Management of SAE/SUSAR by the CEHF

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Commission d'éthique hospitalo-facultaire	**Version :** 4.0
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1. PURPOSE OF THE PROCEDURE

The purpose of this procedure is to define the notion of adverse event during a clinical trial, and to describe the procedure for notifying and managing serious adverse effects..

2. SCOPE

Hopital-faculty Ethics committee (CEHF)

3. DESCRIPTION

3.1. Content

3.2. Definitions

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 (SAE[1]) : 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[2]) adds to the previous definition the notion of suspected relationship to the study.

3.3. Studies submitted according to the Belgian law of 07 May 2004 :

3.3.1. Legal basis for the notifications of adverse events :

- Belgial law of 07 May 2004 (cf CEHF-DSQ-054[I]):

  - CHAPITRE XV. Art. 27
    « § 1er. The investigator immediately notifies the sponsor of all serious adverse events, except those listed in the protocol or in the investigator's brochure as not requiring immediate notification. Immediate notification is followed by detailed written reports. In this notification as in subsequent reports, participants are identified by a code number. § 2. Adverse events and/or Adverse Analytical Findings defined in the protocol as material for safety assessments are notified to the sponsor, in accordance with the notification requirements and within the time limits specified in the protocol. § 3. In the event of the notified death of a participant, the investigator communicates to the sponsor and to the approved ethics committee all the additional information requested. § 4. The sponsor keeps detailed records of all adverse events notified to him by the investigator(s). These registers are given to the Minister at his request if (the experiment) is carried out in Belgium. »

  - *CHAPITRE XVI. Art. 28*
    « § 1er. The sponsor shall ensure that all important information concerning suspicions of unexpected serious adverse effects which have caused or may cause death are recorded and notified as quickly as possible to the Minister and to the competent authorities of all the Member States concerned in the event of trial as well as 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, and that the relevant information concerning the follow-up is then communicated in a new period of 8 days. All suspicions of other unexpected serious adverse effects are notified to the Minister and to the competent authorities of all the Member States concerned in the event of a clinical trial, as well as to the ethics committee concerned as soon as possible, but no later than within a maximum period of 15 days from the day on which the promoter became aware of it for the first time. The

[1] SAE : *Serious adverse event* / Evénement indésirable grave ou effet indésirable grave
[2] SUSAR : *Suspected unexpected severe adverse reaction* / Effet indésirable grave inattendu et suspect

Minister records all suspicions of unexpected serious adverse effects, which have been brought to his attention. The sponsor also informs the other investigators. »
« § 2. Once a year, for the duration of the experiment, the sponsor provides the minister and the ethics committee in Belgium as well as those of the Member States on whose territory the trial is conducted in the event of a multicentre trial , a list of all suspected serious adverse reactions that occurred during this duration, as well as a report concerning the safety of the participants. »
« § 3. The Minister shall ensure that all suspicions of unexpected serious adverse effects of an experimental medicinal product which have been brought to his attention are immediately recorded in a European database accessible only to the competent authorities of the Member States, to the European Agency and to the Commission. The information notified by the promoter is made available to the competent authorities of the Member States by the European Agency. »

	INVESTIGATOR		***SPONSOR***	
	Role	***Deadlines***	**Role**	***Deadlines***
AE[3]	Collect, register, evaluate, follow-up until resolution	*Continuously*	Maintain a register	*Continuously*
SAE[4]	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*
DECES	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[5]	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[6]	-		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*

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

[3] AE : *Adverse event* / Evénement ou effet indésirable
[4] SAE : *Serious adverse event* / Evénement indésirable grave ou effet indésirable grave
[5] SUSAR : *Suspected unexpected severe adverse reaction* / Effet indésirable grave inattendu et suspect
[6] DSUR : *Development Safety Update Report /* Rapport de sécurité annuel

3.3.2. Administrative management of serious adverse effects :

- Receiving the SUSAR[7] by e-mail ;
- Sending of an acknowledgment of receipt, if required ;
- erification of the country in which the event occurred (only SUSARs that took place in Belgium are recorded by the CEHF[8]) ;
- Registration of the SUSAR as well as the accompanying letter in the Z, where the SUSARs are sorted by date of receipt.

3.3.3. Scientific evaluation of serious adverse effects :

On specific request of the concerned principal investigator, or in case of request of the FAMHP, 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 of 7 May 2004 (cf CEHF-DSQ-054[I]):

- f 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 FAMHP/AFMPS[9] 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.

[7] SUSAR : *Suspected unexpected severe adverse reaction* / Effet indésirable grave inattendu et suspect
[8] CEHF : Commission d'Ethique Hospitalo-Facultaire
[9] AFMPS : agence fédérale des médicaments et des produits de santé / *FAMHP : federal agency for medicines and health products*

3.3.4. Report to be sent to the FDA[10] for studies subject to FDA regulations (IND[11] ou IDE[12]) :

Le code 21 CFR 56.108(b)[IV] requires that the CEHF follows written procedures for ensuring prompt reporting to the CEHF, the Medical Direction of the Cliniques universitaires Saint-Luc and the Food and Drug Administration regarding :

1) Any unanticipated problems involving risks to human subjects or others ;
2) any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the CEHF ;
3) any suspension or termination of the CEHF approval.

When reporting suspensions or terminations of IRB approval, please include the IND or IDE number, the full name of the research protocol, the name(s) of the clinical investigators, and the reason(s) for the suspension or termination.

The report of suspension or withdrawal of the CEHF agreement, unexpected problems entailing a risk for the participants or serious or repeated non-compliance with the requirements of the rules in force or of the CEHF may be submitted to the following addresses

- For drug products : CDER-OSI-GCPReferrals@fda.hhs.gov
- For biologic products : CBERBIMONotification@fda.hhs.gov
- For medical devices : bimo@cdrh.fda.gov

3.4. CTR[13] studies – submitted according to the Belgian of May 07, 2017 (cf CEHF-DSQ-054[I])

3.4.1. Legal basis for adverse reaction reporting :

- European regulation EU n°536/2014 (cf CEHF-DSQ-054[I]):

« *Chapitre VII – Article 40. : Base de données électronique pour les notifications de sécurité : 1.L'Agence européenne des médicaments établie par le règlement (CE) no 726/2004 (ci-après dénommée «Agence») constitue et tient à jour une base de données électronique pour les notifications prévues aux articles 42 et 43. Cette base de données constitue un module de la base de données visée à l'article 24 du règlement (CE) no 726/2004 (ci-après dénommée «base de données Eudravigilance»). Electronic database for safety notifications.*
2. The Agency shall develop, in collaboration with the Member States, a standard structured online form for reporting by sponsors of suspected serious and unexpected adverse reactions to the database referred to in paragraph 1. 27.5.2014 L 158/36 Official Journal of the European Union »

« Chapitre VII – Article 44. Assessment by Member States :
1. The Agency shall transmit electronically to the Member States concerned the information notified in accordance with Articles 42 and 43.
2. Member States shall cooperate in the evaluation of this information in accordance with Articles 42 and 43. The Commission may, by means of implementing acts, define and modify the rules governing such cooperation. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 88(2).
3. The responsible ethics committee shall be involved in the evaluation of the information referred to in paragraphs 1 and 2, if the law of the Member State concerned so provides.. »

[10] FDA : Food and Drug Administration
[11] IND : Investigational New Drug Application
[12] IDE : Investigational Device Exemption
[13] CTR : clinical trials regulation

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« The Belgian law of 7 May 2017 relating to clinical trials of medicinal products for human use does not stipulate that ethics committees must be involved in the evaluation of SUSARs[14] and ASRs (Annual Safety Report), therefore, there is no there is no legal obligation under the CTR[15] for ethics committees to be involved in the evaluation.
In the current CTIS[16] model for Belgium, ethics committees and the College do not have access to SUSARs or ASR[17]. Only the FAMHP/AFMPS[18] has access to the ASRs in CTIS and to the SUSARs in EudraVigilance. When Belgium is awarded the saMS (safety-Member State) for an IMP[19], the FAMHP/AFMPS national contact point will coordinate the safety assessment. »

« The board of the CT College considers that the ethics committees have no formal role in the evaluation of SUSARs and ASRs because this responsibility is not assigned to them by current Belgian legislation. »

3.4.2. Administrative management of serious adverse effects

None.

On the basis of the aforementioned elements (cfr 3.4.1), the CEHF[20] is not in charge of evaluating the safety of participants during the CTR clinical trials analysed by the CEHF, nor for those taking place at Saint Luc University Clinics (CUSL); the SUSARs nor the DSUR[21] will be notified to the CEHF in either case.

3.4.3. Scientific evaluation of serious adverse effects :

According to the Belgian law of 07 May 2017, the SUSARs linked to a CTR study taking place in Belgium are only evaluated by the FAMHP/AFMPS.

However, it should be noted that the evaluating ethics committee has access in CTIS to other information relating to the safety of the clinical trial, which can be consulted if deemed necessary. These include serious adverse events, serious breaches and urgent safety measures. If the ethics committees have questions for the promoter or concerns regarding this information, they can transfer them, via the College, to the FAMHP/AFMPS.

In addition, via substantial modifications, the ethics committees will also receive for evaluation all updates of the Investigator's Brochure, including the update of the expected adverse effects.

Finally, if the FAMPH/AFMPS deems it necessary, they can contact the evaluating ethics committee for a particular SUSAR in order to initiate a concerted evaluation.

[14] SUSAR : *Suspected unexpected severe adverse reaction* / Effet indésirable grave inattendu et suspect
[15] CTR : clinical trials regulation
[16] CTIS : *Clinical Trials Information System* – Base de données européenne pour les études CTR
[17] ASR : *Annual Safety Report*
[18] AFMPS : agence fédérale des médicaments et des produits de santé / *FAMHP : federal agency for medicines and health products*
[19] IMP : *investigational medicinal product*
[20] CEHF : Commission d'Ethique Hospitalo-Facultaire
[21] DSUR : *Development Safety Update Report* / Rapport de sécurité annuel

3.5. MDR[22] studies – according to the Belgian law of December 22, 2020

3.5.1. *Legal basis for adverse reaction reporting :*

- European regulation EU 2017-745 (see CEHF-DSQ-054[I]):
« Art.33. European database on medical devices: :
1. The Commission shall update and manage the European database on medical devices (Eudamed). »
« 2. The following electronic systems are part of Eudamed[23]:
(…)
e) the electronic system relating to clinical investigations referred to in Article 73;
f) the electronic system for vigilance and post-market surveillance referred to in Article 92;
g) the electronic system relating to market surveillance referred to in Article 100 . » (…)

- Belgian law of December 22, 2020 (cf CEHF-DSQ-054[I]): Section 3- Data processing : « Art.70. The FAMHP/AFMPS is responsible for Vigilance data processing ».

3.5.2. *Administrative management of serious adverse effects :*

None.

t should however be noted that the term SUSAR[24] s not used in the European MDR regulation. Serious incidents are only listed under the name SAE[25]*.*
Furthermore, since only the FAMHP/AFMPS[26] has access to vigilance data (SAE) on Eudamed, this information is not notified to the evaluating ethics committee.

Exception : in the particular case of studies falling under Art.82 MDR (studies submitted only to the CEHF[27] – cfr CEHF-DSQ-043[VI]), the Sponsor must notify the evaluating ethics committee in the event of the occurrence of SAE. The SAE is then saved on the "Z" server, in the file of the study concerned. However, the scientific evaluation remains the responsibility of the FAMHP/AFMPS.

3.5.3. *Scientific evaluation of serious adverse effects :*

According to the Belgian law of December 22, 2020, SAEs linked to an MDR study taking place in Belgium are only evaluated by the FAMHP/AFMPS.

If the FAMHP/AFMPS deems it necessary, they can send an SAE to the evaluating ethics committee to start a concerted evaluation of the SAE.

[22] MDR : Medical Device Regulation
[23] EUDAMED : European Database on Medical Devices
[24] SUSAR : *Suspected unexpected severe adverse reaction* / Effet indésirable grave inattendu et suspect
[25] SAE : *Serious adverse event* / Evénement indésirable grave ou effet indésirable grave
[26] AFMPS : agence fédérale des médicaments et des produits de santé / *FAMHP : federal agency for medicines and health products*
[27] CEHF : Commission d'Ethique Hospitalo-Facultaire

4. DISTRIBUTION

This procedure is to be distributed

Publicly ☐

Restricted to unit/entity/department ☒

5. RÉFÉRENCES

[I] CEHF-DSQ-054_Liste des Lois, Arrêtés Royaux, Directives Européennes et normes de qualité en vigueur List of Laws, Royal Decrees, European Directives and quality standards in force

[II] AAHRPP-FORM-019_Template SAE SUSAR form

[III] AAHRPP-FORM-018_Template of Development Safety Update Report

[IV] 21 CFR 56.108(b) : Code of federal Regulations on institutional review board (IRB) functions and regulations

[V] Advice for ECs_safety assessment_(17 mars 2022) – édité par le CT College

[VI] CEHF-DSQ-043_Processus CEHF