercial sponsor issues a **standard mail**
    - to the national competent authority of the member state concerned by the SUSAR and to the sponsor's member state (this can be performed by the national coordinator of the concerned country in non commercial trials),
    - to the leading ethics committee (of the concerned country)
    - to all the investigators

  within **7 calendar days** (fatal or life treathening + 8 calendar days for any follow-up information) or within **15 calendar days** (all other SUSARS + 8 calendar days for any follow-up information) after the sponsor is first aware of the reaction.

- the minimum information includes : Eudract n°, sponsor study number, one identifiable code subject, one identifiable reporter, SUSAR description, one suspect IMP, a causality assessment
- it is not mandatory to inform the MAH. The FAMHP informs anonymously the MAH if he is not the sponsor of the trial. Nevertheless, the SUSAR's notification can be delegated to the commercial partner.
- **If the SUSAR concerns a drug non registered in Belgium, documents must be sent to the R&D department of the FAMHP**
- **If the SUSAR concerns a drug registered in Belgium (even if it is an off-label use) documents must be sent to the Vigilance department of the FAMHP.**

  AFMPS – Eurostation Bloc 2
  Place Victor Horta 40, Boîte 10
  B-1060 Bruxelles

5.3.4 REPORTS :

- the sponsor sends a DEVELOPMENT SAFETY UPDATE **REPORT (= DSUR)** (106-AAHRPP-FORM-018) **containing the SAE and SUSARS' list and evaluating the safety of the participants** to
    - the competent authority

- the leading ethics committee
- the investigators

of the Member States in whose territory the clinical trial is being conducted and if ,the treatment of subjects is still ongoing in the Member State concerned until the last patient last visit (LPLV) or until the end of trial criteria as defined in the protocol are being reached.

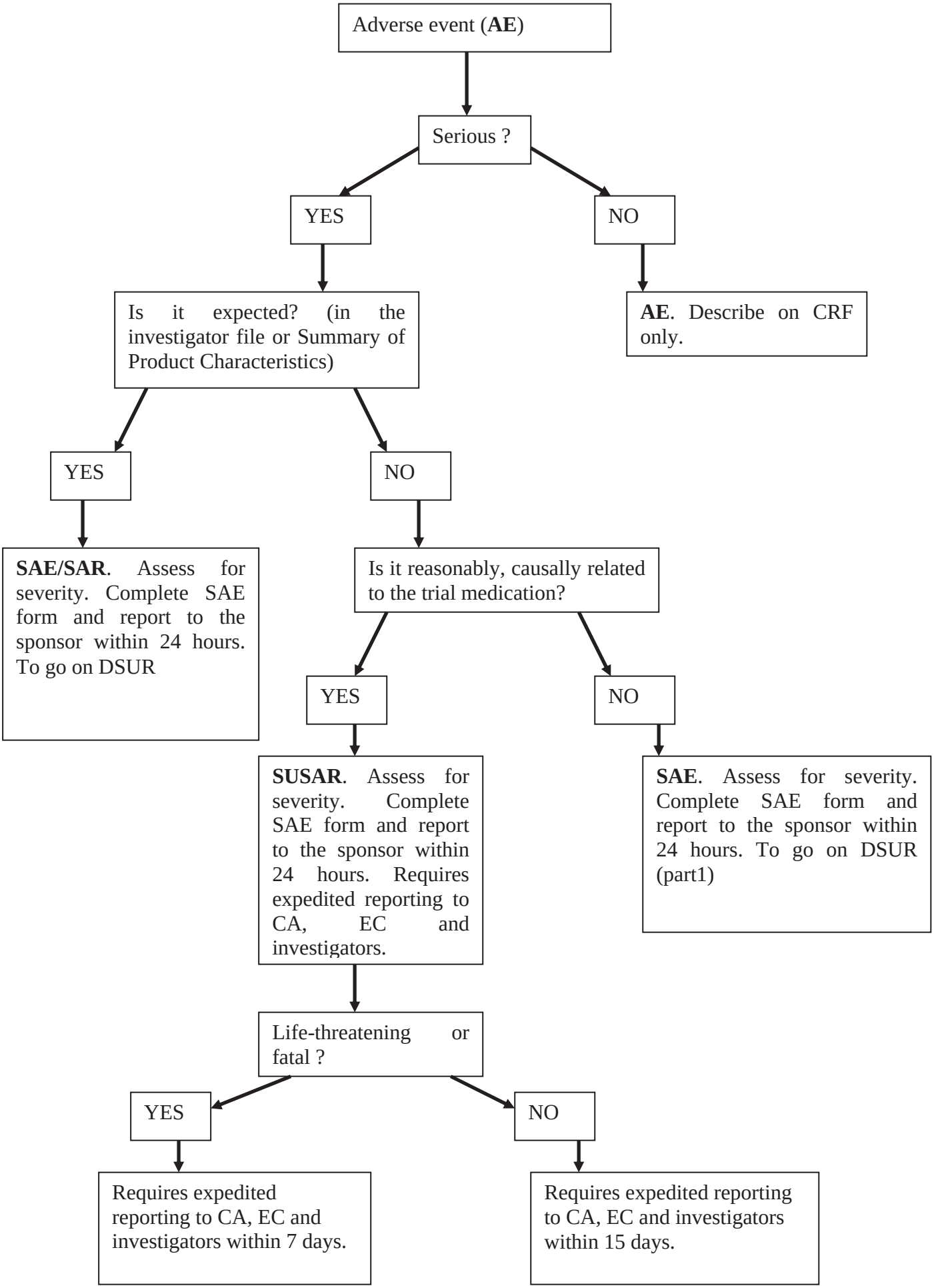
- the reporting time frame for annual reports starts from the date of the first authorization of the clinical trial by a competent authority in any member state. The report should be submitted within 60 days of this cut-off date. In the case of short-term trials (less than 6 months), the safety report may be submitted within 90 days after the end of the trial (as part of the end of study report).
- the DSUR must be issued even if no patient is included in the trial.
- the sponsor can delegate the DSUR preparation to a third party.

5.3.5 SAE REPORTING TO HEALTH AUTHORITIES BY THE STUDY SPONSOR

All the SAE must be fully registered and immediately communicated to the Health Authorities of the member states where the clinical investigations take part.
These SAE must be reported to ct.rd@afmps.be using the European Form available on the FAHMP web site.

5.4 LEADING ETHICS COMMITTEE AND COMPETENT AUTHORITY:

- receive unblinded SUSAR sent by the sponsor.
- receive DSUR
- have the authority to stop a clinical trial if the benefit / risk balance is modified.


Adverse event (**AE**)
Serious ?
YES
NO
AE. Describe on CRF only.
Is it expected? (in the investigator file or Summary of Product Characteristics)
YES
NO
SAE/SAR. Assess for severity. Complete SAE form and report to the sponsor within 24 hours. To go on DSUR
Is it reasonably, causally related to the trial medication?
YES
NO
SUSAR. Assess for severity. Complete SAE form and report to the sponsor within 24 hours. Requires expedited reporting to CA, EC and investigators.
SAE. Assess for severity. Complete SAE form and report to the sponsor within 24 hours. To go on DSUR (part1)
Life-threatening or fatal ?
YES
NO
Requires expedited reporting to CA, EC and investigators within 7 days.
Requires expedited reporting to CA, EC and investigators within 15 days.

5.5: DEVELOPMENT SAFETY UPDATE REPORT (DSUR) (106-AAHRPP-FORM-018)

Objectives: to describe of all new relevant safety information for one clinical trial and to assess the safety conditions of subjects included in the concerned trial.

It should have 3 parts:
1 : a report of the subjects' safety in the clinical trial
2 : a line listing of all suspected SARs including SUSARs.
3 : an aggregate summary tabulation of suspected SARs and SUSARs.

It must be sent by the sponsor of the trial (by regular mail) and signed by the qualified person (the sponsor or someone designed by the sponsor) in the Member States in whose territory the clinical trial is being conducted

1: to the competent authorities:

FOR BELGIUM:

- **If the ASR concerns a drug non registered in Belgium, documents must be sent to the R&D department of the FAMHP**
  AFMPS – Eurostation Bloc 2
  Place Victor Horta 40, Boîte 40
  B-1060 Bruxelles

- **If the ASR concerns a drug registered in Belgium (even if it is an off-label use) documents must be sent to the Vigilance department of the FAMHP.**

  AFMPS – Eurostation Bloc 2
  Place Victor Horta 40, Boîte 10
  B-1060 Bruxelles

2 : to the leading ethics committee

3 : to the investigators for information.

4 : the DSUR is sent in digital form (unprotected pdf format) on CD-ROM.

5 : a cover letter mentions the EudraCT number of the clinical trial to which the report relates.

- **The reporting time frame for annual reports starts from the date of the first authorization of the clinical trial by a competent authority in any member state. The report should be submitted within 60 days of this cut-off date. In the case of short-term trials (less than 6 months), the safety report may be submitted within 90 days of the end of the trial (as part of the end of study report).**
- **The DSUR must be issued even if no patient is included in the trial.**

6 DEFINITIONS AND ABBREVIATIONS

6.1 ABBREVIATIONS:

ADR = ADVERSE DRUG REACTION

AE = ADVERSE EVENT

AFMPS = AGENCE FEDERALE DU MEDICAMENT ET DES PRODUITS DE SANTE

AMM = AUTORISATION DE MISE SUR LE MARCHE

AR = ADVERSE REACTION

CA = COMPETENT AUTHORITY

LEC = LEADING ETHICS COMMITTEE

CE = COMITE D'ETHIQUE

CIOMS = COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES

CTA = CLINICAL TRIAL APPLICATION

DSUR = DEVELOPMENT SAFETY UPDATE REPORT

FAMHP = FEDERAL AGENCY FOR MEDICINES AND HEALTH PRODUCTS

IMP = INVESTIGATIONAL MEDICINAL PRODUCT

INN = INTERNATIONAL NON PROPRIETARY NAME

LPLV = LAST PATIENT LAST VISIT

MAH = MARKETING AUTHORIZATION HOLDER

MEDDRA = MEDICAL DICTIONARY FOR REGULATORY ACTIVITIES

UADR = UNEXPECTED ADVERSE DRUG REACTION

SAE = SERIOUS ADVERSE EVENT

SAR = SERIOUS ADVERSE REACTION

SOC = STANDARD SYSTEM ORGAN CLASSIFICATION

SSAR = SUSPECTED SERIOUS ADVERSE REACTION

SUSAR = SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION

6.2 DEFINITIONS :

(ICH GCP 1996 –Directives 2001/20/CE et 2001/83/CE – Loi relative aux expérimentations sur la personne humaine 7/5/2004)

IMP = INVESTIGATIONAL MEDICINAL PRODUCT

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

AE = ADVERSE EVENT

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment

ADR = ADVERSE DRUG REACTION

All untoward and unintended responses to an investigational medicinal product related to any dose administered. Causality with the IMP is at least suspected.

UADR = UNEXPECTED ADVERSE DRUG REACTION

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorized investigational product or summary of product characteristics for an authorized product).

SAE = SERIOUS ADVERSE EVENT / SAR = SERIOUS ADVERSE REACTION

any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect;

SUSAR = SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION

3 CONDITIONS ARE MANDATORY FOR A SUSAR:

- serious (severity defined by the investigator)
- unexpected : nature or severity of the event are not related to the information provided by the sponsor
- suspected causality to the study drug defined by the investigator

SUSAR CAN ALSO BE EXPECTED ADVERSE EVENTS BUT :

- with an unexpected issue
- with an unexpected **severity**
- with a clinically significant increase in the **frequency** of expected adverse events.
- with new clinical or non clinical data that could negatively influence the patient's security (lack of efficacy).

CAUSALITY ASSESSMENT

ALGORITHME D'IMPUTABILITÉ EMPLOYÉ PAR LE CENTRE COLLABORATEUR DE L'ORGANISATION MONDIALE DE LA SANTÉ POUR LA PHARMACOVIGILANCE – UPPSALA-SUÈDE (HTTP://WWW.WHO-UMC.ORG/DYNPAGE.ASPX?ID=22682)

- **Certain** :

  • Event or laboratory test abnormality, with plausible time relationship to drug intake
  • Cannot be explained by disease or other drugs
  • Response to withdrawal plausible (pharmacologically, pathologically)
  • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon)
  • Rechallenge satisfactory, if necessary

- **Probable/likely:**

  • Event or laboratory test abnormality, with reasonable time relationship to drug intake
  • Unlikely to be attributed to disease or other drugs
  • Response to withdrawal clinically reasonable
  • Rechallenge not required

- **Possible :**

  •Event or laboratory test abnormality, with reasonable time relationship to drug intake

  • Could also be explained by disease or other drugs

  • Information on drug withdrawal may be lacking or unclear

- **Unlikely :**

  • Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)

  • Disease or other drugs provide plausible explanations

Conditional/unclassified :

  •Event or laboratory test abnormality

  • More data for proper assessment needed, or

  • Additional data under examination

Unassessable/unclassifiable :

  • Report suggesting an adverse reaction

  • Cannot be judged because information is insufficient or contradictory

  • Data cannot be supplemented or verified

CIH, 1995, E2A, Gestion des données cliniques sur l'innocuité des médicaments : Définitions et normes relatives à la déclaration rapide (1995 Santé Canada). http://www.chumtl.qc.ca/userfiles/Image/CENTRE_RECHERCHE/CRCHUM/Documentaions/MONs/MON_14_nov06.pdf

Intensity evaluation :

The term 'severity' is used here to describe the intensity of a specific event. This has to be distinguished from the term 'serious'

Seriousness evaluation :

Any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect'.

Expectedness evaluation :

The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labelling and package inserts

7 REFERENCE DOCUMENTS

- 105-AAHRPP-FORM-019: Template SAE form
- 106-AAHRPP-FORM-018: Template Development Safety Update Report (DSUR)

8 - TEMPLATE ASR AAHRPP ACCREDITATION STANDARDS

- Standard I-3
- Element I.8.B
- Element I.8.C
- Element I.8.E
- Element III.2.A
- Element III.2.C
- Element III.2.D

9 LINKS INTRANET

10 LINKS INTERNET

ICH GCP E6(R2) –Directives 2001/20/CE et 2001/83/CE – Loi relative aux expérimentations sur la personne humaine 7/5/2004

http://ec.europa.eu/health/documents/eudralex/vol-10/ : 2011/C172/01

http://www.fagg-afmps.be/fr/humain/medicaments/medicaments_a_base_de_plantes/recherche_developpement/essais_cliniques/ : Circular 586, 593

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/09/WC500097061.pdf (ICH guideline E2F)