"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

This procedure describes non-compliance (deviation or violation) events or unanticipated problems related to a medical research that must be reported by "researchers- sponsors of non-commercial experiments", investigators, their personnel, other concerned employees and the actions taken by the Ethics Committee to evaluate these events.

2 PROCEDURE'S SCOPE

1. Direction
2. Consultations
3. Medico-technic
4. Ward and One-day clinic
8. Ethics Committee

3 RESPONSIBILITIES AND AUTHORITIES

The investigator and the institution must perform the medical research according to the protocol established by the sponsor and approved by the Ethics Committee.
The investigator is not allowed to modify or to deviate from the protocol without the sponsor's approval and the favourable opinion from the Ethics Committee except in emergency situation. The investigator must justify any protocol deviation and inform the sponsor and the Ethics Committee of any unanticipated problem occurring in the course of the study. The sponsor and the Ethics Committee must evaluate any non compliance or unanticipated problem reported and act accordingly.

4 PROCEDURE'S REVISION

5 PROCEDURE'S DESCRIPTION

5.1 Prevention measures (cfr 068-AAHRPP-SOP-033 and 075-AAHRPP-SOP-031).

- The investigator and his clinical research team must carefully read the protocol before the initiation of the experimentation.
- All investigators and staff members of the site must assist to the initiation visit upon which the sponsor or his delegates provide a particular training on the protocol and all specific related procedures.
- The investigator must ensure that all staff members involved in the experimentation are correctly informed about the protocol, the investigated medical drug and all the protocol related procedures.
- Before enrolling the first patient, the investigator and his clinical research team must revise all the protocol requirements with the monitor of the experimentation.

5.2 Non compliance and unanticipated problem reported by investigator, sponsor or anyone establishing the facts (cfr 109-AAHRPP-FORM-057).

5.2.1 Minor deviations (or minor non-compliance) to the protocol are tolerated in case of protocol unforeseen circumstances. These deviations don't increase the minimal risk of the participant and therefore **don't need to be reported to the Ethics Committee. They will be reported by the investigator in the source documents and in the CRF of the study.**

5.2.2 Continuous or not major deviations can be justified by a risk/danger not considered when writing the protocol and to protect participants from this danger. These deviations will be immediately **notified by the principal investigator to the sponsor of the experimentation and to the EC. They provide an increase of the minimal risk to the participant.**

5.2.3 Continuous or not protocol violations involve a voluntary error of adherence to protocol for the purpose of fraud. By definition, a protocol violation report is drafted 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 experiment. These protocol violations provide an increase of the minimal risk to the participant.**

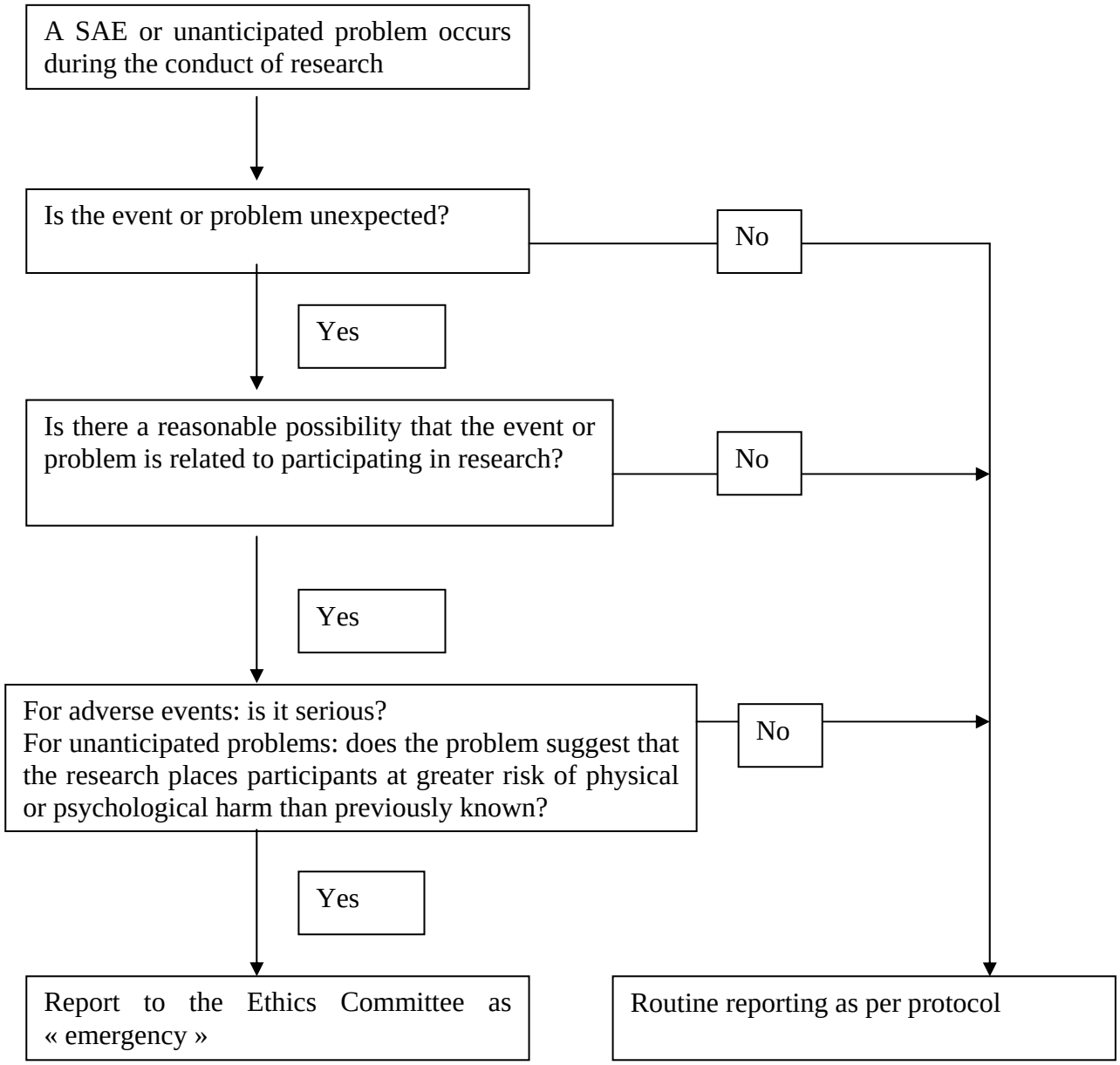
5.2.4 Unanticipated problems related or possibly related to the research can occur at any time during the study and influence its course. They **will be notified within 10 business days by the principal investigator to the sponsor of the experimentation and to the EC**. The transmission of the SUSARs to the Ethics Committee is ruled by the pharmacovigilance procedure and the legal deadlines (104-AAHRPP-SOP-015).

An accidental loss or leak of data related to a clinical research will be notified by the principal investigator to the sponsor of the experimentation and to the EC but also to the data protection officer (gery.mollers@uclouvain.be – 4 23 40), as soon as this event is discovered.

The Ethics Committee can receive report of non compliance by numerous ways, such as (not limited to):

1. Volunteer notification by the principal investigator (deviation)
2. Absence of reaction of the PI to requests from the EC regarding the procedures of monitoring of an experimentation
3. Information provided by clinical research staff members
4. Information provided by other other members of the institution
5. Monitoring report
6. Audit report,
7. Complaints from participants of the experimentation

5.2.4.1 Assessment of the need to report unanticipated problems to the ethics committee :



5.2.5 Summarized table: report of the different types of non compliance

The “protocol deviation form” (109-AAHRPP-FORM-057) is used to inform the Ethics Committee AND the sponsor.

Type	Report to the EC	Report to the Sponsor	By whom ?	When ?	How ?
Minor deviations (or minor non-compliance)	no	yes	Investigator	routine	CRF and source data
Continuous or not major deviations	yes	yes	Investigator	Emergency (at the knowledge of the event)	Protocol deviation form
Continuous or not major violations	yes	yes	Sponsor or the first person to notice	Emergency (at the knowledge of the event)	Protocol deviation form
Unanticipated problems related to the experiment	yes	yes	Investigator	Emergency (at the knowledge of the event)	Protocol deviation form

Specific case of a participant who experiences an unexpectedly substantial impairment to his or her functional abilities that is not foreseeably temporary: this event could influence the ability of the participant to consent for the continuation of the study and it must be reported to the Ethics Committee as an unexpected event with the “protocol deviation form”.
The Ethics Committee will evaluate if:

- The investigator should re-evaluate the participant’s capacity to consent to determine whether he/she is permitted to remain in the study.
- The investigator should re-evaluate the possibility for the patient to remain in the study.

5.3 Evaluation and corrective actions

5.3.1 EVALUATION AND ACTIONS FROM INVESTIGATOR:

Actions made by the principal investigator to reduce the risk encountered by participants or to prevent recurrence of deviations/violations to the protocol.

Examples: staff member training, request of modifications of protocol and/or ICF

The sponsor or investigator must inform the EC:

* deviations related to the protocol and unanticipated problems leading to consequences in term of rights, safety and wellbeing of participants or consequences on integrity of the results of the experimentation
* serious deviations/violations
* repeated deviations/violations

5.3.2 EVALUATION AND ACTIONS FROM THE NON COMMERCIAL SPONSOR

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

- The non-commercial sponsor receives the “Protocol deviation form”

5.3.2.1 If the report concerns his own center, it will be evaluated by the DSMC (cfr 103-AAHRPP-SOP-039) and failing that, only by the Ethics Committee.

- As for information related to protocol violation, the reporter's anonymity will be guaranteed. The reporters' names will not be divulged to the people affected by the complaint, unless this is necessary in order to arbitrate the situation.

5.3.2.2 If the report concerns an external center, it will be evaluated by the DSMC and/or by the study medical manager depending of what was defined at the study start up (cfr 103-AAHRPP-SOP-039).

- Evaluation of the severity according to the following criteria:

- Is the safety of one participant challenged?
- Is the safety of other participants of the experimentation challenged?
- Is the ability of the site to recruit participants challenged?

- Is the participation of an investigator or staff member challenged?
- Are the collected data for a participant incorrect or inappropriate?
- Are the collected data from all the participants incorrect or inappropriate?

- The sponsor sends its comments to the investigator
- The sponsor performs a route-cause analysis and implements appropriate corrective and preventive actions (GCP 5.20)
- The investigator establishes preventive and corrective actions and informs the sponsor.
    - The sponsor examines and gives a favorable opinion towards the corrective actions established: non-compliance is considered corrected
    - The sponsor examines and gives a negative opinion towards the corrective actions established: the sponsor can suspend or withdraw its authorization to the participation of the site to the research protocol.

- The sponsor informs the competent authorities in case of serious violation of the protocol or in case of repeated or serious non-compliance to a protocol of clinical research of medical device.

5.3.3 EVALUATION AND ACTIONS FROM EC:

- The CEHF secretary receives the “Protocol deviation form”.

- As for information related to protocol violation, the reporter's anonymity will be guaranteed. The reporters' names will not be divulged to the people affected by the complaint, unless this is necessary in order to arbitrate the situation.

- The evaluation of provided information will be performed by the scientific secretary of the EC regarding the following criteria:
    - Is the safety of one participant challenged?
    - Is the safety of other participants of the experimentation challenged?
    - Is the ability of the site to recruit participants challenged?
    - Is the participation of an investigator or staff member challenged?
    - Are the collected data for a participant incorrect or inappropriate?
    - Are the collected data from all the participants incorrect or inappropriate?

- The chair/vice-chair examine the information (5 business days timing) related to protocol violations. The secretary sends to Chair and/or Vice-Chair and to the members that are planned to attend the next protocol analysis meeting the following documents : summary of the experiment, description of unanticipated problems involving more than minimal risks to participants or serious or continuing non-compliance, comments of the sponsor or the principal investigator (if any).
- The EC secretary records the decision in the "undesirable events CEHF" file
- The EC sends its comments to the investigator
- The investigator establishes corrective actions and informs the EC.
    - The EC examines and gives a **favorable** opinion towards the corrective actions established: non compliance is considered corrected

- The EC examines and gives a **negative** opinion towards the corrective actions established: the EC can suspend or terminate its authorization to the participation of the site to the research protocol. In this case, the EC will inform the investigator as well as the Medical and the Admininistrative Directors of the Clinical Trial Center of the Cliniques universitaires Saint-Luc. The investigator will inform directly the sponsor. In case of such information might relate to participant's willingness to continue to take part in the research, the CEHF will require that the investigator/sponsor notify this to current participants.

The range of optional actions considered by the EC to be required include:

- Providing additional information to past participants.
- Requiring current participants to re-consent to participation.
- Modification of the continuing review schedule.
- Monitoring of the research.
- Monitoring of the consent process.

  Referral to other organizational entities

5.3.3.1 Supension or termination of EC approval if the experiment concerns an IMP (Belgian Law 7 May 2004)

- If the CEHF has objective reasons to consider that the conditions of the approval are no longer met for the conduct of the experiment or if the EC has information leading to challenging safety or scientific background of the experiment, the EC informs the investigator. He should inform the sponsor and give his answer within 1 week.
- In case of imminent risk, the timing of 1 week can be shortened.

- Upon receipt of comments or absence of comments within the indicated timing, if the EC considers that conditions for approval are no longer met for the conduct of the experiment or if the EC has information leading to challenging safety or scientific background of the experiment, the EC informs the Ministry which can suspend or forbid the experiment. This suspension or interdiction starts immediately after notification to the sponsor.
- If the Ministry considers that conditions for approval are no longer met for the conduct of the experiment or if he has information leading to challenging safety or scientific background of the experiment, he follows the same procedure. In this case, the Ministry directly informs the competent authorities of Member States involved, the involved EC, the European Agency and European Commission about his decision to suspend or forbid the experiment and the reasons justifying his position.
- The decision to suspend or forbid the clinical experiment must be grounded on objective information collected by the EC after analysis of these information by the chair of the EC (in case of emergency) or during the protocol analysis meeting. The opinion of suspension of interdiction will be transmitted to the investigator who will forward it to the sponsor and to the Medical and Administrative Directors of the CTC. The answer of the investigator/sponsor will be analyzed during the protocol analysis meeting that will either revoke the suspension/interdiction on basis of satisfactory answer from the investigator or keep the suspension/interdiction which will be transmitted to the FAMHP if applicable (interventional clinical trial).

5.3.3.2 Suspension or termination of EC approval if the experiment concerns an IND or IDE (FDA Regulation applicable)

Under 21 CFR 56.113, CEHF shall have the authority to suspend or terminate approval of research that is not being conducted in accordance with the CEHF's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the CEHF`s action and shall be reported promptly (no longer than within 30 days) to the investigator, as well as the Medical and the Admininistrative Directors of the Clinical Trial Center and the Food and Drug Administration.

21 CFR 56.108(b) requires that the CEHF follows written procedures for ensuring prompt reporting to the CEHF as well as the Medical and the Admininistrative Directors of the Clinical Trial Center, and the Food and Drug Administration of:

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; or*
3. *any suspension or termination of CEHF approval.*

When reporting suspensions or terminations of CEHF 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. These reports may be submitted via e-mail or in hard copy by fax or mail. Submit information to the following locations/contacts:

5.3.3.2.1 For Drug Products:

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

5.3.3.2.2 For Biologic Products:

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

5.3.3.2.2.3For Medical Devices:

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

6 DEFINITIONS AND ABBREVIATIONS

6.1 Non compliance

Non-compliance with all requirements of the experimentation, GCP and the applicable regulatory requirements.

6.2 Minor deviation

Non compliance involving no increase of the minimal risk of the participant and therefore don't need to be reported to the Ethics Committee.

Example: Evaluation date different from the foreseen date but still in the protocol permitted windows.

6.3 Major deviation

Made of non compliance which are notified by the principal investigator or his staff to the sponsor / Ethics Committee. They may be intentional, but most often are performed unintentionally (from the point of view of the investigator and staff), as a result of ignorance of a member of the research team or the result of a lack of organization and have minor consequences in terms of effects on the rights, safety or well-being of participants or the integrity of the study results.

Examples:

laboratory data missing, missing follow-up visit, the patient receives an incorrect dose, the patient takes a co-medication unauthorized, the patient takes a dose lower or higher than the approved dose, the patient does not comply with the dosing schedule of treatment, the patient stops treatment but is still included in the study, the patient or the investigator does not comply with the time of visits, the patient or investigator omits some checks but the study continues, some assessments are incorrect or missing, some assessments are carried out of schedule

6.4 Violation

The distinction between violation and deviation lies in the absence of notification of non-compliance of the facts to the sponsor / Ethics Committee, the intention to not respect the protocol / GCP (eg include participants who have not received prior information and consent

in accordance with GCP) for the purpose of fraud. The violation involves a voluntary error of adherence to protocol of the investigator or his staff

Examples:

Voluntary inclusion of patients not meeting the criteria for inclusion / exclusion protocol, administration of treatment not corresponding to randomized treatment

6.5 Major or serious deviation/violation

Act or failure to act which is intentional or not, is likely to increase the risk which can be physical, psychological, in terms of security or privacy protection for research participants.

Examples:

Deviation / violation of the protocol leading to death, hospitalization or permanent disability of a participant, evidence of fraud in the collection of data, inclusion of a participant which would correspond to the criteria for exclusion of a study (eg inclusion a patient with renal failure in a test with a nephrotoxic drug for which this patient is excluded). Non-compliance monitoring toxic effects of study treatment: example: complete blood count in patients with cancer treatment can cause neutropenia.

6.6 Continuous deviation/violation

Repeated scheme, act or failure to act which suggests a probable repetition.

Example: not adhering to investigator responsibilities across multiple studies.

6.7 Unanticipated problems

Unanticipated problem involving risk to subjects or others. The following 3 criteria must be met:

- unexpected event
- related or possibly related to the research
- places subjects or others at a greater risk of harm than was previously known or recognized

Example: loss of research data (lost laptop), adverse event that meet the 3 criteria, SUSAR…

6.8 Minimal risk.

A risk is minimal where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as part of routine physical examination.

6.9 Supension and termination of EC approval

Suspension of EC approval can be defined as a temporary halt in EC approval of some or all research activities

Termination of EC approval can be defined as a permanent halt in EC approval of all research activities

6.10 Abbreviations

- PI : Principal investigator
- EC : Ethics Committee
- CRF : Case Report Form
- SAE : Serious Adverse Event
- SUSAR : Suspected Unexpected Serious Adverse Reaction
- ICF : Informed Consent Form

7 REFERENCE DOCUMENTS

109-AAHRPP-FORM-057: Protocol deviation form

8 AAHRPP ACCREDITATION STANDARDS

- Element I.5.D
- Element I.8.B
- Element II.2.D
- Element II.2.F
- Element II.2.G
- Element II.2.H
- Element II.3.B
- Element II.3.G
- Element III.2.C
- Element III.2.D

9 LINKS INTRANET

10 LINKS INTERNET