Follow-up - Procedure for the declaration of a deviation, violation, unexpected event

N° de référence :	CEHF-SOP-127
Commission d'éthique hospitalo-facultaire	
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1. OBJET DE LA PROCÉDURE

This procedure describes the facts of non-compliance[1], deviation, violation[2] and unexpected problems to be reported by the «non-commercial researcher-sponsors», investigators, their staff, the other employees concerned by the clinical research in progress as well as the actions undertaken by the ethics committee for the evaluation of these events.

2. DOMAINE D'APPLICATION

This procedure is applicable to «non-commercial researcher-sponsors », investigators, their staff, other employees involved in clinical research and to CEHF[3] members.

3. DESCRIPTION

3.1. Responsibilities and authorities

The investigator and the institution must carry out the clinical study in accordance with the protocol established by the sponsor and approved by the Ethics Committee.
The investigator shall not modify or deviate from the protocol without the agreement of the sponsor and without prior notice from the Ethics Committee, with the exception of emergencies.
The investigator shall justify any deviation from the approved protocol and inform the sponsor and the Ethics Committee of any unexpected problem that arises during the course of the study.
The sponsor and the Ethics Committee shall assess any non-compliance or any unexpected problems reported and act accordingly.

3.2. Preventative measures [I]

- The investigator and his team must thoroughly review the protocol before the start of the study.
- All investigators and site staff must attend the initiation visit during which the sponsor or his delegate will provide training on the protocol and the specific procedures which depend on it
- The investigator shall ensure that everyone involved in the study is properly informed about the protocol, the drug and the protocol procedures.
- Before enrolling the first patient, the investigator and his team should review all protocol requirements with the study monitor.

[1] **Non-compliance**: Failure to comply with all requirements related to the clinical study, good clinical practice and applicable regulatory requirements.
[2] **Violation** : The distinction between deviation and violation lies in the absence of notification of the facts of non-compliance to the sponsor / to the Ethics Committee, in the will to not respect the protocol / GCPs (example: include participants who have not benefited from an information and consent procedure in accordance with GCPs) for the purpose of fraud. The violation involves a **voluntary** error to follow the protocol by the investigator or his staff.
Examples : Voluntary inclusion of patients not respecting the inclusion / exclusion criteria of the protocol, Treatment administration not corresponding to randomized treatment
[3] CEHF : Ethics committee / Comité d'éthique hospitalo-facultaire

3.3. Non-compliance [4] and unexpected problem reported by the investigator, the sponsor or any person noting the fact (cfr. formulaire CEHF-FORM-128[II])

3.3.1. *Minor deviations* [5]

Minor deviations (or minor non-conformities) to the protocol are entirely acceptable within the management of circumstances not provided for by the protocol. These are deviations that do not increase the minimal risk[6] and shall not be reported to the Ethics Committee. They will be reported by the investigator in the source file and to the sponsor via the CRF[7].

3.3.2. *Major deviations* [8]

Major deviations, whether continuous[9] or not, can be justified by a risk / danger that was not planned when the protocol was written and can be justified to protect the participant from this danger. These major deviations will be immediately notified by the principal investigator to the study sponsor and to the Ethics Committee. They result in an increase of the minimal risk.

3.3.3. *Protocol Violations*[8]

Violations of the protocol, whether continuous[9] or not, are a sign of a desire to deviate from the protocol for the purpose of fraud. By definition, a protocol violation report is made by someone other than the principal investigator. This fraud report will be sent by the complainant to the Ethics Committee and to the sponsor of the study. These violations result in an increase of the minimal risk.

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[4] **Non-compliance** : Failure to comply with all requirements related to the clinical study, good clinical practice and applicable regulatory requirements

[5] **Minor deviations**: Non-compliance events which do not increase the minimum risk and which must not be reported to the Ethics Committee. They will be reported by the investigator to the sponsor via the CRF.
Example : Evaluation carried out on a date not initially planned but remaining in the windows allowed by the protocol

[6] **Minimal Risk**: The risk is minimal when the expected probability and extent of the harm or discomfort produced by the research is not greater than that encountered in daily life or during physical activity or psychological examinations or routine tests. For example, the risk of taking a single blood sample from a healthy individual is no greater when taken as part of an experiment than when it is a routine sampling.

[7] **CRF** : Case Report Form

[8] **Major Deviation / serious violation**: Act or absence of **voluntary or unintentional act** which is **likely to increase a physical, psychological or security or privacy risk for research participants.**
Examples : Deviation / violation of the protocol resulting in the death, hospitalisation or permanent incapacity of a participant, Evidence of fraud in the data collection, Inclusion of a participant who would meet the criteria for exclusion from a study (example : inclusion of a patient with renal insufficiency in a trial with a nephrotoxic drug for which this type of patient is excluded), Non-compliance with the monitoring of the toxic effects of the treatment studied: example: blood count in patients in oncological treatment that may induce neutropenia.

[9] **Continuous Deviation / violation**: Repeated pattern, act or absence of act which suggests a probable repetition.
Example : non-compliance with procedures by the investigator throughout several studies

3.3.4. Unexpected problems

Unexpected research-related or potentially research-related problems may arise throughout the study and influence the course of the study. They will be notified within 10 working days by the principal investigator to the sponsor of the study and to the Ethics Committee. The communication of SUSARS[10] to the Ethics Committee, however, falls under the pharmacovigilance procedure and the legal communication deadlines (AAHRPP-SOP-015[III])

The accidental loss or data breach relating to a clinical study as an unexpected event must be notified by the principal investigator to the study sponsor, to the ethics committee but also to the data protection officer (DPO[11] CUSL or DPO UCLouvain, depending on whether the promoter is CUSL or UCLouvain), as soon as you become aware of the event. The deviation, violation, unexpected event declaration form (CEHF-FORM-128) as well as the data leakage notification form (COSI-FORM-011[IV]) must be completed and sent to the Ethics Committee and to the DPO concerned.

The Ethics Committee can receive an allegation / report of non-compliance through numerous channels which include, but are not limited to:

1) Voluntary notification from the principal investigator (deviation),
2) Absence of reaction from the principal investigator to requests / reminders from the Ethics Committee within the follow-up process,
3) Information provided by other members of the research team,
4) Information provided by other staff members of the institution,
5) Monitoring reports,
6) Audit report,
7) Complaints from research participants.

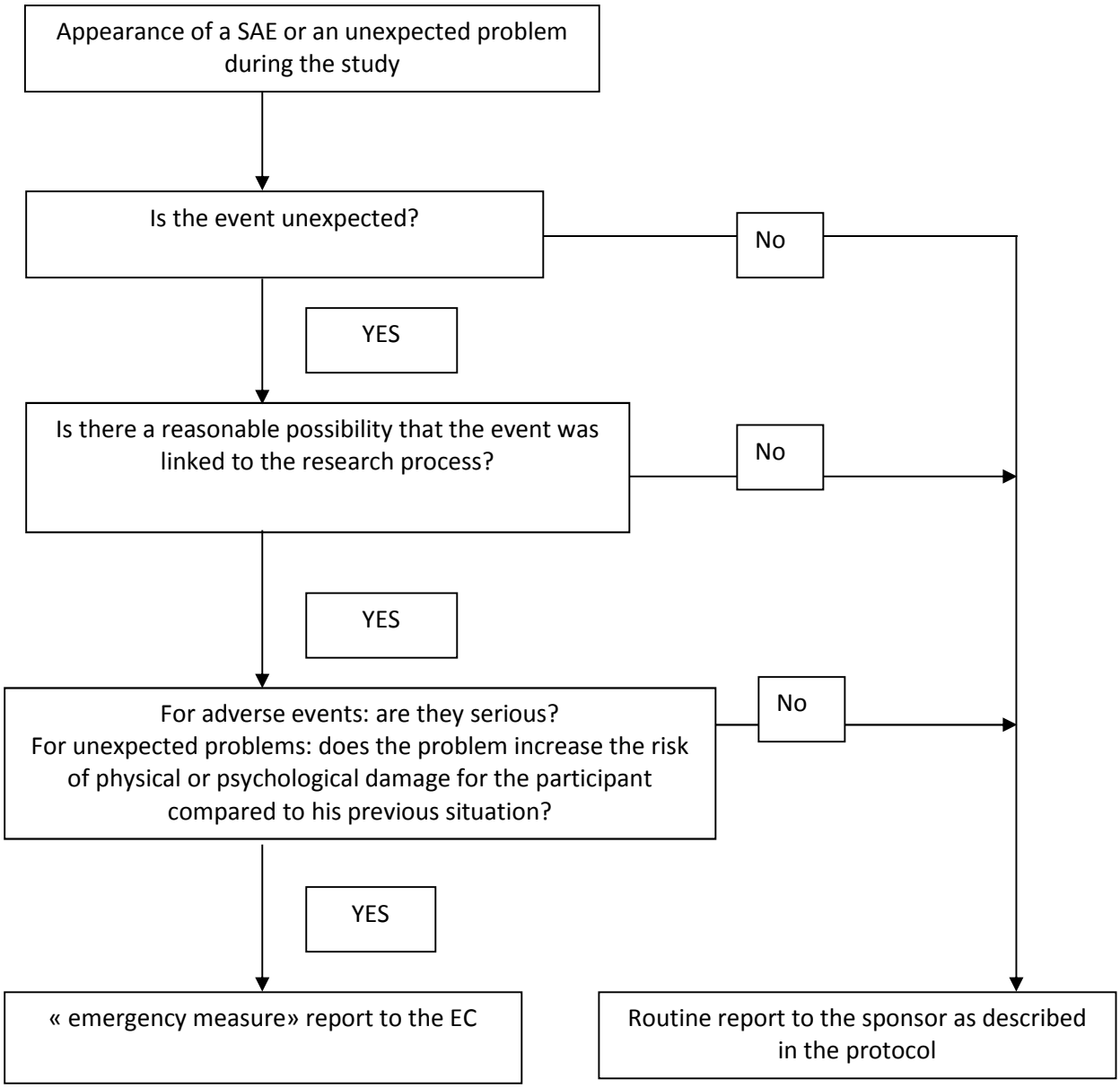
Particular case of the participant who unexpectedly and permanently loses his functional capacity during the study: his event could influence his capacities to consent to the continuation of the study and must be reported by the investigator to the ethics committee as an unexpected problem using the « Protocol Deviation and Unanticipated Problems Form ».

The ethics committee will assess in its feedback if:

- The investigator must re-evaluate the patient's capacity to consent to determine whether he wants to stay in the study
- The investigator must re-evaluate the continued participation of the patient in the study

[10] **SUSAR** : Suspected Unexpected Serious Adverse Reaction
[11] DPO : Data Protection Officer

3.3.4.1. Determination process of the need for an unexpected problem report to the Ethics Committee



[12] **SAE :** Serious Adverse Event

3.3.5. Summary table of the reporting methods for the different types of non-compliance

The « Protocol Deviation and Unanticipated Problems Form » (CEHF-FORM-128^{V}) is used for the communication of the event to the Ethics Committee AND to the sponsor.

Type	Report to the Ethics Committee	Report to Sponsor	By whom ?	When ?	How ?
minor deviations (or minor non-compliance)	no	yes	Investigator	routine	CRF and source file
major deviations continuous or not	yes	yes	Investigator	Emergency (upon acknowledgment)	Protocol Deviation and Unanticipated Problems Form
protocol violations ongoing or not	yes	yes	Sponsor or person who noted it	Emergency (upon acknowledgment)	Protocol Deviation and Unanticipated Problems Form
unexpected research related or potentially research related issues	yes	yes	Investigator	Emergency (upon acknowledgment)	Protocol Deviation and Unanticipated Problems Form

3.4. Evaluation and corrective actions

3.4.1. Corrective Actions by the Investigator

Actions carried out by the principal investigator in order to reduce the risk run by the participants or to prevent the recurrence of deviations / protocol violations.

Examples: Staff training, request for revision of the protocol and / or patient information form.

The investigator will inform the Ethics Committee, within the time limit set, and the sponsor of the actions carried out and their results.

3.4.2. Evaluation and action of the non-commercial sponsor

NB : The commercial sponsor has its own evaluation and action procedures.

- The non-commercial sponsor receives the «Protocol Deviation and Unanticipated Problems Form» (CEHF-FORM-128)

3.4.2.1. Report on its own centre

If it is a report concerning its own centre, it will be evaluated by the DSMC[13] (cfr AAHRPP-SOP-039[VI]) and the absence of the DSMC, the evaluation will be carried out only by the Ethics Committee.

- In the event of information concerning a violation of the protocol, the confidentiality of the reporter will be guaranteed. The names of the rapporteurs will not be disclosed to the persons concerned by the complaint, unless necessary to arbitrate the situation.

3.4.2.2. Report on external centre

If it is a report concerning an outdoor centre, it will be evaluated by the DSMC and/or by the study's medical manager according to what was defined at the start of the study e (cfr AAHRPP-SOP-039[V]).

- Assessment of severity according to the following criteria :
  - Is the safety of a study participant at stake?
  - Is the safety of other (or all) study participants at stake?
  - Is the centre's ability to recruit subjects questioned?
  - Is the participation of an investigator or member of staff in the study questioned?
  - Is the data collected for a study participant incorrect or inappropriate?
  - Is the data collected for all of the study participants incorrect or inappropriate?
- The sponsor sends feedback to the investigator.
- The sponsor sets up a cause assessment and implements corrective and preventive actions (GCPVII 5.20)
- The investigator implements preventive and corrective actions and informs the sponsor
  - The sponsor assesses the corrective actions implemented positively: the non-compliance is corrected
  - The sponsor assesses the corrective actions implemented negatively: the sponsor can suspend or withdraw his authorization for the centre's participation in the research protocol.
  - The sponsor will notify the authorities in the event of a serious violation of the protocol or serious or repeated non-compliance in a clinical trial or medical device protocol.

[13] DSCM : Data Safety Monitoring Committee

3.4.3. Evaluation and actions by the CEHF[14]

- The scientific secretary of CEHF receives the CEHF-FORM-128 «Protocol Deviation and Unanticipated Problems Form»
    - In the event of information concerning a violation of the protocol, the confidentiality of the reporter will be guaranteed. The names of the rapporteurs will not be disclosed to the persons concerned by the complaint, unless necessary to arbitrate the situation.
    - The information provided will be assessed by the scientific secretariat of the CEHF based on the following criteria:
        - Is the safety of a study participant at stake?
        - Is the safety of other (or all) study participants at stake?
        - Is the centre's ability to recruit subjects questioned?
        - Is the participation of an investigator or member of staff in the study questioned?
        - Is the data collected for a study participant incorrect or inappropriate?
    - The chair/vice-chair of the CEHF assesses the provided information relating to violations (delay 5 working days). The scientific secretary sends the following documents to the chair/vice-chair as well as to the members registered for the next protocol evaluation meeting: summary of the study, description of unexpected problems presenting a risk that is more than minimal for the participant or serious or ongoing non-conformities, comments from the sponsor or the investigator (if applicable).
    - The secretariat of the CEHF encodes the decision taken on CEHF-FORM-128.
    - The CEHF sends a feedback to the investigator
    - The investigator implements corrective actions and informs the CEHF
    - The CEHF assesses the corrective actions implemented positively: the non-compliance is corrected.
    - The CEHF assesses the corrective actions implemented negatively: the Ethics Committee can suspend or withdraw its authorization for the centre's participation in the research protocol. In this case, he will notify the investigator, the Medical and Administrative Director of the CTC[15] of his decision. The investigator will inform the promoter directly

    If such information could influence the participant's willingness to continue participating in the study, the CEHF will require the sponsor/ investigator to notify the participants.

    The action potentially required by the CEHF concerns:

    - Transmission of additional information to former participants.
    - The request to participants under study to re-consent to their participation.
    - Modification of the calendar of visits
    - Research monitoring.
    - Monitoring the consent procedure.
    - Referral to other parts of the organization.

[14] CEHF : Ethics ommittee / Comité d'éthique hospitalo-facultaire
[15] CTC : Clinical trial centre

3.4.3.1. Suspension or termination[16] of the agreement of the Ethics Committee (CEHF) when it is a clinical drug trial (Belgian law concerning human experimentation7 Mai 2004[VIII])

- The CEHF informs the investigator if he has objective reasons to consider that the conditions of approval for the conduct of the clinical trial are no longer met or if he has information leading to reassess the safety or the scientific basis of the trial. The investigator will inform the promoter and provide a response within one week.
- In the event of imminent risk, the period of one week may be shortened.
- After receipt of comments or in the absence of comments within the time limits, if the CEHF considers that the conditions for approval for the conduct of the clinical trial are no longer met or if it has information leading to re-evaluation its safety or its scientific basis, it informs the Minister (AFMPS[17]) who will decide to suspend or stop the test. This suspension or ban will take effect immediately after notification to the sponsor.
- The Minister (AFMPS) will follow the same procedure if he considers that the conditions for approval for the conduct of the clinical trial are no longer met or if he has information leading to reassess its safety or its scientific basis. In this case, the Minister will inform the competent authorities of the Member States concerned, the Ethics Committees concerned, the EMA[18] and the European Commission of his decision to suspend or stop the trial and will justify his position to them.
- The decision to suspend or stop the clinical trial must be based on objective information received by the CEHF and after analysis by the chair (in an emergency) or during the protocol analysis meeting. The decision to suspend or terminate will be sent to the investigator who will send it to the sponsor as well as to the Medical and Administrative Director of the CTC[19]. The investigator's response will be analysed during a protocol analysis meeting. On the basis of a satisfactory response, the decision to suspend / prohibit the continuation of the test will be revoked or, if applicable, the decision will be maintained and the information transmitted to the AFMPS if applicable.

[16] **Suspension ou termination of the agreement of the Ethics Committee**: The suspension of the EC agreement can be defined as a temporary suspension of the approval of the EC for some or all of the research activities.
The termination of the EC agreement can be defined as a definitive suspension of the approval of the EC for all research activities

[17] AFMPS : Agence Fédérale des Médicaments et des Produits de Santé

[18] EMA : European Medicines Agency

[19] CTC : Clinical trial centre

3.4.3.2. Suspension or termination of the Ethics Committee agreement if the experiment concerns an IND[20] drug or medical device IDE[21] (applicable FDA[22] regulations)

According to 21 CFR Part 56 §56.113 [IX], the CEHF[23] has the authority to suspend or withdraw its agreement to the conduct of an experiment which is not conducted in accordance with CEHF requirements or which presents serious harm to participants . Any suspension or withdrawal of the agreement will include a description of the reasons for the CEHF's action and will be promptly reported (within 30 days) to the investigator, the CTC[24] Medical and Administrative Director as well as the AFMPS[25] and the Food and Drug Administration (FDA). (AAHRPP[26] requirement)

The 21 CFR Part 56 §56.108(b) regulations require the CEHF to follow written procedures in order to ensure prompt information by the CEHF, the Medical and Administrative Director of the CTC, the AFMPS and the FDA of:

1) Any unexpected problem presenting a risk to humans or others;
2) Any allegation of deviation or major or continuous violation with these regulations or with the requirements of the CEHF; or
3) Any suspension or termination of the CEHF agreement.

Any report concerning a suspension or withdrawal of the CEHF agreement will specify the IND or IDE number, the full title of the protocol, the name of the investigators and the reason (s) for the suspension or termination. These reports can be submitted by email or in hard copy by fax or by mail.

They will be sent to the following contacts at the FDA:

For medicinal products	For biological substances	For medical devices
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	CBERBIMONotification@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 10903 New Hampshire Ave. Building 71, Room 5126 Silver Spring, MD 20993 Phone: (240) 402-8928 Fax: (301) 595-1304	Phone (301) 796-5490 Fax: (301) 847-8136 Email: bimo@cdrh.fda.gov

[20] IND : Investigational New Drug
[21] IDE : investigational device exemption
[22] FDA : Food and Drug Administration
[23] CEHF : Ethics committee / Comité d'éthique hospitalo-facultaire
[24] CTC : Clinical trial centre
[25] AFMPS : Agence Fédérale des Médicaments et des Produits de Santé
[26] AAHRPP : Association for the Accreditation of Human Research Protection Program

4. DISTRIBUTION

Cette procédure est à diffusion

Publique ☒

Restreinte à l'unité/entité/département ☐

5. RÉFÉRENCES

CEHF-DSQ-054_Liste des Lois, Arrêtés Royaux, Directives Européennes et normes de qualité en vigueur

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[I] AAHRPP-SOP-033_Préparation étude - Procédure visite initiation et AAHRPP-SOP-031_Conduite étude - Mise en place étude clinique (randomisation, matériel, données sources, CRF) procédures du Clinical trial Centre

[II] CEHF-FORM-128_Suivi - Formulaire déclaration déviation, violation, événements inattendus

[III] AAHRPP-SOP-015_Conduite étude – suivi - Procédure pharmacovigilance, procédure du Clinical trial Centre

[IV] COSI-FORM-011_Formulaire de notification des Fuites de données

[V] CEHF-FORM-128_Suivi - Formulaire déclaration déviation, violation, événements inattendus

[VI] AAHRPP-SOP-039_Conduite étude - suivi - Procédure mise en place comité de contrôle sécurité données (DSMC), procédure du Clinical trial Centre

[VII] Good Clinical Practice

[VIII] Loi du 7 Mai 2004, cfr CEHF-DSQ-054_Liste des Lois, Arrêtés Royaux, Directives Européennes et normes de qualité en vigueur

[IX] e-CFR : Electronic Code of Federal Regulations, https://www.ecfr.gov/cgi-bin/text-idx?SID=f343acbf640a800effc39a84bac1717c&mc=true&tpl=/ecfrbrowse/Title21/21tab_02.tpl