# Management of SAE/SUSAR by the CEHF

Commission d'éthique hospitalo-facultaire

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| **N° de référence :** | CEHF-SOP-033 |
| **Version :** | 2.0 |
| **Date d'application :** | 14/12/2018 |

## 1. OBJET DE LA PROCÉDURE

The purpose of this procedure is to define the adverse events that have occurred during the study, the procedure for reporting the adverse events to the ethics committee, and the procedure of the ethics committee on how to react to these adverse events.

## 2. DOMAINE D'APPLICATION

8. Commission d'Ethique Hospitalo-Facultaire (CEHF)

## 3. DESCRIPTION

### 3.1. Responsibilities and authorities

The investigator is responsible for the evaluation of adverse events occurring during the study. The Chair of the Ethics Committee may take the responsibility for a temporary or final discontinuation of a study following the evaluation of the reported adverse events.

The Scientific Secretariat of the Ethics Committee is responsible for the receipt of notifications of adverse events and for encoding them in the database CLAIRE from which an Excel spreadsheet containing a list of adverse events is generated. He must also pre-analyse these in order to put them on the agenda of protocol review meetings if necessary.

### 3.2. Reasons for the procedure's revision

Update

### 3.3. Definitions and abbreviations

Side effect : any harmful and unwanted reaction due to an experimental drug or experiment and, in case of an experimental drug, whatever the dose administered.

Adverse event : any harmful medical event in a patient or participant of the treated group of an experiment that is not necessarily related to the treatment.

Unexpected side effect : side effect for which the nature or severity is not consistent with the information related to the experiment and, in case of a clinical trial, with the product information (such as the investigator's brochure for an unauthorized experimental product or, in case of an authorized product, the instructions enclosed with the summary of product characteristics).

Serious adverse event or serious side effect : adverse event or side effect causing death, endangering the life of the participant, requiring hospitalization or hospitalization prolongation, causing significant or lasting impairment or disability, or resulting in a congenital abnormality or malformation, and this in case of clinical trial, whatever the dose.

Suspected Unexpected serious side effect or "Suspected unexpected severe adverse reaction" (SUSAR) adds to the previous definition the notion of suspected relationship to the study.

## 3.4. Legal basis for the notifications of adverse events (LEPH Art. 27. § 3 - LEPH Art. 28. § 1er.

- For the reported death of a participant, the investigator will submit to the sponsor and to the Ethics Committee any additional information requested.
- The sponsor ensures that all important information regarding suspected unexpected serious adverse reactions that have resulted or are likely to result in death are recorded and reported as soon as possible
  - to the Ministry ;
  - to the competent authorities of all the concerned Member States in case of a clinical trial ;
  - to the competent Ethics Committee, in any case, within a maximum period of 7 days from the moment when the sponsor became aware of this case. Relevant information regarding the follow-up will then be communicated within 8 days.
- Any suspicions of other unexpected serious side effects are notified as soon as possible to the Ministry and to the competent authorities of all the concerned Member States in case of a clinical trial and also to the competent Ethics Committee, and at the latest within maximum 15 days from the day when the sponsor was informed for the first time.
- Once a year, for the duration of the experiment, the sponsor provides to the Ministry, to the Ethics Committee in Belgium as well as to the different Member States where the trial takes place in case of an international multicentric experiment, a list of all suspected serious adverse events that occurred during this time, as well as a report on participant safety.

| | **INVESTIGATOR** | | **SPONSOR** | |
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| | **Role** | ***Deadlines*** | **Role** | ***Deadlines*** |
| **AE** | Collect, register, evaluate, follow-up until resolution | *Continuously* | Maintain a register | *Continuously* |
| **SAE** | Define whether it is a SUSAR or not. Inform the sponsor. | *Immediately (24h according to the protocol)* | Report to the holder of the marketing authorisation (MAH) | *Immediately* |
| **DEATH** | Inform the sponsor and the principal Ethics Committee | *Immediately (24h according to the protocol)* | Report to the holder of the marketing authorisation (MAH) | *Immediately* |
| **SUSAR** | Inform the sponsor | *Immediately (24h according to the protocol)* | Report to the competent authorities, to the principal Ethics Committee and to the investigators | *7 days (death) /15 days (other)* |
| **DSUR** | - | | Prepare and report it to the competent authorities, to the principal Ethics Committee and to the investigators (all countries involved in the trial) | *1x / year within 60 days of the anniversary date of acceptance of the test by the authorities* |

In practice,

Only individual reports of serious and unexpected adverse reactions occurred in Belgium and relating to the drugs tested shall be notified to the Ethics Committee that issued single opinion. All individual reports of serious adverse events, not occurring in Belgium and which, according to current legislation, require rapid notification (7/15 days), should be included in a half-yearly report ("line listing")

Two template documents are available for investigators performing non-commercial experiments: one document for notification of adverse events (AAHRPP-FORM-019, Template SAE form) and one document for the annual safety report (AAHRPP-FORM-018, Template of Development Safety Update Report).

## 3.5. Evaluation and reaction of the Ethics Committee

### *3.5.1. Administrative management by the secretariat*

When the CEHF receives by mail, fax or e-mail the following documents:

- SUSAR
- SAE
- Development Safety Update Report –semi-annual report

The CEHF has to:

- Send the acknowledgement of receipt if present.
- Check whether the event occurred in **Belgium**. The other mails are not archived.
- Verify the CEHF reference number if present, or EudraCT or protocol number. Check if it concerns a clinical trial for which we are PEC/**CEP**. If not, the mails are nor archived.

The notification of events concerning a study on going in Saint-Luc, shall be encoded in the CLAIRE database from which is generated an Excel file with a list of adverse events. The following data have to be encoded: the date of receipt, the nature of the event, and if an AR [1] was sent or not and what the CEHF has done with it: archiving, re-evaluation of the risk /benefit ratio or suspension of the study. In case of any doubt, refer to the Chair of CEHF

[1] **AR** : acknowledgement of receipt

### 3.5.2. Scientific evaluation

The secretariat of the Ethics Committee, who receives the side effects /adverse event notifications and the annual safety reports, takes note of them and assesses whether it is necessary to review the risk benefit ratio. If necessary, the file will be put on the agenda of the next protocol review meeting for having a committee opinion. In this case, the following documents will be sent to all members who have confirmed their attendance at the meeting : summary of the study, description of the unexpected problems involving more than a minimal risk to participants or others, comments of the sponsor or investigator (if present).

*Decisions ( Belgian Law 7 May 2004[i]):*

- If the Ethics Committee has objective reasons to consider that the conditions for approving the conduct of an experiment are no longer met or has information raising doubts as for the safety or scientific background of the experiment, the Ethics committee informs the sponsor and the investigator, who have one week for submitting their opinion
- In case of imminent risk, the time period of one week can be reduced
- If after having received the opinions or if the opinions are not provided within the indicated timings, the Ethics Committee always considers that the conditions for an approval for conducting the experiment are no longer met or if there are some doubts as to the safety or scientific background of the experiment, he informs the Ministry who may suspend or prohibit the experiment in question. This suspension or prohibition starts immediately after notification to the sponsor.
- If the Ministry has objective reasons to consider that the requirements for the authorization to conduct an experiment, as referred to in Article 11, are no longer met or if there are some doubts as to the safety or scientific background of the experiment, the same procedure will be followed. In this case, the Ministry directly informs the competent authorities of the Member States, the involved Ethics Committee, the European Agency as well as the European Commission about his decision to suspend or prohibit the trial and the reasons justifying his decision.
- The decision to suspend or to prohibit a clinical experiment has to be based on objective information collected by the Ethics Committee after the analysis of this information by the Chair of the Ethics Committee (if case of emergency) or during protocol review meetings. The notification of suspension or prohibition will be sent to the principal investigator with a copy to the sponsor. The investigator's / sponsor's response will be reviewed during the protocol review meeting which will either revoke the suspension/end of the study based on a satisfactory response from the investigator, or maintain the suspension/ending that will then be transmitted to the l'FAMHP[2] if applicable (interventional clinical trial).
- The CEHF may ask the sponsor to ensure that participants will be informed of new data that may influence their willingness to continue their participation in the study.

[2] **FAMHP** : Federal Agency for Medecins and Health Products

## 3.6. Other safety reports

The European Directive recommends that the competent authority and the Ethics Committee are also notified of the following events:

1) SUSAR post-trial occurring in a participant who has terminated his participation to the study which is reported by an investigator to the sponsor
2) Any new event related to the conduct of the experiment or to the development of the tested product which could affect the safety of the participants, such as :
   a) A serious adverse event which could be associated to the procedure and could modify the conduct of the experiment ;
   b) a lack of efficacy of the molecule tested in participants in whom the drug is used to treat a disease threatening their survival ;
   c) A major safety finding from an animal study such as evidence of carcinogenic effect ;
   d) Any temporary termination of an experiment involving the same product (the same sponsor) and occurring in another country.

## 3.7. Report to be sent to the FDA for studies subject to FDA regulations (IND ou IDE):

Code 21 CFR 56.108 (b) requires the CEHF to follow the following procedures to ensure prompt reporting from CEHF, from the Medical Direction of the Cliniques universitaires Saint-Luc and the Food and Drug Administration regarding :

1) Unexpected problems involving a risk for participants or others ;
2) Cases of repeated non-compliance with this regulation or the requirements of the CEHF ;
3) Suspension or withdrawal of the favourable opinion/ approval of the CEHF

The following items need to be included when reporting to the FDA: the IND or IDE number, the full name of the research protocol, the name(s) of the clinical investigator(s), and the reason(s) for the suspension or termination of the trial. These reports may be submitted via e-mail, by fax or mail. Contacts are:

### *3.7.1. For medicinal products*

The report suspending or withdrawing the CEHF agreement, the unexpected problems involving a risk for the participants or the facts of serious or repeated non-compliance with the requirements of the applicable rules in force or with the CEHF:

Ms. Dana Walters
Dana.Walters@fda.hhs.gov
Division of Scientific Investigations (HFD-45)
Office of Compliance
Center for Drug Evaluation and Research
White Oak Campus
10903 New Hampshire Ave.
BLDG 51, Rm. 5341
Silver Spring, MD 20993
Phone: (301) 796-3150
Fax: (301) 847-8748

### 3.7.2. *For organic products:*

The report suspending or withdrawing the CEHF agreement, unexpected problems involving a risk for the participants or the facts of serious or repeated non-compliance with the requirements of the applicable rules in force or with the CEHF:

Ms. Patricia Holobaugh
Patricia.Holobaugh@fda.hhs.gov
Bioresearch Monitoring Branch (HFM-664)
Division of Inspections and Surveillance
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research/FDA
1401 Rockville Pike, Room 400S
Rockville, MD 20852-1448
Phone: (301) 827-6347
Fax: (301) 827-6748

### 3.7.3. *For medical devices :*

The report suspending or withdrawing the CEHF agreement, unexpected problems involving a risk for the participants or the facts of serious or repeated non-compliance with the requirements of the applicable rules in force or with the CEHF:

Phone (301) 796-5490
Fax: (301) 847-8136
Email: bimo@cdrh.fda.gov

## 3.8. Encoding in the database *Claire*

All SAE, SAE with death, SUSARs, semi-annual reports, annual reports and DSUR will be encoded in the database CLAIRE, either by the investigator or his study nurse, or by the CEHF itself.

# 4. DISTRIBUTION

Cette procédure est à diffusion
Publique ☐
Restreinte à l'unité/entité/département ☐

# 5. RÉFÉRENCES

AAHRPP-FORM-018 - Modèle Development Safety Update Report (DSUR)

AAHRPP\DOMAIN 2 : INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE\Standard II-2: The IRB or EC evaluates each research protocol or plan to ensure the protection of participants.\Element II.2.D. The IRB or Ethics Committee has and follows written policies and procedures to conduct reviews by the convened IRB or Ethics Committee. 1. Element II.2.D.1. â€“ Initial review 2. Ele..., AAHRPP\DOMAIN 2 : INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE\Standard II-2: The IRB or EC evaluates each research protocol or plan to ensure the protection of participants.\Element II.2.F. The IRB or EC has and follows written policies and procedures for addressing unanticipated problems involving risks to participants or others, and for reporting these actions as ap..., AAHRPP\DOMAIN 2 : INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE\Standard II-2: The IRB or EC evaluates each research protocol or plan to ensure the protection of participants.\Element II.2.G. The IRB or EC has and follows written policies and procedures for suspending or terminating IRB or EC approval of research, if

warranted, and for reporting these actions as appropr..., AAHRPP\DOMAIN 2 : INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE\Standard II-3: The IRB or EC approves each research protocol or plan according to criteria based on applicable laws, regulations, codes and guidance.\Element II.3.B. The IRB or EC has and follows written policies and procedures for reviewing the plan for data and safety monitoring, when applicable, and determines that the data and safety monito..., AAHRPP\DOMAIN 2 : INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE\Standard II-2: The IRB or EC evaluates each research protocol or plan to ensure the protection of participants.\Element II.2.H. The IRB or EC has and follows policies and procedures for managing multi-site research by defining the responsibilities of participating sites that are relevant to the protection o..., AAHRPP\DOMAIN 3 : RESEARCHERS AND RESEARCH STAFF\Standard III-2: Researchers meet requirements for conducting research with participants and comply with all applicable laws, regulations, codes, and guidance; the Organization's policies and proce...\Element III.2.D. Researchers and Research Staff follow reporting requirements during a research study in accordance with applicable laws, regulations, codes and guidance; the Organization's polici...

[I] Loi du 7 Mai 2004